Circulating Prolactin and Risk of Type 2 Diabetes: A Prospective Study

Tiange Wang, Yu Xu, Min Xu, Guang Ning, Jieli Lu, Meng Dai, Baihui Xu, Jichao Sun, Wanwan Sun, Shenghan Lai, Yufang Bi, and Weiqing Wang*

* Correspondence to Dr. Weiqing Wang, Key Laboratory for Endocrine and Metabolic Diseases of the Ministry of Health Department of Endocrine and Metabolic Diseases, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Rui Jin Second Road, Shanghai, People’s Republic of China 200025 (e-mail: wqingw@hotmail.com).

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Prolactin plays an important role in maintaining a normal glucose homeostasis during pregnancy and beyond. Studies investigating the association between prolactin and type 2 diabetes beyond pregnancy are rare and none is prospective. We aimed to examine whether prolactin associates with type 2 diabetes prospectively in a Chinese population. In 2009, 2,377 participants aged 40 years or older were enrolled from Shanghai, China. Among 1,596 diabetes-free participants at baseline, 1,510 completed the follow-up investigation in 2013. Participants who had a fasting plasma glucose \( \geq 126 \) mg/dL and/or a 2-hour plasma glucose \( \geq 200 \) mg/dL during a 75-g oral glucose tolerance test had a definite diagnosis of type 2 diabetes or received antidiabetic therapies during follow-up were classified as having type 2 diabetes. During a mean follow-up of 3.7 years, 189 new cases of type 2 diabetes were documented. After multivariate adjustment, women in the highest quartile of prolactin showed the lowest risk for diabetes compared with those in the lowest quartile (hazard ratio = 0.48, 95% confidence interval: 0.26, 0.90). However, such significant associations were not observed in men. Prolactin may be a mediator in the pathogenesis of type 2 diabetes in women; however, more studies are needed to elucidate the underlying sex-specific mechanism.

Abbreviations: FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; SD, standard deviation.

Prolactin is a polypeptide with highly versatile functions, which are related to lactation, reproduction, metabolism, and immune regulation. Physiological changes in circulating prolactin have been associated with pregnancy, lactation, physical activity, sleep, and stress (1, 2). During the pregnancy period, maternal prolactin increases concurrently with the increased demand for insulin to stimulate \( \beta \)-cell proliferation, insulin production, and secretion, in order to accommodate the growing fetal compartment as well as the substantial increase in insulin resistance (3, 4). On the other hand, during the nonpregnancy period, prolactin is also responsible for normal glucose homeostasis by promoting cumulative insulin secretion and inhibiting key caspases of the extrinsic and intrinsic pathways leading to islet apoptosis (5–7).

So far, evidence linking prolactin and glucose metabolism is derived mainly from experimental studies, and relevant population studies are rare. We previously studied the association between circulating prolactin and glucose metabolism and first reported that high circulating prolactin levels are associated with a lower prevalence of diabetes and impaired glucose regulation in middle-aged and elderly Chinese men and postmenopausal women (8). Epidemiologic studies investigating the association between prolactin and type 2 diabetes are limited, and none is prospective. In the present study, we aim to study the association between circulating prolactin and incident type 2 diabetes among Chinese men and women in a prospective study.

METHODS

Participants

Study participants were enrolled from the Songnan Community, Baoshan District, Shanghai, People’s Republic of
In phase 1 (June and July, 2008), we recruited 10,185 registered permanent residents aged 40 years or older to receive a screening examination. We tested fasting plasma glucose (FPG) and preliminarily categorized participants into 3 groups: normal glucose regulation, defined as a FPG of <100 mg/dL, with no history of diabetes; impaired glucose regulation, defined as a FPG from 100 to <126 mg/dL, and with no history of diabetes; and diabetes, defined as a FPG of ≥126 mg/dL or with a history of diabetes. In phase 2 (June through August, 2009), we randomly selected participants from the 3 groups in a ratio of 1.0 (diabetes) to 1.2 (impaired glucose regulation) to 1.44 (normal glucose regulation), oversampling people with lower glucose levels because they might have a lower participation rate than those with higher glucose levels. A total of 4,012 participants were randomly selected and participated in phase 2 and had similar characteristics such as age, sex, and body mass index compared with those who did not participate (6,173 participants). Among the 3,455 study participants with blood and urine samples included in phase 2, we tested the concentrations of serum prolactin, and those who met the following criteria were excluded: 1) without the results of plasma glucose from an oral glucose tolerance test (OGTT) at 0 and 2 hours (n = 32); 2) without sufficient serum for prolactin measurement (n = 280); 3) with a history of pituitary disease or breast tumor (n = 226); 4) with hyperprolactinemia (serum prolactin higher than the laboratory reference: prolactin of >19.40 ng/mL for adult men and >26.53 ng/mL for women) (n = 122); and 5) premenopausal women (n = 418). Finally a total of 2,377 participants (including 1,034 men and 1,343 postmenopausal women) were included in the baseline analysis of prolactin and diabetes (8). From March to May, 2013, the participants were invited to have a comprehensive follow-up examination. Of the 1,596 participants without baseline diabetes at phase 2, 11 died and 75 were lost during the follow-up. Finally, 1,510 participants were included in the present study. The flow chart of the study design is shown in Figure 1. The Committee on Human Research at Shanghai Jiao Tong University School of Medicine, Rui Jin Hospital, approved the study protocol, and all study participants provided written, informed consent. All procedures used in this study were in accordance with institutional guidelines.

