ORIGINAL ARTICLE

Effect of antipsychotic-induced hyperprolactinemia on anthropometric measures, insulin sensitivity and lipid profile in patients with schizophrenia or related psychoses

Kristina Melkersson, Katarina Berinder, Anna-Lena Hulting

Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Correspondence to: Kristina Melkersson, MD., PhD.
Department of Molecular Medicine and Surgery, Karolinska Institutet
c/o Sollentuna/ Sigtuna/ Upplands Väsby Psychiatric Polyclinic
Anton Tamms väg 3, S-194 34 Upplands Väsby, Sweden.
tel: +46 8 12344010; fax: +46 8 58733018; e-mail: Kristina.Melkersson@ki.se

Submitted: 2011-05-07 Accepted: 2011-06-14 Published online: 2011-08-29

Key words: **prolactin; antipsychotic drug; schizophrenia; insulin sensitivity; blood lipids; body mass index**

Neuroendocrinol Lett 2011; **32**(4):428–436 **PMID:** 21876517 NEL320411A12

Abstract

OBJECTIVES: This study consisting of two subprojects was undertaken to evaluate the effects of hyperprolactinemia on cardiovascular disease (CVD) risk parameters such as anthropometric measures, insulin sensitivity and blood lipids in patients with schizophrenia or related psychoses on long term treatment with antipsychotics.

METHODS: In subproject I, 45 patients receiving the 2nd generation antipsychotics risperidone, clozapine or olanzapine were compared regarding prolactin (PRL), body mass index (BMI), insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and blood lipids. In subproject II, 24 patients receiving 1st or 2nd generation antipsychotics were investigated with diurnal profile of PRL and oral glucose tolerance test (OGTT).

RESULTS: Elevated PRL levels were found in about 45% of the patients and occurred more often in patients receiving risperidone or haloperidol, compared to patients receiving clozapine or olanzapine. In contrast, in subproject I, insulin and HOMA-IR were higher and high density lipoprotein cholesterol was lower in patients receiving clozapine or olanzapine, compared with patients receiving risperidone. However, PRL levels did not correlate to BMI, insulin, HOMA-IR or lipids in any of these three treatment groups. In subproject II, OGTT showed impaired glucose tolerance in 25% and new-onset diabetes in 4% of the 24 patients investigated. Additionally, the PRL (median 24 h) levels correlated positively to the 2 h glucose level at OGTT (r_s=0.42, p=0.04).

CONCLUSIONS: Our findings point to that hyperprolactinemia due to 1st and 2nd generation antipsychotics may decrease insulin sensitivity, whereas other mechanisms probably underlie insulin resistance induced by PRL-sparing antipsychotics such as clozapine and olanzapine.

INTRODUCTION

It is well established that patients with the diagnosis of schizophrenia have an increased risk of cardiovascular disease (CVD) (Brown 1997; Goff *et al.* 2005). Overweight and obesity, increased prevalence of diabetes mellitus and excessive cigarette smoking in these patients, which are important risk factors for development of atherosclerosis, can all contribute to this increased risk of CVD (Allison *et al.* 1999; Dahlöf 2010; Kelly & McCreadie 1999; Mukherjee *et al.* 1996). It is also possible that patients diagnosed with schizophrenia have a genetic predisposition to CVD (Melkersson 2009). However, all causes of the increased risk of CVD in patients with schizophrenia are still not fully understood.

For some years, prolactin (PRL) has attracted attention as a metabolic hormone (Ben-Jonathan *et al.* 2006). Hyperprolactinemia has been reported to be associated with abnormalities of glucose and lipid metabolism that may increase the risk of CVD (Ben-Jonathan *et al.* 2006; Serri *et al.* 2006). Patients with hyperprolactinemia due to a PRL-secreting pituitary adenoma, so-called prolactinoma, have been shown to have reduced glucose tolerance, higher fasting serum insulin levels, lower insulin sensitivity index (ISI composite) and higher homeostasis model assessment of insulin resistance (HOMA-IR) index, compared with control subjects (Johnston *et al.* 1980; Landgraf *et al.* 1977; Schernthaner *et al.* 1985; Serri *et al.* 2006; Tuzcu *et al.* 2003, 2009; Yavuz *et al.* 2003). Hyperprolactinemia in patients with prolactinoma has also been linked to weight gain and obesity (Greenman *et al.* 1998; Schmid *et al.* 2006), and to other known risk factors for atherosclerosis development such as hyperlipidemia, increased low density lipoprotein (LDL) cholesterol, endothelial dysfunction, low grade inflammation and thrombogenic effect (Berinder *et al.* 2010; Erem *et al.* 2010; Pelkonen *et al.* 1982; Serri *et al.* 2006; Urban *et al.* 2007; Wallaschofski *et al.* 2003; Yavuz *et al.* 2003). On the other hand, in patients diagnosed with schizophrenia with hyperprolactinemia due to antipsychotic drug treatment, potential relationships between PRL elevation and body weight gain or abnormalities of glucose and lipid metabolism till now have been investigated only in a single study (Svestka *et al.* 2007).

