Different Influences of Classical Antipsychotics and Clozapine on Glucose-Insulin Homeostasis in Patients With Schizophrenia or Related Psychoses

Kristina I. Melkersson, M.D.; Anna-Lena Hulting, M.D., Ph.D.; and Kerstin E. Brismar, M.D., Ph.D.

Background: The aim of this study was to investigate the influence of classical antipsychotics and the atypical antipsychotic agent clozapine on glucose-insulin homeostasis to explain possible mechanisms behind weight gain associated with antipsychotic treatment.

Method: Twenty-eight patients on therapy with classical antipsychotics and 13 patients treated with clozapine (all meeting DSM-III-R criteria for schizophrenia or related psychoses) were studied. Fasting blood samples for glucose and insulin, as well as for 2 markers of the glucose-insulin homeostasis, i.e., the growth hormone (GH)-dependent insulin-like growth factor I (IGF-I) and the insulin-dependent insulin-like growth factor binding protein-1, were analyzed. Body mass index (BMI) was calculated and serum concentrations of the different antipsychotic drugs were measured. In addition, the relationship between the endocrine parameters and drug serum concentrations was examined.

Results: The insulin levels were positively correlated to the serum concentration of clozapine, whereas no correlations were found between insulin and the serum concentrations of perphenazine (N = 12) or zuclopenthixol (N = 9). Insulin elevation was seen in the patients receiving clozapine more frequently than in the patients receiving classical antipsychotics. In addition, the median level of IGF-I was significantly lower in the patients receiving clozapine than in the patients receiving classical antipsychotics. No significant difference in BMI was found between the 2 patient groups, and all patients but 1 were normoglycemic.

Conclusion: The correlation between insulin and the clozapine concentration indicates a probable influence of clozapine on insulin secretion. The normal blood glucose levels in the clozapine group support the theory that clozapine induces concentration-dependent insulin resistance with secondary increased insulin secretion. In addition, lower median level of IGF-I in patients receiving clozapine compared with patients receiving classical antipsychotics points to a lower GH secretion in the clozapine group. This impaired GH secretion together with the clozapine-induced insulin resistance might be mechanisms behind weight gain during clozapine therapy.

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Reprint requests to: Anna-Lena Hulting, M.D., Ph.D., Department of Endocrinology and Diabetology, Karolinska Hospital, S-171 76 Stockholm, Sweden (e-mail:alh@spmed.ks.se).

Previous studies show overweight in varying frequency in patients on treatment with classical as well as atypical antipsychotic agents.[1–3] Weight gain contributes to noncompliance with treatment and may lead to medical morbidity.[4,5] Therefore, it is important to tackle the overweight problem in patients on treatment with antipsychotics. However, the mechanisms behind weight gain induced by antipsychotic drugs are poorly understood, even though several possibilities are suggested, e.g., that the sedative effects of antipsychotics lead to less physical activity and therefore lowered calorie utilization and that thirst due to anticholinergic activity of antipsychotics increases the consumption of high-calorie beverages.[5] The serotonergic blockade of antipsychotic agents, through an antagonism of the serotonin-2C (5-HT_{2C}) receptors, has also been discussed as a possible cause of weight gain induced by antipsychotics.[6,7]

In addition, the classical antipsychotics promote weight gain in varying degrees, e.g., haloperidol has a lower potential to induce weight gain than chlorpromazine and other phenothiazine compounds.[4,8] Treatment with the atypical antipsychotic agent clozapine also can be associated with excessive weight gain, and, as for the classical antipsychotics, the mechanisms of the weight gain remain unclear.[5,9] However, previous case studies on 13 patients have described diabetes mellitus, diabetic coma, or impairment in glycemic control of already diagnosed diabetes after the onset of clozapine therapy.[10–16] Furthermore, in a recent study, patients treated with clozapine showed a trend to be more often classified as having type 2 diabetes mellitus or impaired glucose tolerance compared with patients on treatment with conventional depot neuroleptics.[17] These reports indicate a possible influence of clozapine on

glucose-insulin homeostasis, which in turn may be related to weight gain during clozapine treatment.