**Measurements**

Information on sociodemographic characteristics, medical history, family history, and lifestyle factors was collected by using a standard questionnaire at baseline in 2009. Family history of diabetes was positive if any first-degree relative (mother, father, and siblings) had diabetes. Data on hormone therapy and parity (both women only) were also collected by asking the questions: “Have you ever had hormone replacement therapy?” and “How many liveborn children have you delivered?” Weight, height, and waist circumference were measured by experienced nurses according to a standard protocol. Body mass index was calculated as weight (kg)/height (m)².

All participants underwent a 75-g OGTT (without diabetes present at baseline) after an overnight fast of more than 10 hours, and blood samples were collected at 0 and 2 hours. FPG, OGTT 2-hour plasma glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides were measured by using the glucose oxidase method on an autoanalyzer (ADVIA-1650 Chemistry System; Bayer Corporation, Leverkusen, Germany). Serum insulin was measured by using an electrochemiluminescence assay (Roche Diagnostics, Basel, Switzerland), and hemoglobin A1c was determined by an automated high-performance liquid chromatography analyzer (Bio-Rad, Hercules, California). Serum prolactin was determined by using a chemiluminescent microparticle immunoassay by the Architect assay (Abbott Laboratories, Abbott Park, Illinois). The laboratory reference range of prolactin was 3.46–19.40 ng/mL for adult men and 5.18–26.53 ng/mL for adult women (8). We also performed stability verification of the prolactin measurement. Prolactin concentrations were measured in the fresh serum samples randomly selected from 20 men and 20 women after serum extraction. After storage, the same samples were retested before measurement in the present study. The deviation of the results before and after storage was within the laboratory allowable range (8).

**Incident type 2 diabetes**

Type 2 diabetes was determined according to the 1999 World Health Organization criteria supplemented by a definite diagnosis by physicians. Information included whether participants had been diagnosed with diabetes; with a positive response, further information was collected on the type of diabetes, date, and hospital where it was first diagnosed and whether by OGTT, and diabetes treatments. Participants who received antidiabetic therapies, those who responded positively to the OGTT as a FPG of ≥126 mg/dL, and/or the OGTT 2-hour plasma glucose of ≥200 mg/dL, and/or those who had a definite diagnosis of type 2 diabetes during the follow-up were diagnosed as having incident type 2 diabetes. For each participant, person-years of follow-up were calculated from the date of enrollment in the study to the date of reported physician diagnosis (data collected by questionnaire) or the date of the follow-up visit, whichever occurred first.

**Statistical analysis**

Statistical analysis was performed by using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Continuous variables are summarized as means and standard deviations, and categorical variables are summarized as percentages. Sex-specific cutpoints were used to define quartiles of prolactin. For the differences of characteristics among participants across quartiles of prolactin, P values for trend were tested by using general linear regression for continuous data or logistic regression for categorical data. Cox proportional hazards analysis was used to evaluate the hazard ratios and 95% confidence intervals for each quartile of circulating prolactin, with the lowest quartile as the reference. Potential confounding factors were controlled for in multivariable analyses, including age, body mass index, waist circumference, family history of diabetes (yes or no), smoking status (never, former, or current), triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol,
hormone use, and parity, which are known risk factors for type 2 diabetes. The interaction between the prolactin quartiles and sex on type 2 diabetes was tested by including a multiplicative interaction term in the models. To test for P values for trend across the prolactin quartiles, we modeled prolactin as an ordinal variable, coding with regard to its quartiles as 1, 2, 3, and 4. The reported P values were 2 sided, and P < 0.05 was considered statistically significant.