Prolactin consists of 199 amino acids and is produced by the lactotrophs in the anterior pituitary gland (Thorner *et al.* 1998). The most important PRL-regulating factor is dopamine, which reaches the pituitary via the hypothalamic-hypophyseal portal system and acts at the dopamine$_2$ (D_2) receptors on the lactotrophs, resulting in inhibition of PRL synthesis and secretion (Reichlin 1998). Antipsychotic drugs, which are dopamine antagonists, may, through blockade of the D_2 receptors on the lactotrophs, diminish the dopamine-inhibiting effect on the PRL release, leading to hyperprolactinemia and related symptoms such as menstrual disturbances, impotence, decreased libido, infertility, galactorrhea, gynecomastia and osteoporosis (Abraham *et al.* 2003; Ataya *et al.* 1988; Becker *et al.* 2003; Beumont *et al.* 1974; Ghadirian *et al.* 1982; Inoue *et al.* 1980; Keely *et al.* 1997; Meaney *et al.* 2004; Melkersson 2005; Weizman *et al.* 1985). Whether antipsychotic-induced hyperprolactinemia increases the risk of CVD in patients with schizophrenia is however poorly elucidated, despite the fact that the vast majority of these patients are on therapy with antipsychotic drugs long term, frequently during their whole adult lifetime.

Therefore, the aim of this study was to evaluate the effects of hyperprolactinemia on CVD risk parameters such as anthropometric measures, insulin sensitivity and blood lipids in patients with schizophrenia or related psychoses on long term treatment with antipsychotics in therapeutic doses. The study included two subprojects. In subproject I, we studied the effect of serum PRL in relation to body mass index (BMI), insulin levels, HOMA-IR index, blood lipids and growth factors in patients treated with the 2nd generation antipsychotics risperidone, clozapine or olanzapine, which cause elevation of PRL differently. In subproject II, we investigated potential relationships between the diurnal profile of PRL and BMI, % body fat, oral glucose tolerance (OGT), levels of insulin and C-peptide, HOMA-IR index, blood lipids, growth factors or thyroid hormones in patients treated with various 1st or 2nd generation antipsychotics.

PATIENTS & METHODS

Ethical approval

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

Subproject I

Consecutive outpatients on therapy with risperidone, clozapine or olanzapine, and with diagnoses of schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association 1994), were asked to participate in this subproject. Patients with physical illness, substance-related disorder, or drugs other than the current antipsychotics that could influence the laboratory evaluation were excluded. Taken together, in total 45 patients were included, of whom 12 patients were receiving risperidone, 15 patients clozapine and 18 patients olanzapine.

All blood samples were taken between 8 and 10 a.m. in a fasting state prior to medication, and serum was stored at –20°C until analysis. The laboratory investigation included analyses of PRL, blood (B)-glucose, insulin, total cholesterol, high density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, growth hormone (GH) and insulin-like growth factor-I (IGF-I).

Subproject II

Fifteen of the 45 patients in subproject I who agreed to participate also in subproject II and 9 additional consecutive patients with diagnoses of schizophrenia (n=8) or schizoaffective disorder (n=1) according to the DSM-IV criteria (American Psychiatric Association 1994) and without physical illness, substance-related disorder, or drugs other than the current antipsychotics that could influence the laboratory evaluation, were included in this subproject. The total 24 patients were hospitalized in a research ward at the Karolinska Hospital during 24 hours for anthropometric measurements and blood sampling.

The laboratory investigation included 75 g-OGTT, analyses of PRL every hour during 24 hours, and analyses of B-glucose, insulin, C-peptide, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, GH, IGF-I and thyroid hormones in a point blood sample taken at 8 a.m. in a fasting state prior to medication.

Anthropometric measurements

Height and weight were measured in all patients in both subprojects, and BMI was calculated as weight divided by the square of height (kg/m^2) (Labhart 1986). For the patients in subproject II, in addition body fat % was assessed by bioelectrical impedance (Lukaski *et al.* 1985), using a body composition analyzer (Tanita, TBF-300).

