Association of Serum Prolactin Level with Impaired Glucose Regulation and Diabetes

Chitresh Chahar¹, Kapil Chahar², BS Ankit¹, Ajeet Gadhwal¹, RP Agrawal³

Abstract

Background: Increase in prolactin during pregnancy has been identified as a major stimulus for β cells. These effects have been demonstrated in both in-vitro and in-vivo non-pregnant animal models. Recently, bromocriptine has also been approved for the therapy of type 2 diabetes, regardless of the baseline prolactin level, with its mechanism of action poorly understood. Hence, this study was planned to assess whether prolactin levels within normal range associates with prediabetes and diabetes.

Methods: A total of 300 participants, 180 males and 120 females, with equal number of subjects in the prediabetes, diabetes and normal group were analyzed. The participants were categorized into sex-specific quartiles of serum prolactin, with the first quartile representing subjects with the lowest prolactin levels and the fourth quartile having the highest levels. In addition, multinomial logit analyses were performed to evaluate the odds ratio and 95% confidence interval of having prediabetes & diabetes for each quartile.

Results: Prolactin levels in the normal group were 10.99 ± 3.65 ng/ml for the males and 12.25 ± 3.67 ng/ml for the post-menopausal females. The prolactin levels for the males in prediabetes group were 9.46 ± 3.43 ng/ml and for diabetes group were 8.98 ± 3.43 ng/ml (p value = 0.005). In females, the prolactin levels were 10.20 ± 3.99 ng/ml for the prediabetes group and 9.60 ± 3.85 ng/ml for the diabetes group (p value = 0.007). The mean fasting plasma glucose for the four male quartiles in their numerical order were 135 mg/dl, 128 mg/dl, 120 mg/dl and 110 mg/dl (p value = 0.04) and the mean HbA1c in the same order for the quartiles were 7%, 6.4%, 6.1% and 5.9% (p value = 0.01). Similarly, the mean fasting plasma glucose for the four female quartiles in their numerical order were 138 mg/dl, 128 mg/dl, 124 mg/dl and 107 mg/dl (p value = 0.03) and the mean HbA1c in the same order for the quartiles were 7.2%, 6.7%, 6.3% and 5.8% (p value = 0.01). The age adjusted odds ratio for 2nd, 3rd and 4th quartiles as compared to the 1st quartile for prediabetes in men were 0.82, 0.72 and 0.61 and for diabetes were 0.84, 0.65 and 0.55, respectively. Risk for diabetes in females ranged from 0.04 to 0.72 for the 3rd quartile and 0.03 to 0.56 for the 4th quartile as compared to 1st quartile. The risk for prediabetes in females ranged from 0.06 to 0.95 for 3rd quartile and 0.04 to 0.74 for the 4th quartile as compared to 1st quartile.

Editorial Viewpoint

• Increased prolactin level during pregnancy is a stimulus for β cells.
• The study assesses relationship between prolactin levels and prediabetes and diabetes.
• Prolactin levels were lower in prediabetes and lowest in diabetes.
• Prolactin level did not correlate with obesity and dyslipidemia.

Introduction

Prolactin hormone is named after its primary physiological role in preparing the breast for lactation in the postpartum period. Also, in normal physiologic concentrations, it is trophic to corpus luteum function, giving rise to the name luteotrophic hormone. However, prolactin receptor is also expressed in other tissues and cells such as lymphoid cells, adipocytes and pancreatic β cells\(^1\). Physiologic increase in prolactin levels during pregnancy has been identified as major stimulus for β cells to adapt towards increased metabolic demands.\(^2\) The most important changes are enhanced glucose mediated insulin secretion and enhanced β-cell mass. Failure for this reprogramming to occur...
Conclusion: Mean prolactin levels in both males and females were lower in prediabetics and lowest in diabetics. Prolactin, on quartile based analysis, associated with better HbA1c and fasting plasma glucose. Decreasing relative risk trends for both prediabetes and diabetes were found with increasing serum prolactin concentrations. No association was found with obesity and dyslipidemia.