RESULTS

During a mean follow-up period of 3.7 years, 189 cases of diabetes were documented (incidence rate: 3.4/100 person-years). Baseline characteristics of study participants by quartiles of prolactin are presented in Table 1. In men and in postmenopausal women, compared with the participants in the lowest quartile, those in the highest quartile were older (P_trend ≤ 0.041). In men, a higher prolactin level was significantly associated with a lower proportion of current smokers and a lower mean level of low density lipoprotein cholesterol (all P’s ≤ 0.033). In postmenopausal women, FPG and 2-hour OGTT plasma glucose levels gradually decreased across quartiles of prolactin (both P’s ≤ 0.008). The prolactin concentrations were higher in women than in men and were lower in participants who developed diabetes (men: mean = 8.92 (standard deviation (SD), 3.16) ng/mL; median, 8.57 (interquartile range, 6.71–11.12) ng/mL; women: mean = 9.40 (SD, 4.36) ng/mL; median, 8.38 (interquartile range, 6.36–11.19) ng/mL) than in those who were free of diabetes at follow-up (men: mean = 8.96 (SD, 3.22) ng/mL; median, 8.42 (interquartile range, 6.59–10.64) ng/mL; women: mean = 9.93 (SD, 4.14) ng/mL; median, 9.12 (interquartile range, 6.94–11.76) ng/mL), but no significant difference was observed (Web Table 1 available athttp://aje.oxfordjournals.org/).

The associations between circulating prolactin and incident type 2 diabetes are shown in Table 2. In men, the crude rates per 100 person-years of incident diabetes were 3.1%, 3.6%, 3.6%, and 4.0% across the lowest quartile to the highest quartile of prolactin, respectively. No significant association between prolactin and incident diabetes was found in men. In women, the crude rates per 100 person-years of incident diabetes decreased from 4.6% to 2.5% across serum prolactin quartiles. The age-adjusted hazard ratios for incident diabetes were 0.58 (95% confidence interval: 0.35, 0.97) for the second, 0.54 (95% confidence interval: 0.32, 0.90) for the third, and 0.45 (95% confidence interval: 0.26, 0.77) for the fourth quartiles of prolactin, compared with the first quartile. In this multivariate-adjusted model, the hazard ratio for incident diabetes in the highest compared with the lowest quartile of prolactin was 0.48 (95% confidence interval: 0.26, 0.90). There was a significant interaction between sex and prolactin levels for the association with incident diabetes (P_interaction = 0.028).
Given that women in the lowest quartile of prolactin \((n = 378)\) had the highest incidence of type 2 diabetes, we further divided these women into finer subdivisions (quartiles) to further estimate the characteristics of this group. As shown in Web Figure 1, in the 378 women, the crude rate per 100 person-years for type 2 diabetes was 6.2\%, 3.7\%, 2.7\%, and 4.5\% across the 4 subdivisions of the lowest quartile of prolactin, respectively. Women with circulating prolactin less than 5 ng/mL showed the highest incidence, suggesting that women with prolactin less than 5 ng/mL might be at particular risk for incident type 2 diabetes.

**DISCUSSION**

In the present study, a high circulating prolactin level was significantly associated with a lower incidence of type 2 diabetes in postmenopausal women, but not in middle-aged and elderly men. To the best of our knowledge, this is the first...
Table 2. Incident Type 2 Diabetes According to Prolactin Quartiles, Shanghai, People’s Republic of China, 2009–2013

<table>
<thead>
<tr>
<th>Quartile of Prolactin by Sex</th>
<th>Prolactin, ng/mL</th>
<th>Cases, Person-Years</th>
<th>Crude Rate per 100 Person-Years, %</th>
<th>Age Adjusted</th>
<th>Multivariate Adjusteda</th>
<th>Multivariate Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>5.69 (4.78–6.12)</td>
<td>18</td>
<td>575.2</td>
<td>3.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>7.51 (7.01–7.89)</td>
<td>21</td>
<td>577.4</td>
<td>3.6</td>
<td>1.30 0.68, 2.48</td>
<td>1.28 0.65, 2.49</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>9.36 (8.87–10.07)</td>
<td>20</td>
<td>560.2</td>
<td>3.6</td>
<td>1.26 0.65, 2.45</td>
<td>1.23 0.63, 2.43</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>12.97 (11.62–15.11)</td>
<td>23</td>
<td>576.5</td>
<td>4.0</td>
<td>1.25 0.64, 2.42</td>
<td>1.11 0.55, 2.21</td>
</tr>
<tr>
<td>P_trend</td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
<td>0.84</td>
<td>N/A</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>5.84 (5.08–6.41)</td>
<td>38</td>
<td>822.0</td>
<td>4.6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>7.89 (7.27–8.38)</td>
<td>24</td>
<td>823.0</td>
<td>2.9</td>
<td>0.58 0.35, 0.97</td>
<td>0.65 0.38, 1.11</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>10.19 (9.55–10.96)</td>
<td>24</td>
<td>827.1</td>
<td>2.9</td>
<td>0.54 0.32, 0.90</td>
<td>0.58 0.34, 1.00</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>14.52 (12.95–17.25)</td>
<td>21</td>
<td>837.0</td>
<td>2.5</td>
<td>0.45 0.26, 0.77</td>
<td>0.49 0.27, 0.87</td>
</tr>
<tr>
<td>P_trend</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>0.011</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range, N/A, not applicable.
a The hazard ratio with corresponding 95% confidence interval has been adjusted for age, body mass index, waist circumference, family history of diabetes, smoking status, triglycerides, high density lipoprotein cholesterol, and low density lipoprotein cholesterol.
b This hazard ratio with corresponding 95% confidence interval has been further adjusted for hormone use and parity.

study to investigate the association between circulating prolactin and incident diabetes in a prospective study.