Assays

Serum PRL was measured by a commercial fluoroimmunometric assay kit (Delfia Prolactin, Wallac Inc., Turku, Finland). With this method, the upper limit of normal for PRL was < 10 µg/L for men and postmenopausal women and < 20 µg/L for fertile women. Blood glucose was determined by a glucose-oxidase method using the 950 Immunologic-Rate-Colorimetric system (Johnson and Johnson Clinical Diagnostics, Inc., NY, USA). Insulin, C-peptide and GH were measured in serum by commercial fluoroimmunometric assay kits (Delfia insulin, Delfia c-peptide and Delfia hGH, Wallac, Inc., Turku, Finland). Total cholesterol was determined using an enzymatic method similar to that proposed by Allain *et al.* (1974), and triglycerides using an enzymatic method as described by Spayd *et al.* (1978). High density lipoprotein cholesterol, and LDL cholesterol in subproject I and also in subproject II when triglycerides were above 4 mmol/L, were determined by β–quantification direct methods according to Cole *et al.* (2001). Otherwise, LDL cholesterol in subproject II was indirectly determined according to the formula by Friedewald *et al.* (1972). Insulin-like growth factor-I was measured in serum by means of a radioimmunoassay method designed by Bang *et al.* (1991) and expressed as age-correlated standard deviation scores based on samples from healthy men and women (Hilding *et al.* 1999). The detection limit was 8 µg/L. Including the extraction step, the intra-assay and interassay coefficients of variation were 4% and 11%, respectively. Thyroid-stimulating hormone (TSH), triiodothyronine (T_3) and thyroxine (T_4) were all measured using routine assays. The HOMA-IR index was calculated according to the formula: fasting insulin (µU/mL) × fasting glucose (mmol/L)/ 22.5 (Haffner *et al.* 1997; Matthews *et al.* 1985).

Statistical analysis

As the different variables were assumed to be non-normally distributed, nonparametric statistical methods were used. Data are described as median and range. In the statistical analysis, the Kruskal-Wallis analysis of variance by ranks was employed to evaluate differences among groups. When a significant difference among the groups was detected, pairwise comparisons between medians were performed as described (Siegel & Castellan 1988). To be able to compare frequencies of variables between groups, the chi-square or Fisher exact tests were used, and to evaluate differences within groups, the Mann-Whitney test was employed. In addition, the strength of the relationship between two parameters was calculated using the Spearman rank correlation coefficient (r_s). A p-value of less than 0.05 was considered statistically significant. All calculations were made with the statistical program Statistica 9.0 (Statsoft, Inc., Tulsa, OK, USA).

RESULTS

Subproject I

Data on sex, age, diagnosis, duration of disease, duration of therapy with current antipsychotic, and daily dose as well as serum concentration of antipsychotics for the patients in subproject I are given in Table 1. More men than women were included, but the proportion of men to women did not differ among the treatment groups (Table 1). The patients received either risperidone, clozapine or olanzapine, and the only concomitant medications used were benzodiazepines, biperiden hydrochloride, lithium (n=1), orphenadrine hydrochloride, zolpidem and zopiclone. The median daily dose was 3 (range 2–8) mg of risperidone, 400 (range 100–600) mg of clozapine and 11 (range 7.5–20) mg of olanzapine. All patients had been receiving the current antipsychotic for at least 2.5 months, although the treatment time was longer for the patients receiving clozapine than for those receiving risperidone or olanzapine (Table 1). Within treatment groups, no significant sex differences were found in age, duration of disease, treatment time, or daily dose and serum concentration of antipsychotics (Table 1).

Median and range of the variables studied in the three treatment groups are described in Table 2. Elevated PRL levels were found in 92% (8 men and 3 women) of the patients receiving risperidone, and in 33% (4 men and 2 women) of the patients receiving olanzapine, but in

none of the patients receiving clozapine. The frequency of elevated PRL level was significantly higher both in the patients receiving risperidone compared to those receiving clozapine ($p<0.0001$) or olanzapine ($p=0.002$), and in the patients receiving olanzapine compared to those receiving clozapine ($p=0.02$). There was also a significant difference in median PRL level among the three treatment groups ($p<0.0001$), i.e. the median PRL level was higher both in the patients treated with risperidone, compared to those treated with clozapine ($p<0.0001$) or olanzapine ($p=0.02$), and in the patients treated with olanzapine, compared to those treated with clozapine ($p=0.005$) (Table 2). Moreover, significant differences in B-glucose, insulin, HOMA-IR index and HDL cholesterol were found among the treatment groups ($p=0.01$, $p=0.0009$, $p=0.0009$ and $p=0.03$, respectively), with conversely higher median B-glucose, insulin and HOMA-IR index and lower median HDL cholesterol in the clozapine- or olanzapine-treated patients, compared with the risperidone-treated patients (Table 2).

