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The relationship between prolactin levels and glucose homeostasis in antipsychotic treated schizophrenic patients

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Abstract

Objectives—To determine if prolactin levels are associated with glucose-insulin homeostasis in antipsychotic treated patients with schizophrenia.

Method—Prolactin levels and glucose homeostasis (quantified using oral glucose tolerance testing (OGTT), insulin measurement, and homeostasis model assessment) were measured in fifteen patients with elevated prolactin levels secondary to antipsychotic treatment for schizophrenia (mean age 30.4 yrs (SD: 5.3)). The effect of reducing prolactin levels by switching patients' antipsychotic treatment to clozapine was ascertained by performing the measures before and after the switch to clozapine.

Results—There was no significant correlation between prolactin and glucose-insulin measures at baseline. There was a large reduction in prolactin (593 mIU/L) after switching to clozapine, but this was not associated with changes in glucose-insulin measures.

Conclusion—Prolactin is not a significant determinant of glucose-insulin homeostasis in patients taking antipsychotics for schizophrenia. There was no benefit from lowering prolactin levels using clozapine. This could be because prolactin does not have a major effect on glucose homeostasis or that the effects of prolactin reduction are countered by clozapine.

INTRODUCTION

Antipsychotic treatment is associated with prolactin elevation within the hyperprolactinemic range in over a third of patients¹. Of the antipsychotics, clozapine has the least effect on prolactin levels, and so switching to clozapine is recommended for symptomatic hyperprolactinemia².

Prolactin influences carbohydrate metabolism and insulin sensitivity, through effects on insulin receptors^{3,4}. Elevated prolactin levels are associated with hyperglycemia, hyperinsulinemia and insulin resistance relative to controls in animal studies^{5,6}. Similarly, in humans, hyperprolactinemia secondary to pituitary adenomas is associated with elevated glucose and insulin levels, and insulin insensitivity compared with controls^{7,8}. Treatment with bromocriptine to reduce prolactin levels over two months is associated with reductions in glucose and insulin levels⁸.

Patients taking antipsychotics for psychotic disorders show increased rates of glucose dysregulation, and hyperinsulinemia². Despite the animal and human data linking prolactin with hyperglycemia, a MEDLINE search reveals no studies examining the relationship between prolactin and glucose control in patients taking antipsychotics. We have previously found that weight gain and insulin resistance are not significant determinants of glucose control in patients taking antipsychotics. We therefore investigated the hypotheses that prolactin is associated with glucose and insulin levels in patients taking antipsychotics, and that lowering prolactin levels, by switching to clozapine, is associated with a reduction in glucose-insulin indices.

METHOD

The South London and Maudsley NHS Trust research ethics committee approved the study. All in-patients within the Trust starting clozapine in one year (n=41) were invited to participate; 21 agreed. After complete description of the study to the subjects, written informed consent was obtained. The assessment was performed one week before commencing clozapine (baseline), and repeated after a mean 2.5 months (SD: 0.9) of treatment (follow-up). Inclusion criteria were: DSM-IV diagnosis of schizophrenia/schizoaffective disorder, switching to sole antipsychotic treatment with clozapine. Exclusion criteria were: treatment or disorders of glycemic control.

Subjects

21 patients had baseline assessments before titrating clozapine according to clinical response. Four dropped out (hypotensive reactions), and 2 declined further participation. In the completers (n=15), mean age was 30.4 yrs (SD 5.3), 7 were female, 7 black African/African-Caribbean and 8 white British. 10 smoked and 9 drank alcohol (all <21 units/week). The glucoregulatory measures of some (n=14) formed part of an earlier report⁹, but the prolactin data has not been previously reported.

The mean dose of clozapine at follow-up was 350 mg (SD: 110.6). Prior to switching, the subjects were on the following antipsychotics: olanzapine (n=6, two in combination with sulpride, and one with flupenthixol), quetiapine (n=1), risperidone (n=2), sulpride (n=3), chlorpromazine (n=1), and flupenthixol (n=2), and the following additional medications which were not altered during the study: antimuscarinic (n=6), hypnotic (n=3), mood stabiliser (valproate, n= 3 including one in combination with lithium, carbamazepine, n=1, lithium, n=2), and fluoxetine (n=4).

Three patients had a family history of diabetes (first-degree relative, n=1; second-degree relative, n=2). Patients consumed a standard diet containing >150g carbohydrate/day for at least three days prior to assessment.

Assessment

A standard OGTT was performed to World Health Organisation (WHO) specifications. After fasting under observation from mid-night, venous blood samples were taken at 9am to measure fasting plasma glucose, insulin and prolactin levels. Subjects then drank 75g anhydrous glucose in 300ml of water within 5 minutes, and venous blood samples were taken after 30 minutes (confirming glucose absorption), and 2-hours. Plasma glucose was measured using an enzymatic reference assay (intra- and inter-assay variation <1% across the concentration range (Cobas Integra 400, Roche Diagnostics)). Insulin was assayed using an ELISA kit (inter and inter-assay variation <4% across the concentration range (Mercodia Iso Insulin ELISA, Diagenics)). Body mass index (BMI=weight (kg)/ height² (m)), diet and medications were recorded. Prolactin was measured using chemiluminescent immunoassays (intra- and inter-assay variation <6% across the concentration range (Bayer ADVIA Centaur, Los Angeles, CA)).