In addition to insulin, 2 other hormones, insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein-1 (IGFBP-1), are of importance for glucose-insulin homeostasis. IGF-I, in free form, stimulates glucose uptake in muscles.[18] The majority of IGF-I (99%), however, circulates bound to binding proteins IGFBP-1–6.[19] IGFBP-1 is expected to regulate the availability and bioactivity of IGF-I,[19] and its production in the liver is insulin regulated.[20,21] Since insulin inhibits the hepar production of IGFBP-1, the diurnal rhythmicity of IGFBP-1 shows a pattern with highest levels when the insulin concentrations are low. Therefore, measurement of IGFBP-1 concentrations can be used as an indirect parameter of insulin secretion.[20,21] Circulating IGF-I, which is produced mainly in the liver, is in turn particularly growth hormone (GH) dependent, but also nutrition and insulin dependent.[18] Thus, low level of IGF-I is a marker for GH deficiency, which is known to cause weight gain.[22]

The aim of this study was to investigate the influence of classical antipsychotics and clozapine on hormones involved in glucose-insulin homeostasis to explain possible mechanisms behind weight gain induced by antipsychotics. We analyzed glucose, insulin, IGF-I, and IGFBP-1 and attempted to determine if these endocrine parameters were related to body mass index (BMI, in kg/m^2) as well as to doses and serum concentrations of the different antipsychotic agents.

METHOD

Patients

Consecutive outpatients treated at the Department of Psychiatry, St. Görans Hospital, Stockholm, Sweden, were asked to participate in the study. Patients who had a substance-related disorder, diabetes mellitus, or other physical illness that could influence glucose-insulin homeostasis were excluded. The investigation included 41 patients diagnosed with either schizophrenia or schizophreniform, schizoaffective, or delusional disorder according to DSM-III-R criteria[23] (Table 1). Twenty-eight of the patients (16 men and 12 women) were treated with different types of classical antipsychotics, and 13 patients (7 men and 6 women) received monotherapy with the atypical agent clozapine. Some of the patients also received benzodiazepine derivates and/or anticholinergic medications, but none received concomitant antidepressant medications or mood stabilizers.

The median age of the patients treated with classical antipsychotics (N = 28) was 42 years (range, 27–72 years) and differed from that of the patients on clozapine therapy (N = 13), which was 35 years (range, 26–47 years) (p = .03) (Tables 2A and 2B). The duration of disease ranged from 1 to 52 years (median = 17 years) for the patients receiving classical antipsychotics and from 3 to 25 years (median = 12 years) for the patients receiving clozapine. The therapy with the classical antipsychotics, including haloperidol, perphenazine, remoxipride, thioridazine, and zuclopenthixol, was carried out with either a single or combined drug regimen. Fourteen patients on treatment with classical agents received oral medication, 11 received neuroleptic depot injections, and 3 received both tablets and injections. The median and range of the daily dose of classical antipsychotics, as well as those of clozapine, are given in Table 3. All patients had been on treatment with antipsychotics for at least 6 months, with a median treatment period of 5.0 years (range, 0.5–39.5 years) for the patients receiving classical antipsychotics compared with 2.7 years (range, 0.5–7.3 years) for the patients receiving clozapine (not significant). The laboratory investigation included fasting blood levels of glucose and fasting serum concentrations of insulin, IGF-I, IGFBP-1, and antipsychotic drugs. In addition, BMI was calculated.

Table 1. Psychiatric Diagnosis According to DSM-III-R Criteria and Confirmed by 2 Psychiatrists in 41 Patients

	Treatment Group, N	
Psychiatric Diagnosis	Classical Antipsychotics (N = 28)	Clozapine (N = 13)
Schizophrenia, not subclassified	1	2
Schizophrenia, disorganized type	1	2
Schizophrenia, paranoid type	9	1
Schizophrenia, undifferentiated type	12	6
Schizophreniform disorder	2	0
Schizoaffective disorder	1	1
Delusional disorder	2	1

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

Analysis of Blood Samples

All blood samples were drawn in the fasting state, collected in the morning prior to the oral tablet dose or just before neuroleptic depot injections.

Blood glucose levels were determined by a glucose oxidase method using the 950 Immunologic-Rate-Colorimetric (IRC) system (Johnson & Johnson Clinical Diagnostics, Inc., 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.[24] The intra-assay coefficient of variation (CV) was 5% and the interassay CV 10%. The detection limit was 56 pmol/L. IGF-I was measured by an RIA method designed by Bang et al.[25] and expressed as age-correlated standard deviation scores based on samples from healthy men and women.[26] The detection limit was 8 μg/L. Including the extraction step, the intra-assay and interassay CVs were 4% and 11%, respectively. IGFBP-1 concentrations were determined according to the RIA

Table 2A. Sixteen Men and 12 Women on Treatment With Classical Antipsychotics[a]