Prolactin levels correlated negatively to the triglyceride levels in the olanzapine group ($r_s=-0.56$, $p=0.02$). However, no other correlations were found between PRL levels and BMI, insulin sensitivity variables (B-glucose, insulin, HOMA-IR index), blood lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) or growth factors (GH, IGF-I) in the treatment groups.

Subproject II

Characteristics of the 24 patients in subproject II are given in Table 3. The patients received either haloperidol, risperidone, clozapine or olanzapine, and the only concomitant medications used were benzodiazepines, lithium (n=1), orphenadrine hydrochloride, zolpidem and zopiclone. All patients had been receiving the current antipsychotic for at least half a year (Table 3). Within the patient group, no significant sex differences were found in age, duration of disease, treatment time, type or daily dose of antipsychotics (Table 3).

Median and range of the variables studied in all patients and in men and women separately, are given in Table 4. A significant difference in % body fat was found between men and women, whereas no sex differences were found for the other variables (Table 4). Elevated PRL (median 24 h) levels were found in 46% (5 men and 6 women) of the patients. PRL (median 24 h) levels correlated to PRL (8 a.m.) levels in all patients

Tab. 1. Sex, age, diagnosis, duration of disease, duration of therapy with current antipsychotic, and daily dose as well as serum concentration of antipsychotics for the patients in the three treatment groups in subproject I.

Treatment group	Sex (n)	Age[b] (year)	Diagnosis (DSM-IV)	Duration of disease[b] (year)	Duration of therapy with current antipsychotic[b] (year)	Daily dose of antipsychotic[b] (mg)	Serum concentration of antipsychotic[b] (nmol/L)
Risperidone	A: 12 M: 8 W: 4	A: 41 (28-48) M: 41 (28-48) W: 44 (39-46)	Schizophrenia, paranoid type (n = 2) undifferentiated type (n = 8) Schizoaffective disorder (n = 2)	A: 15.4 (2.0-24.0) M: 15.4 (2.0-24.0) W: 12.8 (5.5-22.4)	A: 1.4 (0.2-6.7) M: 1.0 (0.2-6.7) W: 3.3 (1.0-4.8)	A: 3 (2-8) M: 4.5 (2-8) W: 2 (2-3)	A: 45 (24-198)[c] M: 78 (24-198)[c,d] W: 39 (34-68)[c]
Clozapine	A: 15 M: 10 W: 5[a]	A: 41 (29-58) M: 41 (29-58) W: 46 (31-58)	Schizophrenia, desorganized type (n = 1) paranoid type (n = 8) undifferentiated type (n = 6)	A: 20.1 (8.3-42.1) M: 20.1 (8.3-23.9) W: 26.0 (12.1-42.1)	A: 7.2 (0.7-16.3)[#] M: 7.1 (0.7-16.3)[##] W: 9.1 (6.1-10.1)[###]	A: 400 (100-600) M: 400 (200-600) W: 350 (100-525)	A: 1140 (312-2812) M: 1120 (312-2050) W: 2200 (320-2812)
Olanzapine	A: 18 M: 12 W: 6[a]	A: 42 (23-58) M: 41 (23-52) W: 43 (27-58)	Schizophrenia, paranoid type (n = 10) undifferentiated type (n = 5) Schizoaffective disorder (n = 2) Psychotic disorder, not otherwise specified (n = 1)	A: 11.0 (1.0-34.5) M: 13.1 (1.6-23.1) W: 9.0 (1.0-34.5)	A: 2.2 (0.2-7.1) M: 1.9 (0.5-7.1) W: 3.0 (0.2-5.5)	A: 11 (7.5-20) M: 11 (7.5-20) W: 12.5 (7.5-20)	A: 114 (39-279) M: 168 (39-279) W: 96 (54-131)

A = all, M = men, n = number, W = women
[a]Of whom 1 was postmenopausal
[b]The data are given as median and range
[c]Sum of risperidone and 9-hydroxyrisperidone, i.e. the active moiety of risperidone (Huang *et al*. 1993)
[d]n = 7
[#]Significantly different from all risperidone-treated and olanzapine-treated patients, $p = 0.0002$ and $p = 0.0004$, respectively
[##]Significantly different from the risperidone-treated and olanzapine-treated men, $p = 0.003$ and $p = 0.03$, respectively
[###]Significantly different from the risperidone-treated and olanzapine-treated women, $p = 0.03$ and $p = 0.02$, respectively

