Insulin Resistance is Associated with Hypercortisolemia in Polynesian Patients Treated with Antipsychotic Medication

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Short running title: Insulin Resistance and Antipsychotic Medication.

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OBJECTIVE- Type 2 diabetes is more prevalent in the indigenous Polynesian population of New Zealand (Maori) than in Europeans. The aim of this study was to determine whether insulin resistance in Maori psychiatric patients was associated with antipsychotic treatment and to investigate the mechanism of an association.

RESEARCH DESIGN AND METHODS- Thirty adult Maori psychiatric patients receiving antipsychotic medication for longer than six months and thirty healthy, age, gender and BMI matched controls were enrolled. Early morning fasting blood samples were analysed for plasma levels of glucose, insulin, HbA\textsubscript{1c}, triglycerides, total cholesterol, IGF-1, cortisol, cortisol binding globulin (CBG), and adiponectin.

RESULTS- The patient group had significantly higher median fasting insulin plasma levels compared with the control group (p = 0.002), which was independent of BMI, age and gender. In addition, the patient group had significantly higher total cortisol (p = 0.03) and lower CBG levels (p = 0.004) resulting in significantly higher levels of free cortisol (p = 0.004) than the control group. The patient group was also significantly more hypoglycemic (p = 0.026) and hypertriglyceridemic (p = 0.028) than the control group. There was no significant difference in BMI, waist circumference, HbA\textsubscript{1c}, total cholesterol, IGF-1 or adiponectin levels between the two groups.

CONCLUSION- An increase in insulin resistance is associated with Maori psychiatric patients treated with antipsychotic medication. Therefore, Polynesian ethnicity should be considered in prescribing practice and general care of this group. In addition, the hypothalamic pituitary adrenal axis may have an important role in the mechanism by which this insulin resistance develops.

Abbreviations: HbA\textsubscript{1c}, glycosylated hemoglobin A1c; HOMA, homeostasis model of assessment; BMI, body mass index; CBG, cortisol binding globulin; HPA, hypothalamic-pituitary-adrenal axis.
Antipsychotics are used to treat the symptoms of psychosis, such as delusions, perceptual disturbance, thought disorder and disorganised behaviour. Psychosis is common in schizophrenia and bipolar disorder, and is also seen in major depressive disorder, dementia and some personality disorders. In New Zealand, in 2005, 8,750 prescriptions for antipsychotic medication were written for every 100,000 of population (1). Unfortunately, many studies have associated the treatment of patients with antipsychotic medication with the development of impaired glucose tolerance, insulin resistance and Type 2 diabetes (2-4), but the mechanism underlying this association is not known. However, before the advent of antipsychotic medication in the 1960s, studies indicated that patients with schizophrenia had higher rates of diabetes than the normal population (5). This suggests that environmental or genetic factors may also be important to the development of insulin resistance in psychiatric patients.

Type 2 diabetes affects 21.1% of the indigenous, Polynesian, population of New Zealand (Maori) compared with only 7.5% of New Zealand Europeans (6, 7). Therefore, type 2 diabetes is a major cause of morbidity and mortality in Maori (6) and Maori may be vulnerable to the effects of antipsychotic medication on glucose metabolism. In our study, both patients and controls were drawn from the Maori population to determine whether treatment with antipsychotic medication was associated with an increase in insulin resistance in this population. We also investigated possible mechanisms by measuring plasma factors that have previously been implicated in the development of insulin resistance i.e. IGF-1, adiponectin and cortisol.

RESEARCH DESIGN AND METHODS

Subjects. Before carrying out this study written informed consent was obtained from each individual as approved by the Canterbury Ethics Committee. Ethnicity was assessed by self-report according to the 1996 New Zealand census question (8) and each subject had at least one Maori parent.

The patient group consisted of 30 Maori psychiatric patients recruited from both acute inpatient psychiatric wards and community outpatient psychiatric clinics. All patients had a psychotic illness: diagnoses of schizophrenia, DSM IV-TR 295.0, (n = 24), schizoaffective disorder, DSM IV-TR 295.7, (n = 3), bipolar I disorder, DSM IV-TR 296.7, (n = 2) and psychotic disorder NOS, DSM IV-TR 298.9, (n = 1). Patients were included if they were aged between 18 and 60 years, did not have a prior diagnosis of type 2 diabetes, had received antipsychotic medication for longer than six months, and were not treated with other medications known to affect weight, such as sodium valproate. Patients had been treated with the antipsychotics clozapine (n = 10), olanzapine (n =12), risperidone (n = 6), quetiapine (n = 1), and flupenthixol (n = 1). The median time span for treatment was 6.5 months (range 6-11 months).