in response to the increased metabolic demands leads to gestational diabetes. Moreover, this glucose metabolic regulation effect of prolactin is recognized not to be confined to the period of pregnancy as these effects have been demonstrated in both in-vitro cell cultures and in-vivo non-pregnant rodent models. On the other end of the spectrum, high levels of prolactin such as those seen in patients with prolactinoma are associated with higher risk of hyperglycemia accompanied by obesity and insulin resistance and dopamine agonist treatment such as bromocriptine is used to reverse these. Likewise, the drugs that block dopamine D2 receptors such as antipsychotics increase appetite and result in significant weight gain. Bromocriptine has been approved for the therapy of type 2 diabetes. Timed short acting bromocriptine administration within 2 h of awakening is believed to exert its beneficial metabolic effects exclusively through the central nervous system. Causes for improved glycaemia under bromocriptine are not fully understood, but there is evidence for improved insulin sensitivity. Interestingly, potency of bromocriptine to decrease prolactin levels seems to be a surrogate marker for its effectiveness to improve glycaemia in patients with diabetes, suggesting common underlying mechanism.

Although previous investigations about the potential effects of prolactin within normal range on glucose and fat metabolism are scarce, existing studies suggest an influence of prolactin on these processes. In this study, we tried to explore this association.

Aims and Objectives

1. To determine whether the variation of circulating prolactin concentration in normal range associates with prediabetes and diabetes.
2. To ascertain whether BMI differs in subgroups of patients with different prolactin levels.
3. To study variation in lipid profile parameters in patient’s groups with differing prolactin levels.

Material and Methods

It was a single centered cross sectional study carried out between the period of July 2014 to June 2015. 300 Subjects were selected from the people presenting for check-up at medicine outpatient facility in the PBM hospital, either previously aware of their glycemic status or newly diagnosed with prediabetes (IGT, IGF) and diabetes. Participants were recruited to represent three groups of glycemic status in equal numbers namely:

- Diabetes.
- Prediabetes i.e. Subjects with impaired fasting glucose and impaired glucose tolerance.
- Normal glycemic status.

Patients with type 1 diabetes, premenopausal women and individuals with elevated prolactin levels (outside the normal range) such as prolactinoma patients were excluded, as also, subjects with thyroid disorders and/or on thyroid related medications and patients on any medication known to affect serum prolactin levels. Subjects with chronic medical illnesses were also excluded.

All the patients attending the medicine outpatient facility fulfilling the inclusion criteria underwent detailed history, clinical examination and laboratory testing. The data were collected on a specially designed proforma. Postmenopausal status was defined as: all women ≥60 years of age and all women between 40–60 years who reported no menstrual cycle for consecutive 12 months.

Weight was measured with an analog portable weighing scale to the nearest 0.5 kg. Height was measured to the nearest 0.1 cm. WHO Asia Pacific guidelines were used to define overweight and obesity.

Plasma glucose in the venous samples were measured using the hexokinase method. HbA1c testing was done by ion exchange chromatography, with reporting done in percentage values. Prediabetes and diabetes were defined according to the American Diabetes Association standards as follows:

1. Prediabetes:
   - Impaired fasting glucose: Fasting plasma glucose: 100–125 mg/dl.
   - Impaired glucose tolerance: 2-h plasma glucose in the 75-g OGTT 140 mg/dl to 199 mg/dl

2. Diabetes:
   - Based on self-reported physician’s diagnosis; use of antidiabetic medication.
   - Fasting (>8 hrs) plasma glucose ≥126 mg/dl
   - 2-h plasma glucose ≥200 mg/dl
   - HbA1c concentrations > 6.5%

3. Normal / Control: absence of both above.

Lipid profile was done by autoanalyzer (Chemwell® 2910 Automated EIA and Chemistry Analyzer – Ark Diagnostics).
Table 1: Comparison of subjects in three groups based on glucose regulation status