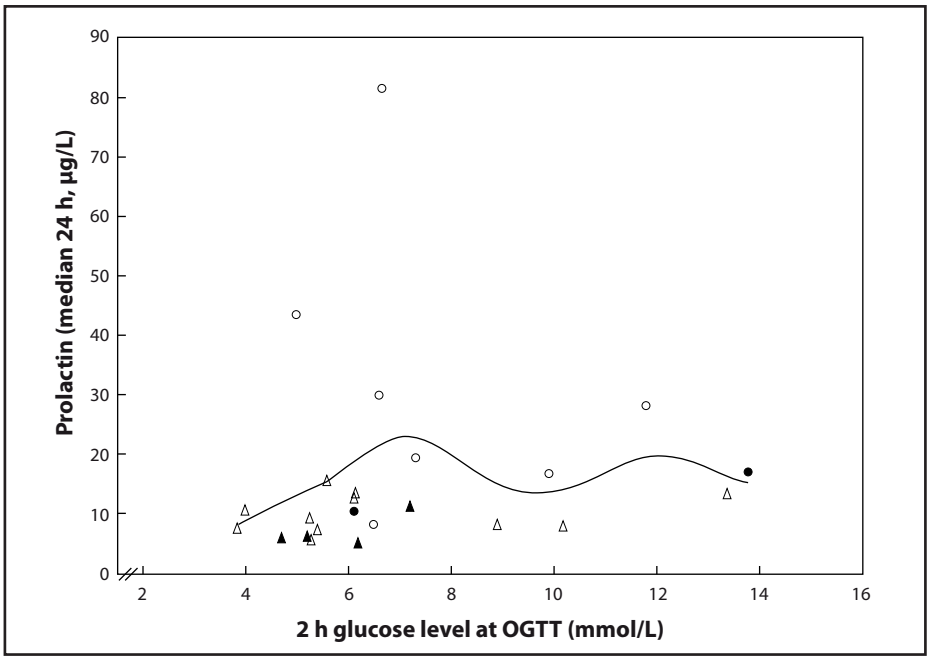

Fig. 1. Prolactin (median 24 h) levels were non-linearly correlated to the 2 h glucose levels at oral glucose tolerance test (OGTT) in the 24 patients in subproject II (r_s=0.42, p=0.04). (●) indicates haloperidol-treated, (○) risperidone-treated, (▲) clozapine-treated and (△) olanzapine-treated patients.

Tab. 2. Median and range of prolactin (PRL), body mass index (BMI), blood (B)-glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR) index, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, growth hormone (GH) and insulin-like growth factor I (IGF-I) in the three treatment groups in subproject I

Variable (reference range)	Ris (n = 12)	Clo (n = 15)	Ola (n = 18)	*p*-value			
				Overall Δ between groups	Δ between Ris and Clo groups	Δ between Ris and Ola groups	Δ between Ola and Clo groups
PRL, µg/L (M < 10; fertile W < 20; postmenopausal W < 10)	25.8 (15.8–76.5)	4.0 (2.9–16.0)	9.4 (5.7–55.0)	< 0.0001	< 0.0001	0.02	0.005
BMI, kg/m^2 (M ≤ 27; W ≤ 25[a])	27 (20–35)	28 (21–47)	27 (21–34)	NS	---	---	---
B-glucose, mmol/L (3.5–6.4)	4.8[b] (4.0–5.3)	5.3 (4.5–6.9)	5.3 (4.5–6.6)	0.01	0.01	NS (0.053)	NS
Insulin, pmol/L (< 79)	36[b] (15–65)	86 (33–291)	64 (21–157)	0.0009	0.001	0.02	NS
HOMA-IR index[c]	0.9[b] (0.4–2.1)	3.0 (1.0–9.5)	2.2 (0.7–4.4)	0.0009	0.006	0.03	NS
Total cholesterol, mmol/L (< 40Y < 5.5; 40–59Y < 6.0; ≥ 60Y M < 6.0, W < 6.5)	5.1 (3.8–6.7)	5.5 (4.4–7.4)	5.6 (4.4–7.1)	NS	---	---	---
HDL cholesterol, mmol/L (M > 0.8; W > 0.9)	1.2 (0.9–1.7)	0.9 (0.5–1.4)	1.0 (0.4–1.7)	0.03	0.04	NS	NS
LDL cholesterol, mmol/L (< 31Y 1.2–4.3; < 51Y 1.4–4.7; ≥ 51Y 2.0–5.3)	3.2 (1.8–3.7)	3.1 (2.3–4.6)	3.1 (2.3–4.2)	NS	---	---	---
Triglycerides, mmol/L (≤ 50Y 0.3–1.8; > 50Y 0.4–2.2)	1.3 (0.6–2.4)	1.8 (1.0–4.8)	1.5 (0.7–3.5)	NS	---	---	---
GH, µg/L (< 15)	0.05[b] (0.02–2.14)	0.05 (0.00–1.59)	0.05 (0.00–1.57)	NS	---	---	---
IGF–I, SD (± 2)	–0.9[b] (–1.4–0.4)	0.0 (–2.0–2.4)	–0.9 (–1.7–1.4)	NS	---	---	---