During pregnancy, prolactin levels together with prolactin receptors elevate in parallel with the increased β-cell mass and glucose-stimulated insulin secretion to upregulate islet cell function and maintain a normal glucose homeostasis (9–11). During the nonpregnant period, prolactin regulates whole-body insulin sensitivity and glucose metabolism by expanding β-cell mass (12), improving hepatic insulin sensitivity (13), and modulating immune function (5, 7, 14) and has an indirect action by increasing hypothalamic dopamine synthesis to improve energy and glucose homeostasis (15, 16).

In addition, prolactin acts as an adipokine in down-regulating lipoprotein lipase and fatty acid synthase (17, 18), as well as regulating the bioactivities of adiponectin, interleukin-6, and glucose-stimulated insulin secretion to upregulate islet β-cell mass (12), improving hepatic insulin sensitivity (13), and modulating immune function (5, 7, 14) and has an indirect action by increasing hypothalamic dopamine synthesis to improve energy and glucose homeostasis (15, 16).

In addition to pregnancy, several environmental factors, such as physical activity, sleep, and stress, could affect the concentrations of circulating prolactin (1). Our data also suggested potential correlations of prolactin with smoking and low density lipoprotein cholesterol in men, which was in line with the previous findings that circulating prolactin was inversely associated of prolactin were prospectively associated with a lower risk of incident type 2 diabetes in women but not in men. After further adjustment for hormone use and parity status, the association between prolactin and incident type 2 diabetes remained significant in women, suggesting that the association may not be confounded by hormone use and parity. Although the exact underlying mechanisms are not clear, several potential reasons may explain this apparent discrepancy between men and women. As an estrogen-responsive pituitary hormone, prolactin was expressed at higher levels in females than males (23, 24). Although serum prolactin levels in women decrease steadily with age, especially with a significant decline after the menopause (23), prolactin levels were still higher in postmenopausal women than in men in the present study (9.87 (SD, 4.17) ng/mL vs. 8.95 (SD, 3.21) ng/mL) (P < 0.0001). Another possible explanation may be the more pronounced activity of prolactin in females than in males, especially in aspects of energy regulation, immune response, and food intake (25, 26), which play important roles in glucose and insulin regulation. Moreover, females were more likely to be affected to a greater extent by the variations of prolactin or its receptor levels. For instance, females experienced a more progressive reduction in abdominal fat mass and plasma leptin concentrations in the absence of prolactin receptors than males did (27). Thus, it is possible that the long-term effect of circulating prolactin on glucose metabolism may be more significant in women than that in men.

In addition to pregnancy, several environmental factors, such as physical activity, sleep, and stress, could affect the concentration of circulating prolactin (1). Our data also suggested potential correlations of prolactin with smoking and low density lipoprotein cholesterol in men, which was in line with the previous findings that circulating prolactin was inversely associated...
with smoking and low density lipoprotein cholesterol (28, 29). However, the underlying mechanisms were unclear and validations were warranted.

Several limitations must be considered. First, the present study included a relatively small number of participants, and the follow-up duration was not long, which could potentially result in a lack of statistical power to detect associations. Second, considering the variation of prolactin secretion in different stages of the menstrual cycle, we preformed the current study only in postmenopausal women. Further study in premenopausal women is needed. Third, potential unmeasured confounders (such as physical activity, sleep, and stress) for this association may exist.

In conclusion, our findings lend support to the postulation that the variation of serum prolactin levels associated with incident type 2 diabetes outside pregnancy suggests that prolactin may be a mediator in the pathogenesis of type 2 diabetes. Potential sex-specific mechanisms and associations between circulating prolactin levels and incident diabetes in humans need to be elucidated in future studies.

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Author affiliations: State Key Laboratory of Medical Genomics, Key Laboratory for Endocrine and Metabolic Diseases of the Ministry of Health, the Chinese National Clinical Research Center for Metabolic Diseases, and the Shanghai Clinical Center for Endocrine and Metabolic Diseases, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China (Tiange Wang, Yu Xu, Min Xu, Guang Ning, Jieli Lu, Meng Dai, Baihui Xu, Jichao Sun, Wanwan Sun, Yufang Bi, Weiqing Wang); and Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland (Shengan Lai).

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