Variable	Sex	Age (y)	BMI (kg/m^2)	f(B)-Glucose (mmol/L)	fs-Insulin (pmol/L)	IGF-I (µg/L)	IGF-I (age-correlated SD score)	IGFBP-1 (µg/L)
Reference range	n/a	n/a	Men ≤ 27, women ≤ 25	3.0–6.0	< 144	n/a	± 2 SD	Men 5–93, women 9–101
Patient								
1	M	27	30	4.6	136	301	0.71	6
2	M	29	24	4.7	101	265	0.36	17
3	M	31	27	4.0	65	146	–1.68	6
4	M	34	25	4.3	65	296	1.05	25
5	M	40	24	5.7	108	154	–0.97	24
6	M	41	21	4.8	65	314	1.67	22
7	M	42	22	5.3	115	152	–0.90	13
8	M	43	30	5.8	179	360	2.28	16
9	M	45	27	5.9	93	174	–0.24	9
10	M	45	28	5.3	280	193	0.14	3
11	M	49	21	5.4	57	112	–1.60	62
12	M	54	40	4.8	151	195	0.69	3
13	M	55	29	5.8	208	215	1.10	10
14	M	56	40	5.1	129	131	–0.63	6
15	M	70	28	4.7	122	147	0.60	40
16	M	71	25	4.5	115	194	1.66	32
17	F	30	22	4.2	57	137	–1.97	52
18	F	31	22	4.7	86	196	–0.62	23
19	F	37	33	5.2	151	185	–0.48	25
20	F	37	29	5.1	72	226	0.25	18
21	F	38	35	5.0	93	226	0.30	8
22	F	39	21	4.9	79	197	–0.14	14
23	F	39	29	5.1	93	435	2.73	15
24	F	41	25	4.2	115	240	0.69	21
25	F	42	29	4.8	273	178	–0.33	8
26	F	43	29	4.6	72	146	–0.99	13
27	F	51	27	5.2	57	248	1.39	18
28	F	72	26	5.7	115	151	0.81	54
Median	n/a	42	27	5.0	105	...	0.28	16.5
Mean ± SD	n/a	44 ± 12	27 ± 5	5.0 ± 0.5	116 ± 59	...	0.21 ± 1.17	20 ± 15

[a]Blood levels of glucose, insulin, insulin-like growth factor I (IGF-I), and insulin-like growth factor binding protein-1 (IGFBP-1) are fasting morning samples. The concentrations of IGF-I are expressed as age-correlated SD scores, based on samples from healthy men and women.[26] Oral antipsychotic treatment was given 12 to 14 hours before blood withdrawal and neuroleptic depot injections 2 to 4 weeks before, respectively.
Abbreviations: BMI = body mass index, f(B)-Glucose = fasting blood glucose level, fs-Insulin = fasting serum insulin level.

Table 2B. Seven Men and 6 Women on Treatment With the Atypical Antipsychotic Agent Clozapine[a]

Variable	Sex	Age (y)	BMI (kg/m^2)	f(B)-Glucose (mmol/L)	fs-Insulin (pmol/L)	IGF-I (µg/L)	IGF-I (age-correlated SD score)	IGFBP-1 (µg/L)
Reference range	n/a	n/a	Men ≤ 27, women ≤ 25	3.0–6.0	< 144	n/a	± 2 SD	Men 5–93, women 9–101
Patient								
1	M	29	22	4.5	65	274	0.48	13
2	M	32	31	7.0	244	193	–0.61	12
3	M	32	26	4.0	172	326	1.28	3
4	M	35	24	5.1	108	100	–2.82	13
5	M	37	23	5.7	144	119	–2.08	11
6	M	43	24	5.5	108	99	–2.39	19
7	M	47	29	5.7	208	152	–0.61	18
8	F	26	27	4.0	230	276	0.33	4
9	F	35	22	6.0	79	164	–1.03	20
10	F	35	27	4.7	79	98	–2.82	22
11	F	37	22	4.3	57	138	–1.54	33
12	F	38	29	4.7	115	269	0.93	17
13	F	42	29	5.4	280	145	–1.07	21
Median	n/a	35*	26 (NS)	5.1 (NS)	115 (NS)	...	–1.03*	17 (NS)
Mean ± SD	n/a	36 ± 6	26 ± 3	5.1 ± 0.9	...	145 ± 74	–0.92 ± 1.39	16 ± 8

[a]Blood levels of glucose, insulin, IGF-I, and IGFBP-1 are fasting morning samples. The concentrations of IGF-I are expressed as age-correlated SD scores, based on samples from healthy men and women.[26] Oral antipsychotic treatment was given 12 to 14 hours before blood withdrawal.
Abbreviation: NS = not significant vs. value for patients receiving classical antipsychotics.
*Significant difference vs. value for patients receiving classical antipsychotics, $.01 < p < .05$.

Table 3. Median and Range of the Daily Dose of Classical Antipsychotics and Clozapine in 41 Patients on Long-Term Treatment

Treatment Group	N	Median Daily Dose of Antipsychotic Drug (mg)	Range
Classical antipsychotics[a]	28	232	75–1420
Clozapine	13	200	25–600

[a]Dose expressed as chlorpromazine equivalents.

method of Póvoa et al.,[27] slightly modified with a lower detection limit, 1.6 μg/L. The intra-assay and interassay CVs were 3% and 10%, respectively.