Clo = clozapine, M = men, n = number, NS = non-significant, Ola = olanzapine, Ris = risperidone, W = women, Y = years, Δ = difference
[a]According to Labhart (1986)
[b]n = 11
[c]Normal glucose tolerance 2.1 ± 0.2, impaired glucose tolerance 4.3 ± 0.5, non-insulin-dependent diabetes mellitus 8.3 ± 0.7, according to Haffner *et al.* (1997)

Tab. 3. Age, diagnosis, duration of disease, duration of therapy with current antipsychotic, type and daily dose of antipsychotics in all patients and in men and women, separately, in subproject II.

Patients (n)	**Age**[b] (year)	**Diagnosis** (DSM-IV)	**Duration of disease**[b] (year)	**Duration of therapy with current antipsychotic**[b] (year)	**Type of antipsychotic**	**Daily dose of antipsychotic**[b] (mg chlorpromazine equivalent dose[c])
All: 24	43 (23-58)	Schizophrenia, paranoid type (n = 9) undifferentiated type (n = 11) Schizoaffective disorder (n = 3) Psychotic disorder, not otherwise specified (n = 1)	16.5 (1.7-34.3)	3.1 (0.5-14.4)	Haloperidol (n = 2) Risperidone (n = 7) Clozapine (n = 4) Olanzapine (n = 11)	260 (90-900)
Men: 11	42 (23-50)	Schizophrenia, paranoid type (n = 5) undifferentiated type (n = 5) Psychotic disorder, not otherwise specified (n = 1)	17.0 (1.7-28.4)	2.1 (0.5-14.4)	Haloperidol (n = 1) Risperidone (n = 2) Clozapine (n = 2) Olanzapine (n = 6)	300 (150-800)
Women: 13[a]	44 (27-58)	Schizophrenia, paranoid type (n = 4) undifferentiated type (n = 6) Schizoaffective disorder (n = 3)	16.0 (5.5-34.3)	4.0 (0.6-12.0)	Haloperidol (n = 1) Risperidone (n = 5) Clozapine (n = 2) Olanzapine (n = 5)	150 (90-900)

n = number
[a]Of whom 3 were postmenopausal
[b]The data are given as median and range
[c]Calculated as previously described (Melkersson *et al*. 2001; Woods 2003)

(r_s=0.91, p<0.0001), and in men and women, separately (r_s=0.96, p<0.0001 and r_s=0.87, p=0.0001, respectively). The OGTT showed impaired glucose tolerance in 25% (2 men and 4 women) and new-onset diabetes mellitus in 4% (1 woman) of the patients (Table 4). The PRL (median 24 h) levels were non-linearly correlated to the OGT (i.e. to the glucose level 2 h after 75 g peroral glucose load) in all patients (r_s=0.42, p=0.04) (Figure 1), but not in men and women, separately. Additionally, there was a tendency towards a correlation between PRL (8 a.m.) levels and the OGT (i.e. the glucose level 2 h after 75 g peroral glucose load) in all patients (r_s=0.34, p=0.10). No significant correlations were however found between PRL (median 24 h) levels and the other variables studied in all patients, or in men and women, separately.

There were also significant differences found both in frequency of elevated PRL (median 24 h) levels and median PRL (median 24 h) levels between different antipsychotic treatments (p=0.03 and p=0.006, respectively). Elevated PRL (median 24 h) levels were found in two (100%) of the haloperidol-treated patients, five (71%) of the risperidone-treated patients, three (27%) of the olanzapine-treated patients and none (0%) of the clozapine-treated patients, and median PRL (median 24 h) level was higher in the patients treated with risperidone (19.6 µg/L), compared to those treated with clozapine (5.3 µg/L, p=0.007), olanzapine (10.2 µg/L, p=0.04) or haloperidol (15.0 µg/L). However, no significant difference was found in glucose tolerance between different antipsychotic treatments.

DISCUSSION

In this study, slightly to moderately elevated PRL levels were present in around 45% of patients with schizophrenia or related psychoses on long term therapy with 1st or 2nd generation antipsychotics in therapeutic doses. Elevated diurnal and morning PRL levels occurred more often and were more pronounced in patients receiving risperidone or haloperidol, compared to patients receiving clozapine or olanzapine, which is in line with previous studies (Claus *et al.* 1992; Esel *et al.* 2001; Kinon *et al.* 2003; Melkersson 2005).