The control group (n = 30) were drawn from a group of Maori (n = 40) who had responded to an offer of free testing for diabetes and volunteered for the study. Maori volunteers were excluded if they were familiarly related to other subjects, had a prior diagnosis of type 2 diabetes, or reported a significant current
or chronic illness. Members of the patient group were pair wise matched with the volunteer who was closest in age, gender, and BMI.

Clinical measurements and procedures. Participants were asked to fast for 12 h before giving a blood sample between 0730 and 0900 h. Glucose tolerance status was determined using World Health Organization criteria (9). Insulin resistance was determined using the homeostasis model of assessment (HOMA) computer model with results expressed as percentage sensitivity (HOMA%S) (10). Free cortisol was determined according to Coolens et al, 1987 (11). The height and weight of subjects were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight/height^2 (kg/m^2) and was used as an estimate of overall adiposity.

Laboratory procedures. Plasma levels of glucose, total cholesterol and triglycerides were determined using an Aeroset analyzer (Abbott Laboratories, IL, USA). Hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) was measured using the Biorad Variant II HPLC system. Insulin levels were measured using an immunoassay analyzer (IMX, Abbott Laboratories). Total cortisol and CBG levels were measured in house by radioimmunoassay and ELISA respectively (12). Plasma IGF-1 concentrations were measured, in duplicate, using a radioimmunoassay (Diagnostic System Laboratories, Inc). Plasma adiponectin concentrations were measured, in duplicate, by radioimmunoassay (LINCO Research Inc., Missouri, MO, USA).

Statistical analysis. The Wilcoxon signed rank test for non-parametric data was used to compare the patient and control groups and results are presented as medians and the interquartile range. A value of p equal to, or less than, 0.05 was considered to be statistically significant. To examine the relationships between measured variables Spearman’s correlation coefficients were determined.

RESULTS

Median fasting plasma insulin levels were significantly higher in the patient group (84 pM, range 44.8-190) than in the control group (38.5 pM, range 28.9–77.0), p = 0.002 (Table 1). HOMA%S were significantly lower in the patient group (52.9, range 25.5-108.9) than in the control group (117.2, range 58.4-156.7), p = 0.006, (Table 1).

Plasma Triglyceride levels were significantly higher in the patient group (1.7 mM, range 1.3-2.6) than in the control group (1.25 mM, range 0.9-1.8), p = 0.028.

Median fasting plasma glucose levels were lower in the patient group (4.6 mM, range 4.1-5.0), than the control group (5.1 mM, range 4.7-5.4), p = 0.026, however, both groups were in the clinically healthy range.

Plasma total cortisol was significantly higher in the patient group (436.5 nM, range 370.3-510.3) compared to the control group (374.5 nM, range 323.3-449.3), p = 0.03. Plasma CBG levels were significantly lower in the patient group (447.5 nM, range 349.3-580.8) than in the control group (580.5 nM, range 528.3-707.5), p = 0.004. Therefore, the median plasma free cortisol was significantly higher in the patient group (54.4 nM, range 43.7-74.4) compared to the control group (33.6 nM, range 22.0-46.7), p = 0.004.

There was no significant difference in BMI or waist circumference between the groups, however, both the patient and control group were overweight.
There was no significant difference in gender, age, HbA1c, cholesterol, IGF-1 and adiponectin between the two groups (Table 1). In addition, there was no significant difference between patients subgrouped according to whether they were taking olanzapine (n = 12) clozapine (n = 10) or risperidone (n = 6) with respect to free cortisol (p = 0.49), CBG (p = 0.29) and insulin (p = 0.35).

Free cortisol positively correlated with plasma insulin levels (rs = 0.262, p = 0.043), and negatively with fasting plasma glucose levels (rs = -0.366, p = 0.004). The correlation between free cortisol and insulin in patients did not significantly differ from the correlation in controls (p = 0.058).

CONCLUSIONS

A number of ethnic groups, such as the Pima Indians of Arizona and the Polynesians of the Pacific have a much higher risk for type 2 diabetes compared with Caucasians (6, 14). The total Polynesian population worldwide is about 1.5 million (15, 16) and includes native Hawaiians, Tongans, Samoans and New Zealand Maori. Maori comprise approximately 15% (600,000) of the total New Zealand population (8) and arrived in New Zealand, from Southeast Asia via the South Pacific, about 900 years ago. Type 2 diabetes affects 21.1% of Maori compared with only 7.5% of New Zealand Europeans (6) (7) and insulin resistant diabetics are two to five times more likely to die from CVD than those without diabetes (17-19). In addition, increased triglyceride concentration found in populations in the Asia-Pacific region increased the relative risk for coronary heart disease by 1.33 fold (20). Therefore, the overall health of Polynesians is vulnerable to any additional factors that could increase the development of type 2 diabetes.