BMI was calculated according to the formula BMI = kg/m^2, where kg = the body weight in kilograms and m = the height in meters.[28]

To compare the doses of the different classical antipsychotics, irrespective of the use of oral antipsychotic medication or neuroleptic depot injections, the patients' daily doses of the depot drugs were transformed into oral chlorpromazine equivalent doses in 2 steps.[29,30] The daily dose was first adjusted for bioavailability according to current data: 20% for perphenazine,[31] 70% for haloperidol,[32] and 50% for the other drugs.[33] The dose was then transformed to chlorpromazine-equivalent doses by the chlorpromazine table for oral equipotency.[34]

Serum concentration of the antipsychotic drug remoxipride was analyzed by a high-performance liquid chromatography (HPLC) method with photometry detection described by Nilsson[35] and thioridazine by another HPLC method described by Yasui et al.[36] Concerning the serum concentrations of haloperidol, perphenazine, and zuclopenthixol, published HPLC methods subject to minor modifications were used.[37–39] Serum concentration of clozapine was measured by an unpublished HPLC method (U. Bondesson, Ph.D.). In brief, the serum was alkalized and clozapine extracted by hexan-dichlormetan. The organic layer was evaporated, and the residue dissolved in 50% methanol solution. The sample was then injected into an HPLC system (column Lichropher 60 RP, Merck & Co., Inc.) with an UV detector set to 240 nm.

Statistical Methods

As the different variables were assumed not to be normally distributed, nonparametric tests, i.e., the Mann-Whitney test, the Fisher exact test, and analysis of variance (ANOVA) on ranks, were 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 (Bonferroni correction not made). The ANOVA on ranks was performed using Sigma Stat for Windows (Jandel Scientific GmbH, Erkarth, Germany) and the other statistical analyses by using Statview 4.5 for Macintosh (Abacus Concepts Inc., Berkeley, Calif.).

RESULTS

Endocrine Parameters

Data on the patients are given in Tables 2A and 2B. The median BMI was slightly elevated but did not differ between the groups; the median level of BMI was 27 (range, 21–40) for patients receiving classical antipsychotics and 26 (range, 22–31) for patients receiving clozapine. Furthermore, the BMI (reference ≤ 27 in men and ≤ 25 in women) was elevated in 54% (15/28) of patients receiving classical agents and in 46% (6/13) of patients receiving clozapine.

All but 1 patient were normoglycemic, and the median level of blood glucose was similar for patients on treatment with classical agents as for patients on clozapine therapy: 5.0 (range, 4.0–5.9) versus 5.1 (range, 4.0–7.0) mmol/L (see Tables 2A and 2B).

The median level of insulin was not significantly higher for patients receiving clozapine compared with the patients receiving classical agents: 115 (range, 57–280) versus 105 (range, 57–280) pmol/L (see Tables 2A and 2B). However, there was a tendency for more patients in the clozapine group to have elevated insulin levels compared with those receiving classical antipsychotics (6/13 [46%] vs. 6/28 [21%], p = .15).

The median level of IGF-I (expressed as age-correlated SD score) was significantly lower in the patients receiving clozapine compared with the patients receiving classical antipsychotics, –1.03 versus 0.28 (p = .02). In addition, 4 (31%) of 13 patients on clozapine therapy showed decreased IGF-I levels (< –2 SD), whereas 2 patients receiving classical agents had increased levels (> +2 SD). All the others had IGF-I levels within normal limits (± 2 SD) (see Tables 2A and 2B).

The median level of IGFBP-1 was similar in both patient groups: 16.5 μg/L (range, 3–62 μg/L) for patients receiving classical agents and 17 μg/L (range, 3–33 μg/L) for patients receiving clozapine (see Tables 2A and 2B). However, the 2 patient groups both had a significantly (p < .05) lower median level of IGFBP-1, 16.5 μg/L and 17 μg/L, respectively, compared with that in healthy subjects, 27 μg/L (S. Söderberg, Ph.D., unpublished data). This difference also remained when age was taken into account.