More interesting are the findings in subproject II of impaired glucose tolerance in 25% and new-onset diabetes mellitus in 4% of patients treated with 1st or 2nd generation antipsychotics and a positive correlation between diurnal PRL levels and the 2 h glucose level at OGTT. There were, however, no significant correlations found between diurnal PRL levels and fasting levels of insulin, C-peptide or HOMA-IR index that are indirect measurements of insulin sensitivity. Taken together, these findings point to that hyperprolactinemia may affect insulin sensitivity, not only related to prolactinomas (Landgraf *et al.* 1977; Schernthaner *et al.* 1985; Serri *et al.* 2006; Tuzcu *et al.* 2003, 2009; Yavuz *et al.* 2003), but also during antipsychotic drug treatment.

On the other hand, in subproject I, when comparing patients on therapy with three different 2nd generation antipsychotics, we found that fasting insulin levels and HOMA-IR index were higher in clozapine- or olanzapine-treated patients, compared with risperidone-treated

Tab. 4. Median and range of prolactin (PRL), body mass index (BMI), % body fat, oral glucose tolerance (OGT), insulin, C-peptide, homeostasis model assessment of insulin resistance (HOMA-IR) index, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, growth hormone (GH), insulin-like growth factor I (IGF-I) and thyroid hormones (TSH, T3, T4) in all patients and in men and women, separately, in subproject II.

Variable (reference range)	A (n = 24)	M (n = 11)	W (n = 13)	M vs W *p*-value
PRL, 8 a.m., µg/L (M < 10; fertile W < 20; postmenopausal W < 10)	11.3 (4.2–76.5)	8.9 (4.2–28.1)	13.9 (6.5–76.5)	0.06
PRL, median 24 h, µg/L	10.7 (4.9–81.3)	9.1 (4.9–29.9)	13.0 (5.9–81.3)	0.09
BMI, kg/m^2 (M ≤ 27; W ≤ 25 [a])	27 (19–39)	27 (19–35)	29 (20–39)	0.49
Body fat, % (M: 20–25; W: 19–24[b])	32.6 (13.1–46.3)	26.7 (13.1–32.7)	41.1 (22.2–46.3)	0.0004
OGT, [fasting glucose level], glucose level 2 h after 75 g glucose load, mmol/L (impaired glucose tolerance [< 6.1] ≥ 6.7–10.0; non-insulin-dependent diabetes mellitus [≥ 6.1] ≥ 10.0)	[4.9 (4.1–6.8)] 6.2 (3.9–13.8)	[4.9 (4.1–6.1)] 6.1 (4.0–9.9)	[4.9 (4.3–6.8)] 6.7 (3.9–13.8)	0.73 0.23
Insulin, pmol/L (< 79)	57 (21–226)	54 (21–157)	60 (26–226)	0.69
C-peptide, nmol/L (0.22–0.68)	0.71 (0.34–1.81)	0.68 (0.34–1.20)	0.88 (0.37–1.81)	0.30
HOMA-IR index[c]	1.9 (0.7–10.9)	1.8 (0.7–4.4)	1.9 (0.8–10.9)	0.69
Total cholesterol, mmol/L (< 40Y < 5.5; 40–59Y < 6.0; ≥ 60Y M < 6.0, W < 6.5)	5.2 (3.8–6.5)	5.6 (4.4–6.2)	5.0 (3.8–6.5)	0.33
HDL cholesterol, mmol/L (M > 0.8; W > 0.9)	1.1 (0.7–2.0)	1.1 (0.7–2.0)	1.1 (0.8–1.7)	0.65
LDL cholesterol, mmol/L (< 31Y 1.2–4.3; < 51Y 1.4–4.7; ≥ 51Y 2.0–5.3)	3.5 (2.5–4.9)	3.6 (2.6–4.8)	3.2 (2.5–4.9)	0.39
Triglycerides, mmol/L (≤ 50Y 0.3–1.8; > 50Y 0.4–2.2)	1.6 (0.6–3.2)	1.8 (0.6–3.2)	1.4 (0.6–2.4)	0.36
GH, µg/L (< 15)	0.07 (0.01–2.14)	0.03 (0.01–0.57)	0.07 (0.02–2.14)	0.25
IGF-I, SD (± 2)	–0.9 (–2.8–1.3)	–0.8 (–1.7–1.3)	–1.0 (–2.8–1.3)	0.86
TSH, mU/L (0.2–4.0)	2.2 (0.6–6.2)	1.8 (0.6–6.2)	2.5 (1.1–4.7)	0.69
T3, nmol/L (1.1–2.5)	2.0 (1.3–2.4)	2.1 (1.3–2.4)	1.9 (1.5–2.4)	0.28
T4, nmol/L (60–140)	108 (80–157)	116 (80–157)	93 (85–136)	0.12