<table>
<thead>
<tr>
<th></th>
<th>Males (n=180; 60 each)</th>
<th>Females (n=120; 40 each)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Prediabetic</td>
<td>Diabetic</td>
<td>p value</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>52.3 ± 6.4</td>
<td>52.7 ± 5.9</td>
<td>53.5 ± 5.4</td>
<td>0.50</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.76 ± 2.44</td>
<td>24.43 ± 2.26</td>
<td>25.99 ± 2.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>39 ± 6</td>
<td>36 ± 5</td>
<td>34 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TGL* (mg/dl)</td>
<td>116</td>
<td>136</td>
<td>154</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T. Chol. (mg/dl)</td>
<td>162 ± 18</td>
<td>173 ± 16</td>
<td>178 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>10.99 ± 3.65</td>
<td>9.46 ± 3.43</td>
<td>8.98 ± 3.43</td>
<td>0.005</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>9.81 ± 3.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Prediabetic</td>
<td>Diabetic</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>56.1 ± 5.5</td>
<td>55.9 ± 4.0</td>
<td>55.8 ± 5.1</td>
<td>0.98</td>
</tr>
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</tr>
</tbody>
</table>

*Reported as geometric mean.

Observations and Results

A total of 300 participants, 180 males and 120 females were enrolled, with equal number of subjects in the prediabetes, diabetes and normal group. As a result, the final cohort comprised of 60 males and 40 postmenopausal females in each group. The three study groups based on glycemic status have been compared in Table 1. They were comparable with respect to the mean age, with age ranging from 39-65 yrs. for males and 47-68 yrs. for females. The differences with regard to mean BMI and lipid profile parameters were statistically significant.

The mean serum prolactin levels for the male and female participants were 9.81 ± 3.59 ng/ml and 10.68 ± 3.98 ng/ml respectively. Prolactin levels in the normal group were 10.99 ± 3.65 ng/ml for the males and 12.25 ± 3.67 ng/ml for the females. The prolactin levels for the males in prediabetes group were 9.46 ± 3.43 ng/ml and for diabetes group were 8.98 ± 3.43 ng/ml. In females, the prolactin levels were 10.20 ± 3.99 ng/ml for the prediabetes group and 9.60 ± 3.85 ng/ml for the diabetes group. Post-hoc analysis of the mean prolactin levels for the three groups by Tukey test revealed the differences to be significant between the normal and the prediabetes group, and the normal and the diabetes group. The differences observed between the prediabetes and diabetes group were not significant.

The subjects were reclassified on the basis of serum prolactin concentrations into four quartiles, with 1st quartile containing subjects with lowest serum prolactin concentrations and 4th quartile subjects’ having the highest concentrations. The four quartiles therefore generated for males were prolactin ≤7.20ng/ml, between 7.2-9.80, between 9.8-12.60 and ≥12.60, with 45 subjects in each. Similarly, for the post-menopausal females the four prolactin quartiles were ≤7.60ng/ml, between7.6-10.60ng/ml, 10.6-13.4ng/ml and ≥13.40ng/ml, with 30 subjects in each quartile. The four quartiles in both males and females were analyzed for differences pertaining to age, BMI, FPG, HbA1c and lipid profile parameters (Table 2). A trend of decrease in age with increasing prolactin quartile was noted which however was not statistically significant. The mean fasting plasma glucose and average HbA1c levels of the subjects in the four quartiles differed significantly. The mean fasting plasma glucose for the four male quartiles in their numerical order were 135 mg/dl, 128 mg/dl, 120 mg/dl and 110 mg/dl and the mean HbA1c in the same order for the quartiles were 7%, 6.4%, 6.1% and 5.9%. Similarly, the mean fasting plasma glucose for the four female quartiles in their numerical order were 138 mg/dl, 131 mg/dl, 124 mg/dl and 107 mg/dl and the mean HbA1c in the same order for the quartiles were 7.2%, 6.7%, 6.3% and 5.8%. The differences in BMI and lipid profile parameters between the four quartiles were not statistically significant in either males or females.
Multinomial logit regression analysis was performed to calculate the age-adjusted odds ratio of prediabetes and diabetes across the prolactin quartiles for both males and females (Figure 1). A trend for decreasing risk for prediabetes and diabetes was observed with increasing prolactin quartiles for both males and females. The age adjusted odds ratio for 2nd, 3rd and 4th quartiles as compared to the 1st quartile for prediabetes in men were 0.82, 0.72 and 0.61 and for diabetes were 0.84, 0.65 and 0.55 (Table 3). However, the 95% confidence intervals were quite wide. In the females, the decreasing trend of adjusted odds ratio with 95% confidence intervals for the prediabetes and diabetes were significant for 3rd and 4th quartiles as compared to 1st quartile. Risk for diabetes ranged from 0.04 to 0.72 for the 3rd quartile and 0.03 to 0.56 for the 4th quartile as compared to 1st quartile. Similarly, the risk for prediabetes ranged from 0.06 to 0.95 for 3rd quartile and 0.04 to 0.74 for the 4th quartile as compared to 1st quartile.