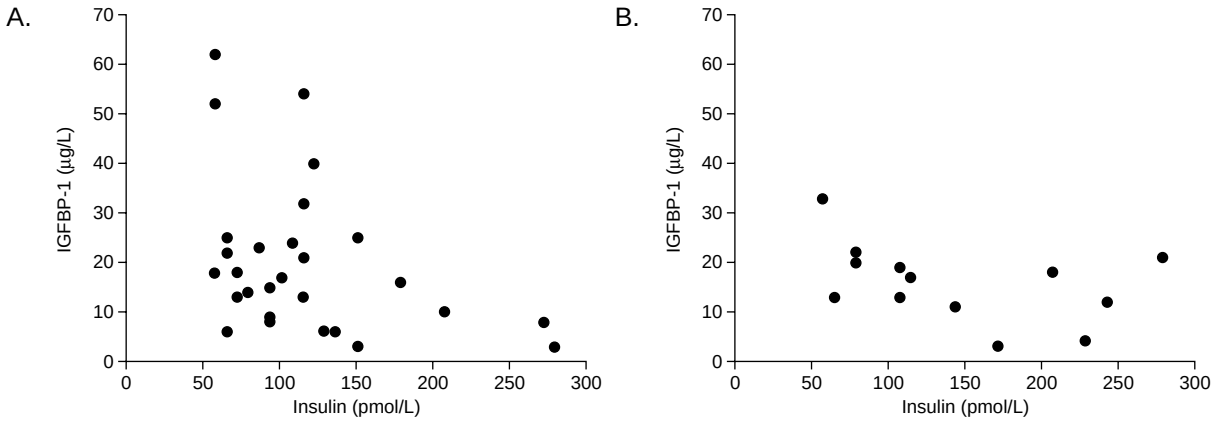
IGFBP-1 levels were inversely correlated to insulin in patients receiving classical antipsychotics (r_s = –0.39, p = .04), whereas for patients on clozapine therapy, no clear correlation was found (r_s = –0.45, p = .12; Figures 1A and 1B).

An inverse correlation was found between IGF-I and IGFBP-1 for patients on clozapine therapy, but not for patients receiving classical agents (r_s = –0.59, p = .04 vs. r_s = –0.11, p = .57; Figures 2A and 2B).

Endocrine Parameters and BMI

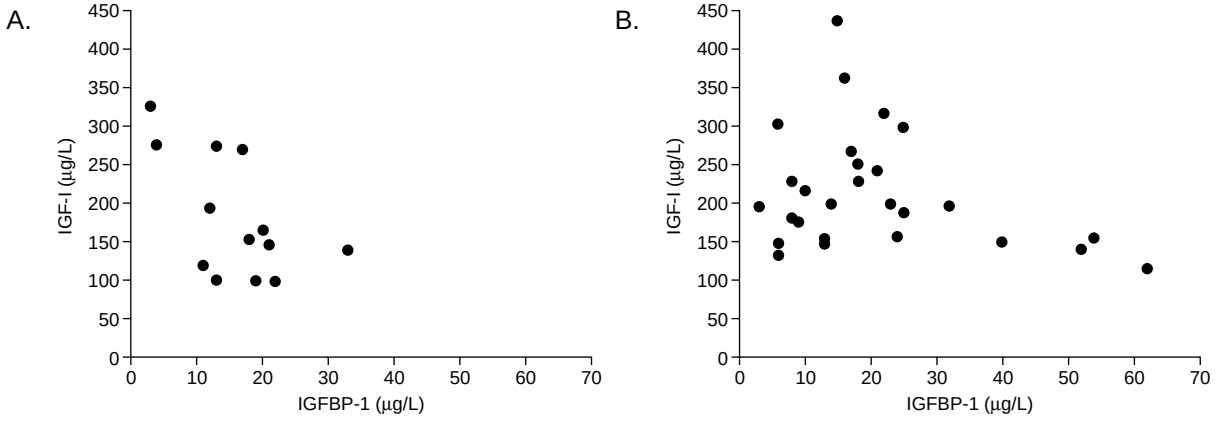
Insulin levels correlated to BMI in both patient groups (Figures 3A and 3B). In addition, IGFBP-1 levels were in-

Figure 1. Relationship Between Serum Levels of IGFBP-1 and Insulin in Patients Receiving (A) Classical Antipsychotics or (B) Clozapine[a]



[a]IGFBP-1 concentrations correlated inversely to insulin levels in the 28 patients on treatment with classical antipsychotics (A: $r_s = –0.39$, $p = .04$), whereas no clear correlation was found in the 13 patients treated with clozapine (B: $r_s = –0.45$, $p = .12$).

Figure 2. Relationship Between Serum Levels of IGF-I and IGFBP-1 in Patients Receiving (A) Classical Antipsychotics or (B) Clozapine[a]



[a]IGF-I levels correlated inversely to IGFBP-1 concentrations in the 13 patients on therapy with clozapine (A: $r_s = –0.59$, $p = .04$), whereas no correlation was found in the 28 patients treated with classical antipsychotics (B: $r_s = –0.11$, $p = .57$).

versely related to BMI in patients receiving classical antipsychotics ($r_s = –0.55$, $p = .004$). However, for patients on clozapine therapy, we did not find a correlation between IGFBP-1 and BMI ($r_s = –0.14$, $p = .64$; Figures 4A and 4B).