A = all, M = men, n = number, W = women
[a]According to Labhart (1986)
[b]According to Beck-Nielsen and Hother-Nielsen (2000)
[c]Normal glucose tolerance 2.1 ± 0.2, impaired glucose tolerance 4.3 ± 0.5, non-insulin-dependent diabetes mellitus 8.3 ± 0.7, according to Haffner *et al.* (1997)

patients. However, PRL levels did not correlate to fasting insulin levels or HOMA-IR index in any of the three treatment groups, indicating that other mechanisms not related to PRL may be involved in the insulin resistance induced by clozapine and olanzapine (Melkersson *et al.* 1999, 2000; Smith *et al.* 2009).

Hyperprolactinemia in patients with prolactinoma has also been linked to hyperlipidemia, increased LDL cholesterol, weight gain and obesity (Berinder *et al.* 2010; Erem *et al.* 2010; Greenman *et al.* 1998; Pelkonen *et al.* 1982; Schmid *et al.* 2006). However, in this study, in patients with schizophrenia or related psychoses exhibiting hyperprolactinemia due to antipsychotics, diurnal and morning PRL levels did not correlate to either blood lipid levels or anthropometric measures like BMI and % body fat. This absence of relations may be explained by the fact that the correlations reported in prolactinoma patients yield higher PRL levels than the

slightly to moderately elevated PRL levels that usually are found in patients treated with antipsychotics in therapeutic doses. Also Svestka *et al.* (2007) reported a lack of relations between PRL levels and triglyceride or cholesterol levels in female patients with psychotic disorder treated with 2nd generation antipsychotics. In addition, Berinder *et al.* (2010) recently demonstrated a positive correlation between LDL cholesterol and PRL levels upon diagnosis of prolactinoma in eight women with median PRL 72 (49–131) μg/L and six men with median PRL 1260 (123–9600) μg/L, which disappeared during dopamine agonist therapy when PRL had decreased to similar levels as in this patient cohort, but had not yet normalized, i.e. PRL was between 1 and 77 μg/L. Furthermore, Schmid *et al.* (2006) observed elevated BMI (≥ 30 kg/m^2) in 25% of patients with macroprolactinoma implicating higher PRL levels, compared with in only 9.9% of patients with microprolactinoma implicating lower PRL levels. Thus, on the assumption that the PRL elevation during the antipsychotic treatment is slight to moderate as in this study, the PRL-effect on blood lipids and body weight seems to be limited.

Important modifiable risk factors for development of atherosclerosis and CVD are hypertension, high levels of LDL cholesterol, cigarette smoking and diabetes mellitus, with decreased insulin sensitivity as an early atherosclerosis marker (Dahlöf 2010; Yavuz *et al.* 2003). Therefore, our finding of a positive correlation between diurnal PRL levels and impaired glucose tolerance, implicating decreased insulin sensitivity, suggests that hyperprolactinemia especially during long term antipsychotic therapy may be a contributive risk factor for cardiovascular morbidity and mortality in patients with schizophrenia. The thrombogenic effect of hyperprolactinemia, mediated through enhanced platelet reactivity (Urban *et al.* 2007; Wallaschofski *et al.* 2003), and its low grade inflammatory effect (Serri *et al.* 2006) might also contribute to the increased CVD risk in patients with schizophrenia, but these have not been investigated in this study.

The patients included in subproject Π were treated with different types of antipsychotics which may have given rise to the finding of a non-linear, instead of linear, correlation between diurnal PRL levels and the OGT. Future studies on relations between diurnal PRL levels and OGT in patients treated with the same antipsychotic drug are therefore warranted.

In conclusion, around 45% of patients with schizophrenia or related psychoses on therapy with 1st or 2nd generation antipsychotics had slightly to moderately elevated diurnal and morning PRL levels. Moreover, diurnal PRL levels were significantly correlated to the glucose tolerance, evaluated by OGTT, in patients treated with various 1st or 2nd generation antipsychotics. Taken together, these findings point to that hyperprolactinemia due to antipsychotic therapy may decrease insulin sensitivity and increase CVD risk and underscore the importance of active monitoring and treatment of hyperprolactinemia and its metabolic consequences in antipsychotic-treated patients.

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish Research Council and the Swedish Society of Medicine, and was presented in part as an abstract at the 10th World Congress of Biological Psychiatry, 29 May – 2 June 2011, in Prague, Czech Republic.

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