Insulin resistance was evaluated using the HOMA-IR method: $\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/l)}] / 22.5^{10}$.

DATA ANALYSIS

The data were normally distributed apart from prolactin and insulin levels, which were skewed and are therefore presented as median values with the interquartile range (IQR). Paired sample t-tests were used to compare mean fasting glucose, HOMA-IR, and 2-hour

glucose levels at baseline and follow-up. Correlations between baseline prolactin levels and baseline insulin, HOMA-IR, fasting and 2-hour glucose levels were tested using Spearman's rank correlation. Linear regression was used to test the hypothesis that change in prolactin level was associated with change in glucose-insulin homeostasis using change in fasting and 2-hour glucose levels, insulin and HOMA-IR levels as dependent variables, and change in prolactin level as the independent variable. The standardized residuals showed a normal distribution when plotted, indicating that this assumption of linear regression holds.

RESULTS

There was a significant decrease in prolactin levels (median (IQR): baseline= 761.0 (1012), follow-up=168 (336) mIU/L, $t=4.6$, $df=14$, $p<0.0001$), and a significant increase in fasting glucose levels (mean (SD): baseline=5.4 (0.6), follow-up=5.6 (1.5) mmol/L, $t=2.6$, $df=13$, $p=0.02$), and 2-hour glucose levels (mean (SD): baseline=5.4 (0.99), follow-up=7.3(2.5) mmol/L, $t=3.1$, $df=13$, $p=0.009$). Insulin levels did not change significantly (median (IQR): baseline=89 (110), follow-up=58 (116.3) pmol/L, $t=1.2$, $df=14$, $p=0.3$); nor did BMI (mean (SD) baseline=29.3(6.9), follow-up=30(6.9) m/kg², $t=0.7$, $df=13$, $p=0.8$) or HOMA-IR (median (IQR) baseline=3.7 (4.3), follow-up=4.5(7.8), $t=0.9$, $df=13$, $p=0.3$).

Association between prolactin and glucose-insulin homeostasis at baseline and following the switch to clozapine

There was no correlation between baseline prolactin and baseline insulin ($\rho=-0.02$, $p=0.95$), HOMA-IR ($\rho=-0.18$, $p=0.5$), fasting ($\rho=0.16$, $p=0.58$) or 2-hour ($\rho=-0.4$, $p=0.13$) glucose levels. Figure 1 shows the relationship between the change in prolactin and glucose levels. There was no significant relationship between change in prolactin level and change in fasting ($\beta=-0.43$; $t=-1.6$; $df=11,13$; $p=0.15$) or 2-hour glucose level ($\beta=0.4$; $df=11,13$; $t=1.4$; $p=0.18$), or HOMA-IR ($\beta=-0.17$; $df=11,13$; $t=-0.997$; $p=0.34$).

DISCUSSION

This is the first study to test the role of prolactin in glucose-insulin homeostasis among patients taking antipsychotics. There was no association between prolactin and glucose levels. Reducing prolactin from hyperprolactinemic to near normal levels did not reduce glucose levels, further indicating that prolactin is not a significant influence on glucose homeostasis in patients taking antipsychotics. These results contradict a previous study⁸, which found reductions in glucose-insulin homeostatic measures following intervention to reduce prolactin levels in a similar number of hyperprolactinemic patients. However, Yavuz et al studied hyperprolactinemia secondary to pituitary adenomas, not antipsychotics, and used bromocriptine to reduce prolactin levels. Since using bromocriptine in patients with schizophrenia risks worsening psychosis, clozapine was used.

Limitations

It is possible that the hypothesis has been falsely rejected (a 'type II error'). However, the power calculation indicates the sample size ($n=15$) has an 80% power of detecting a correlation of $\rho>0.5$ when $\alpha=0.05$. Correlations less than this are unlikely to be clinically significant, given that they will explain less than 25% of the variance which is similar to the variances of the measures. Additionally the direction of change in all the glucose indices is consistently opposite to that hypothesised, further indicating that this is a true negative finding. The lack of association is clear from the scatterplot (figure 1).

The study cannot exclude the possibility that an effect of prolactin levels on glucose homeostasis is masked by another factor, such as a much larger glucodysregulatory effect of

antipsychotic treatment, but indicates that prolactin is unlikely to have a clinically significant effect on glucose regulation compared to other factors. Patients in this study were normoglycemic- it is possible that prolactin reduction would be beneficial in already hyperglycemic patients.

Conclusions

Prolactin does not have a major influence on glucose homeostasis in patients taking antipsychotic drugs. Reducing prolactin levels with clozapine is unlikely to benefit glucose control. Switching to clozapine in order to reduce prolactin and improve glucose control is not supported by these findings.

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Figure 1.

The relationship between prolactin and glucose levels, showing no association between change in prolactin levels and change in glucose levels.