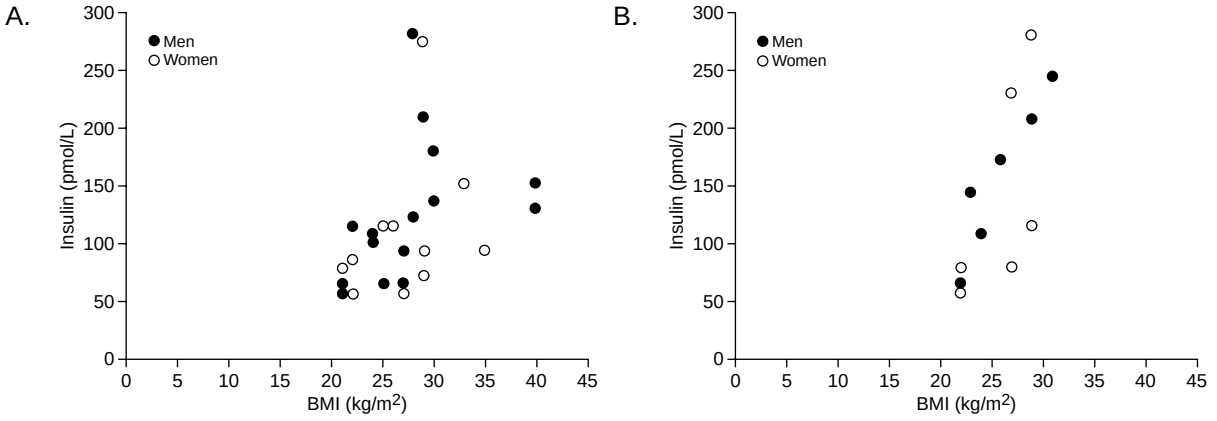
Endocrine Parameters and Antipsychotics

Insulin levels were positively correlated to the serum concentration of clozapine ($r_s = 0.60$, $p = .03$; Figure 5A). However, there was no clear correlation found between insulin levels and the daily dose of clozapine ($r_s = 0.47$, $p = .11$). Neither did we find correlations between IGFBP-1 levels and the clozapine concentration ($r_s = –0.43$, $p = .13$; Figure 5B) or between BMI and the clozapine concentration ($r_s = 0.34$, $p = .24$). Correlations were not found between insulin levels and the serum concentrations of perphenazine (N = 12) or zuclopenthixol (N = 9), nor between insulin and the daily reference dose of classical antipsychotics (expressed as chlorpromazine equivalents). Serum concentrations of haloperidol, remoxipride, and thioridazine were not investigated for correlations, since these agents were used by few patients.

DISCUSSION

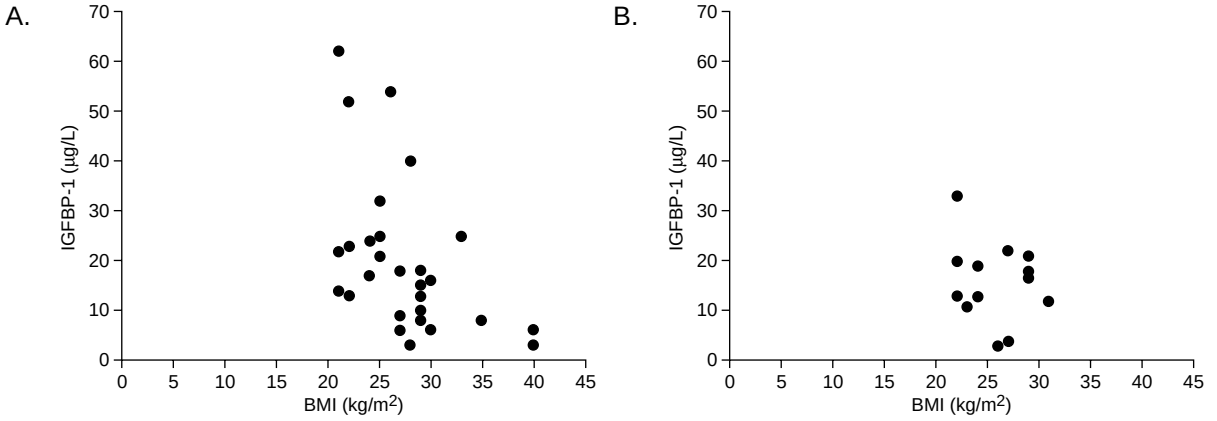
In this study, the patients on clozapine therapy showed insulin levels that correlated to the serum concentration of the agent, irrespective of normal or elevated insulin values. This finding points to a probable influence of clozapine on insulin secretion from the pancreatic beta cells via enhancement of insulin release. The results in our patients treated with classical antipsychotics were different, since