Excess body mass, insulin resistance and elevated triglycerides are determining factors for the metabolic syndrome (9, 21), which in turn is associated with increased risk for diabetes (22). Both the patient and control groups in our study were classed as overweight, which is consistent with previous reports that increased BMI is more prevalent in Maori (63%) than in Europeans (21%) (6). However, the patient group was more insulin resistant and hypertriglyceridemic than the control group, implying additional risks of future diabetes and CVD for Maori treated with antipsychotic medication. It has been suggested that the association of antipsychotic treatment with both weight gain and diabetes, in patients, is confounded by the lack of exercise and alterations in diet common to psychiatrically ill patients. However, in our study, patients and controls were matched for BMI, which indicated that the increased insulin resistance is additional to that conferred by weight gain. The increased insulin resistance was also independent of age or gender.

In our study Maori patients treated with antipsychotic medication had HOMA%S similar to that reported in Northern Europeans treated with antipsychotic medication (23, 24). This suggested that individual Maori are not more prone to antipsychotic associated insulin resistance than individual Europeans.

The majority of the patient group were treated with a dibenzodiazepine antipsychotic (clozapine or olanzapine 70%) and were diagnosed with schizophrenia (80%), which reflected their recruitment from inpatient, and outpatient psychiatric units, which in New Zealand are tasked with the treatment of
severe mental illness. Both clozapine and olanzapine have been suggested by others to be both more diabetogenic and obesogenic than other antipsychotic medications (3, 23, 25). Our study was insufficiently powerful to determine significant differences in effects between individual antipsychotics.

Glucocorticoid hormones (mainly cortisol in man) are so named because it was recognised long ago that one of their actions is on carbohydrate metabolism (26). These hormones are produced in the adrenal cortex under the control of the hypothalamic-pituitary-adrenal axis (HPA) and at times of stress provide a longer-term signal to damp many of the acute responses to illness and ‘re-set’ metabolism in favour of providing substrates for oxidative metabolism. In a recent study of antipsychotic naive patients with schizophrenia it was found that these patients were more insulin resistant and also more hypercortisolemic than healthy age and gender matched controls (27). Since hypercortisolemia (Cushing’s syndrome) leads to insulin resistance, glucose intolerance, high blood pressure and triglyceridemia and the authors suggested that hypercortisolemia could be the primary defect that leads to the development of the insulin resistance in antipsychotic naive patients with schizophrenia (27). However, in studies examining the effects of antipsychotic medication on patients with schizophrenia, changes in total plasma cortisol levels have generally not been measured or have been an inconsistent finding (27, 28).

CBG binds 75% of circulating cortisol in plasma and is produced by the liver. Total plasma cortisol is made up of both bound and free fractions and it is free cortisol that is active, because it crosses cell membranes and interacts with receptors. Therefore, measuring both plasma CBG levels and total plasma cortisol levels allows free plasma cortisol to be estimated, which is a better measure of cortisol activity than the measurement of total plasma cortisol alone (29). Our results indicated that both total cortisol and free cortisol levels were higher in the plasma of the patient group than in the plasma of the control group. In addition, free cortisol positively correlated with plasma insulin levels, which is consistent with a cause and effect relationship. This suggested that factors such as antipsychotic medication or stress could directly reduce CBG plasma levels, leading to hypercortisolemia, and subsequent increased insulin resistance. However, total daily exposure to cortisol may not be accurately reflected by a single morning measurement and obtaining samples at other times of the day could add to the validity of this relationship.

The insulin receptor/IRS-1/PI 3-kinase signaling system has been implicated in the mechanism of corticosteroid-induced insulin resistance. In liver and muscle, dexamethasone treatment resulted in a reduction in insulin-stimulated IRS-1-associated PI 3-kinase, suggesting it may play a role in the pathogenesis of insulin resistance at the cellular level in an animal model (30, 31). However, it remains possible that the environmental stress resulting from psychotic episodes or unknown genetic variation peculiar to individuals susceptible to psychotic episodes is the primary cause of low CBG and hypercortisolemia rather than direct effects of antipsychotic medication. The glycemic effects of having psychotic episodes vs. the effects antipsychotic medication could be examined by determining whether the prevalence of
insulin resistance is as common in patients with psychotic illness treated with antipsychotic medication as patients with non-psychotic psychiatric illness treated with antipsychotic medication. In an animal study, dogs challenged with antipsychotic medication developed insulin resistance, which indicated that the association of insulin resistance and antipsychotic medication is unlikely to be entirely related to a psychotic illness (32).