**Discussion**

The role prolactin might be playing in regulating metabolic homeostasis, in particular glycemic status, under non-lactating conditions has not received much attention. Most of the knowledge on prolactin in this area comes from studies conducted in-vitro and on rodents. Except for the research conducted in prolactinoma patients, limited information is available in this aspect in humans. Bromocriptine, a dopamine agonist, has been approved for diabetes mellitus type 2. The efficacy of bromocriptine has been shown to correlate with its potency to decrease prolactin levels, but in few epidemiological studies it has been observed that increased prolactin levels are associated with lower fasting plasma glucose and HbA1c. The present study was carried out to investigate this discrepancy.

**Table 2: Comparison of the subjects in the four quartiles based on the serum prolactin levels**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male (n=45 each quartile)</th>
<th>Female (n=30 each quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>≤7.20</td>
<td>7.2-9.80</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>54.4±5.9</td>
<td>53.0±6.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9±2.5</td>
<td>24.4±2.6</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>135±44</td>
<td>128±43</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.0±1.8</td>
<td>6.4±1.8</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>35±4</td>
<td>36±4</td>
</tr>
<tr>
<td>TGL* (mg/dl)</td>
<td>138</td>
<td>136</td>
</tr>
<tr>
<td>T. Chol. (mg/dl)</td>
<td>173±15</td>
<td>171±17</td>
</tr>
</tbody>
</table>

*Reported as geometric mean.

**Table 3: Association of circulating prolactin level with diabetes and prediabetes**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes</td>
<td>1</td>
<td>0.82 (.29-2.35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0.84 (.30-2.36)</td>
</tr>
</tbody>
</table>

*Age-adjusted Odds Ratios with 95% Confidence Intervals.

**Fig. 1: Forest plot showing adjusted odds ratio and their 95% confidence intervals for “pre-diabetes” and diabetes in male and female population quartiles with increasing serum prolactin**
different with average prolactin values being lower in prediabetes group and lowest in diabetic group. This was surprisingly opposite to what was expected from the observation that bromocriptine, a potent inhibitor of prolactin, improves glycaemia and has been approved recently by FDA for use in patients with diabetes. In addition, bromocriptine has been observed to be therapeutic in all the patients of diabetes irrespective of whether their serum prolactin concentrations were elevated or in normal range. Also, it goes against the observation that antipsychotics, with their anti-dopaminergic activity leading to elevated prolactin levels, have been traditionally associated with increased risk of diabetes. Although, most evidence suggesting an association between antipsychotic medications and diabetes have been based on retrospective studies not controlled for important confounders and a review of prospective data by the expert group presented in the consensus meeting on “Schizophrenia and diabetes 2003” failed to show any difference in the incidence of glycemic related abnormalities. However, the present study findings are in line with the ones previously observed by Wang et al (2013). They too observed the mean prolactin levels to be significantly lower in patients with prediabetes and diabetes while comparing prediabetic and diabetic Chinese adults with their normal counterparts. In addition, the mean fasting plasma glucose and HbA1c values in their study decreased with increasing serum prolactin quartiles. Moreover, Wagner et al (2013), while analysing the data from subjects without diabetes in the German region of Tubingen, too observed a similar trend in HbA1c between the four prolactin quartiles. Moreover, they even conducted hyperinsulinaemic-euglycemic clamp test in a subgroup of patients, the result of which demonstrated statistically significant positive association between prolactin levels and insulin sensitivity. In our study, on multinomial logistic regression analysis, a trend of decreasing relative risk for prediabetes and diabetes was found in both males and females with increasing concentrations of serum prolactin. Balbach et al (2013), carrying out population based study in Pomrenia region of Germany too observed risk for diabetes to be higher in individuals with lower prolactin levels. They observed the relative risk for diabetes to be 1.55 in subjects in the lowest prolactin quartile as compared to those in the highest quartile for males with confidence intervals ranging from 1.13 to 2.14. Similarly, they reported relative risk for females in lowest quartile to be 1.70 times in comparison to those in highest quartiles, with 95% confidence intervals ranging from 1.10 to 2.62.