Figure 3. Relationship Between Serum Insulin Levels and BMI in Patients Receiving (A) Classical Antipsychotics or (B) Clozapine[a]



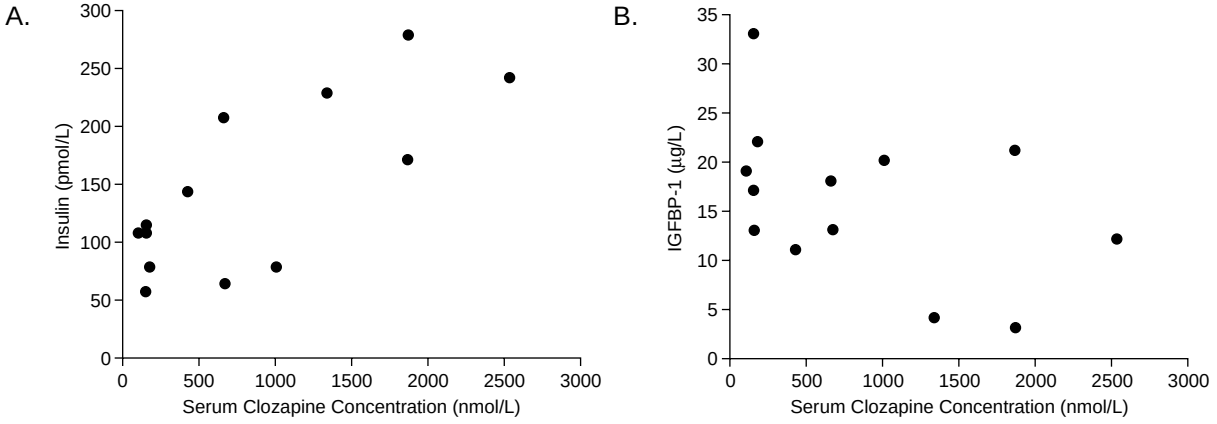
[a]Insulin levels correlated to BMI in the 28 patients on treatment with classical antipsychotics (A: $r_s = 0.56$, $p = .005$) and in the 13 patients treated with clozapine (B: $r_s = 0.79$, $p = .006$).

Figure 4. Relationship Between Serum IGFBP-1 Levels and BMI in Patients Receiving (A) Classical Antipsychotics or (B) Clozapine[a]



[a]IGFBP-1 levels correlated inversely to BMI in the 28 patients receiving classical antipsychotics (A: $r_s = –0.55$, $p = .004$), whereas no correlation was found in the 13 patients treated with clozapine (B: $r_s = –0.14$, $p = .64$).

Figure 5. Relationship Between Serum Levels of (A) Insulin or (B) IGFBP-1 and Serum Clozapine Concentration[a]



[a]Insulin levels correlated to the serum concentration of clozapine in the 13 patients investigated (A: $r_s = 0.60$, $p = .03$), whereas no clear correlation was found between IGFBP-1 levels and clozapine concentration (B: $r_s = –0.43$, $p = .13$).

no correlations between insulin and the serum concentrations of perphenazine or zuclopenthixol were found. In addition, the finding that the patients treated with clozapine showed a trend to more often having elevated insulin levels, compared with the patients on therapy with classical antipsychotics, may further support an effect of clozapine on insulin secretion, especially since BMI did not differ between the 2 groups.

As in healthy subjects,[21,40] IGFBP-1 was inversely correlated to levels of insulin in the patients on therapy with classical agents, whereas we found no such correlation in the patients receiving clozapine. In fact, patients on clozapine therapy also had low IGFBP-1 levels at fasting insulin that were within normal limits. This finding can be explained by a higher diurnal insulin secretion in patients receiving clozapine compared with patients receiving classical antipsychotics. Morning levels of IGFBP-1 are known to correspond better than the morning levels of insulin to integrated diurnal insulin levels.[40,41] The biological half-life of clozapine is 15 hours, and in our patients the clozapine medication was given 12 to 14 hours before blood withdrawal. Thus, the analyses were made at steady state, but we do not know whether the serum concentration of clozapine would have been more strongly correlated to the insulin levels closer to the time of tablet intake. However, in that the correlation coefficient was actually higher for the clozapine group than for the patients receiving classical antipsychotics, it cannot be ignored that the absence of an expected correlation between IGFBP-1 and insulin in the patients receiving clozapine might be due to the limited number of patients in that group.

Moreover, the inverse correlation between IGFBP-1 and BMI, which is insulin dependent in healthy subjects,[18,42] could not be found in the patients receiving clozapine in contrast to the patients on classical antipsychotics. This finding may further support the theory that the regulation of normal insulin secretion is altered during clozapine therapy.