The lower median value for glucose in the patient group was surprising but was within the healthy range (<7 mM). In addition, there was no significant difference in HbA1c levels between patients and controls, and the trend was in the expected direction (slightly higher HbA1c levels in patients).

There was no difference in IGF-1 levels between Maori receiving antipsychotics and the controls. Low plasma levels of IGF-1 are associated with insulin sensitivity and are considered to be a marker for insulin resistance (33). Although IGF-1 is primarily a growth factor, it has been proposed to also play a role in insulin resistance via muscle IGF-1 receptor enhancement of glucose uptake (34). Our study is consistent with previous reports indicating that antipsychotic medication associated insulin resistance in psychiatric patients does not involve IGF-1 (35).

Similarly, there was no difference in plasma adiponectin between Maori treated with antipsychotics and the control group. Adiponectin is a hormone produced by adipocytes that acts both in peripheral tissues and in the central nervous system to regulate peripheral glucose levels and bodyweight (36, 37). Adiponectin levels are reduced in patients with insulin resistance and type 2 diabetes (38). The results of our study are consistent with previous reports (39) but conflict with other reports of increased levels of plasma adiponectin in patients treated with olanzapine and risperidone (40).

In summary, treatment with antipsychotic medication (predominantly olanzapine and clozapine) is associated in psychotically ill Maori with significant increased insulin resistance and hypertriglyceridemia, both of which are risk factors for type 2 diabetes and CVD. In addition, these findings were not solely related to BMI or central obesity. Because Maori are at much higher risk than the general New Zealand population for developing type 2 diabetes, any additional increase in insulin resistance and elevated triglycerides is particularly detrimental to the health of this group. In addition, our results indicated that these patients had both higher morning total and free cortisol plasma levels, due to lower cortisol binding globulin levels and that the free plasma cortisol was positively correlated with the plasma insulin levels. Therefore, activation of the HPA axis may be important in the development of insulin resistance in patients with a psychotic illness prescribed antipsychotic medication.

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REFERENCES

associated with insulin sensitivity in subjects with different degrees of glucose tolerance. Diabetes Care 28(1):120-5,2005


### Table 1. Clinical characteristics for subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient group</th>
<th>Control group</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>26/4</td>
<td>26/4</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.5 (25.0-41.5)</td>
<td>37.7 (25.8-45.2)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>29.5 (25.5-33.1)</td>
<td>30.6 (26.7-32.9)</td>
<td>0.199</td>
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<tr>
<td>Waist (cm)</td>
<td>96.3 (90.0-105.5)</td>
<td>100 (92.3-106.3)</td>
<td>0.393</td>
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<tr>
<td>Fasting Insulin (pM)</td>
<td>84.0 (44.8-190.0)</td>
<td>38.5 (28.9-78.0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>HOMA%S</td>
<td>52.9 (25.5-108.9)</td>
<td>117.2 (58.4-156.7)</td>
<td>0.006*</td>
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<tr>
<td>Triglycerides (mM)</td>
<td>1.7 (1.3-2.6)</td>
<td>1.25 (0.9-1.8)</td>
<td>0.028*</td>
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<tr>
<td>Fasting glucose (mM)</td>
<td>4.6 (4.1-5.0)</td>
<td>5.1 (4.7-5.4)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Total cortisol (nM)</td>
<td>436.5 (370.3-510.3)</td>
<td>374.5 (323.3-449.3)</td>
<td>0.03*</td>
</tr>
<tr>
<td>CBG (nM)</td>
<td>447.5 (349.3-580.8)</td>
<td>580.5 (528.3-707.5)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Free cortisol (nM)</td>
<td>54.4 (43.7-74.4)</td>
<td>33.6 (22.0-46.7)</td>
<td>0.004*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 (5.4-6.0)</td>
<td>5.6 (5.3-5.8)</td>
<td>0.124</td>
</tr>
<tr>
<td>Total cholesterol(mM)</td>
<td>4.9 (3.9-5.5)</td>
<td>5.1 (4.4-5.8)</td>
<td>0.107</td>
</tr>
<tr>
<td>IGF-1(ug/l)</td>
<td>197.0 (138.3-251.0)</td>
<td>201 (146.3-228.0)</td>
<td>0.861</td>
</tr>
<tr>
<td>Adiponectin (ug/l)</td>
<td>3.6 (2.5-6.2)</td>
<td>5.2 (2.6-8.6)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Data are median (lower quartile – upper quartile). *p values < 0.05 considered statistically significant. Subjects were matched for measured variables above the line i.e. Gender, Age and BMI.