It has been observed that prolactin increases the levels and activity of glucose sensors in β-cells i.e. glucokinase, hexokinase, and glucose transporter 2 thereby reducing the threshold of glucose-stimulated insulin release, in addition to inducing insulin gene transcription. Prolactin up-regulates a cluster of genes associated with cell-cycle regulation while down-regulating apoptosis-related genes. The best characterized molecular pathway through which prolactin brings into motion these effects has been the activation of JAK2/STAT5 (Signal Transducer and Activator of Transcription). However, it has been shown in subsequent research that STAT5 is not essential for prolactin to act. Prolactin also regulates islet structure and function by inducing phosphorylation of insulin receptor kinase substrate-1 and -2 via PI3K activation, and it also activates the MAPK pathway.

BMI did not correlate with varying prolactin levels in this study, with all the four quartile having no statistically significant difference between them. Whereas prolactin has well-established weight promoting/orexigenic roles in fish and birds, it has moderate, inconsistent, or no effects on body weight in most mammals.

Similar to the findings with BMI, the differences in lipid profile parameters between the four quartiles were not statistically significant. There have been very few studies directly investigating the association between lipid profile parameters and prolactin, with all of them being in patients with prolactinoma. As discussed below, prolactin exerts several specific effects on the adipocytes, although they have yet not translated into global changes in body weight and lipid profile in the studies performed till date.

Studies have discovered that human adipose tissue produces prolactin and also expresses prolactin receptors. Prolactin down regulates lipoprotein lipase and fatty acid synthase. It has been demonstrated to increase leptin synthesis and secretion. On the other end, chronically high prolactin levels induce central leptin resistance and inhibit adiponectin production. Collectively, these studies raise the prospect that prolactin affects lipid metabolism and insulin sensitivity through its action as an adipokine.

Limitations

The study is limited by it being based on single centre, small sample size and cross-sectional in nature, therefore the observed associations do not allow us to deduce any causality. Also, as the single most important regulator of prolactin secretion is the inhibitory dopamine, prolactin could represent a surrogate parameter of dopaminergic tone within the CNS. In fact, it has been recently demonstrated that by simultaneously enhancing the discharge and spike duration of tuberoinfundibular dopamine cells,
serum prolactin can promote or inhibit dopamine release depending on its level. It is well known that the brain can influence peripheral insulin sensitivity through several pathways. Especially, hepatic glucose fluxes seem to be under tight CNS regulation, which therefore could very well be also reflected by prolactin levels, similar to the fact that prolactin levels have never been directly associated with insulin secretion. In addition, to performing such a study in pre-menopausal females, prospective studies will be needed to provide further insight into this relationship. The other limitation was due to the fact that a diurnally changing parameter was quantified at only one point of time.

Conclusion
- Lower prolactin levels were associated with prediabetes and diabetes as compared to control group.
- On quartile based analysis higher prolactin levels were found to associate with lower HbA1c and fasting plasma glucose.
- Decreasing relative risk trend for both prediabetes and diabetes were found in males and females with increasing prolactin levels.
- No significant differences were observed between various quartile with respect to BMI and various lipid profile parameters.

References