Also, drugs that are structurally different from the peroral antidiabetic sulfonylurea preparations are known to promote insulin secretion through inhibiting the adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels on the pancreatic beta cells.[43] Some antipsychotic agents in the phenothiazine group are among these drugs, and chlorpromazine in particular has been shown to be a potent inhibitor of K_{ATP} channel activity in vitro.[44] However, this finding is not supported by the finding in vivo, where chlorpromazine has been reported to induce hyperglycemia and diabetes.[45,46] In this study, the normal blood glucose levels, instead of hypoglycemia, in the patients receiving clozapine may support the theory that clozapine induces peripheral insulin resistance and secondary increased insulin secretion, even though a direct stimulatory effect of clozapine on the pancreatic beta cells cannot be excluded. However, the true mechanism behind the probable influence of clozapine on insulin secretion is thus far unclear.

On the other hand, the patients treated with classical antipsychotics had fasting insulin and IGFBP-1 concentrations that correlated to their BMI. These findings are consistent with those for subjects with obesity-associated insulin resistance.[18] Accordingly, the finding of elevated insulin levels and low median IGFBP-1 in the patients receiving classical antipsychotics may be explained by their elevated BMI.

To our knowledge, no comparable studies have been carried out in which insulin, IGF-I, and IGFBP-1 levels in patients on treatment with classical antipsychotics or clozapine were investigated. However, in a recent study by Hägg et al.,[17] patients treated with clozapine showed a trend to more often be classified as having type 2 diabetes mellitus or impaired glucose tolerance compared with patients on treatment with conventional depot neuroleptics. In addition, some case reports indicate that the atypical antipsychotic agent clozapine may influence the glucose-insulin homeostasis; in 4 case studies on schizophrenic patients, all 4 patients developed diabetogenic comas after the onset of clozapine therapy.[11–14] In another 3 case reports, 2 schizophrenic patients with diabetes mellitus well controlled by peroral antidiabetic agents began to require insulin during clozapine therapy, and another 7 schizophrenic patients developed diabetes mellitus after starting clozapine treatment.[10,15,16] In addition, Ghaeli and Dufresne[47] in 1995 reported elevated serum triglyceride levels in 4 patients receiving clozapine, and in a further study they found that 39 patients on therapy with clozapine had a higher mean serum triglyceride level than 28 patients treated with typical antipsychotics.[48] Since hyperlipidemia may be connected with peripheral insulin resistance and secondary increased insulin secretion,[49] the results of Ghaeli and Dufresne[48] further suggest that clozapine may influence glucose-insulin homeostasis, probably by inducing insulin resistance. However, in our study, blood lipid levels were not measured in the patients, and a possible effect of clozapine on blood lipid levels could not be confirmed.

We also found that the patients treated with clozapine had a lower IGF-I level than the patients receiving classical antipsychotics, which may be secondary to a lower GH secretion in the clozapine group, since nutrition and insulin levels were not decreased.[18] Since GH deficiency is known to cause weight gain,[22] a possibly down-regulated GH secretion together with an increased insulin secretion due to insulin resistance might be mechanisms behind weight gain during clozapine therapy. Moreover, a low level of IGF-I in itself is accompanied by insulin resistance and increased insulin secretion.[41]

The main limitation in the present study is that the sample of patients receiving clozapine was quite small (N = 13) and therefore may not be representative. How-

ever, this was an explorative study, with the aim of finding possible mechanisms behind weight gain induced by antipsychotics that could give ground for further research. In addition, since the risk of developing insulin resistance and type 2 diabetes mellitus increases with age, one should expect less frequently elevated insulin levels in the younger group, i.e., in our patients treated with clozapine than in the patients receiving classical antipsychotics. In contrast, we found a trend toward more frequently elevated insulin levels in the younger group, i.e., in the patients treated with clozapine.

In conclusion, in this study, we found insulin levels correlating to serum concentrations of clozapine, but not to concentrations of perphenazine or zuclopenthixol, pointing to a probable influence of clozapine on pancreatic insulin secretion. Our findings also suggest that clozapine induces peripheral insulin resistance, even though a direct stimulatory effect of clozapine on the pancreatic beta cells cannot be excluded. In addition, we found lower IGF-I levels in the patients treated with clozapine compared with the patients receiving classical antipsychotics, pointing to a lower GH secretion in the clozapine group. This impaired GH secretion together with clozapine-induced insulin resistance might be 2 mechanisms behind weight gain during clozapine therapy. The probable ability of clozapine to induce insulin resistance is also a clinical point to be noted, particularly in treatment with higher serum concentrations of clozapine and in patients with risk factors for, or who already have, overt diabetes mellitus.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), perphenazine (Trilafon and others), thioridazine (Mellaril and others).

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