Circulating Prolactin Associates With Diabetes and Impaired Glucose Regulation

A population-based study

**OBJECTIVE**—Prolactin is a major stimulus for the β-cell adaptation during gestation and guards postpartum women against gestational diabetes. Most studies of the role of prolactin on glucose metabolism have been conducted in humans and animals during pregnancy. However, little is known concerning the association between circulating prolactin and glucose metabolism outside pregnancy in epidemiological studies. We aimed to determine whether the variation of circulating prolactin concentration associates with diabetes and impaired glucose regulation (IGR) in a cross-sectional study.

**RESEARCH DESIGN AND METHODS**—We recruited 2,377 participants (1,034 men and 1,343 postmenopausal women) without hyperprolactinemia, aged 40 years and older, in Shanghai, China. Diabetes and IGR were determined by an oral glucose tolerance test. Multinomial logit analyses were performed to evaluate the relationship of prolactin with diabetes and IGR.

**RESULTS**—Prolactin levels decreased from normal glucose regulation to IGR to diabetes. Multinomial logit analyses, adjusted for potential confounding factors, showed that high circulating prolactin was associated with lower prevalence of diabetes and IGR. The adjusted odds ratios (95% CI) for IGR and diabetes for the highest compared with the lowest quartile of prolactin were 0.54 (95% CI 0.33–0.81) and 0.38 (0.24–0.59) in men and 0.54 (0.36–0.81) and 0.47 (0.32–0.70) in women.

**CONCLUSIONS**—High circulating prolactin associates with lower prevalence of diabetes and IGR in the current study. Further studies are warranted to confirm this association.

**RESEARCH DESIGN AND METHODS**

**Study participants**

We enrolled study participants from Songnan Community, Baoshan District, Shanghai, China, in two phases as reported previously (11–13). In phase 1 (June and July 2008), all registered permanent residents aged 40 years or older were invited to receive a screening examination, and 10,185 individuals participated. Participants were classified into one of three groups according to fasting plasma glucose (FPG) levels: normal glucose regulation (NGR, FPG <5.6 mmol/L and no history of diabetes), impaired glucose regulation (IGR, 5.6 ≤FPG < 7.0 mmol/L and no history of diabetes), and diabetes (FPG ≥7.0 mmol/L or a history of diabetes).

In phase 2 (June through August 2009), we randomly selected participants from the three groups on a ratio of 1.0 (diabetes):1.2 (IGR):1.44 (NGR) because subjects with lower glucose levels might have a lower participation rate than those with higher glucose levels. A total of 4,012 participants were randomly selected and received a comprehensive examination that included a detailed...
questionnaire, anthropometric measurements, a standard 75-g oral glucose tolerance test (OGTT), and blood and urine collection. The 4,012 participants and the other residents (6,173 participants) were similar in characteristics such as age, sex, BMI, and blood pressures. Among 3,455 study participants with blood and urine samples included in the second survey, those who met the following criteria were excluded: 1) 32 without the results of plasma glucose from the OGTT at 0 and 2 h; 2) 280 without sufficient serum for prolactin measurement; 3) 226 with a history of pituitary disease, breast tumor, or receiving hormone replacement therapy; 4) 122 with hyperprolactinemia (serum prolactin higher than laboratory reference: prolactin >19.40 ng/mL for men and >26.53 ng/mL for women); and 5) 418 premenopausal women. Finally, 2,377 participants (including 1,034 men and 1,343 postmenopausal women) were included in the analysis. The population selection process led to an oversampling of individuals with IGR and diabetes.

All procedures used in this study were in accordance with institutional guidelines. The committee on human research at Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, approved the study protocol, and all study participants provided written informed consent.

Measurements
Interviews collecting sociodemographic characteristics, medical history, family history, and lifestyle factors were conducted by trained personnel. Clinical examinations, including measurements of weight and height were performed by experienced nurses according to a standard protocol.

All participants received the OGTT, and blood samples were collected at 0 and 2 h. FPG and postprandial plasma glucose (PPG) were measured using the glucose oxidase method on an autoanalyzer (ADVIA-1650 Chemistry System, Erlangen, Germany). Plasma and serum samples were collected and immediately stored in Eppendorf tubes at −80°C. Serum insulin was measured by using an electrochemiluminescence assay (Roche Diagnostics, Basel, Switzerland), and hemoglobin A1c (HbA1c) was determined by the method of automated high-performance liquid chromatography analyzer (Bio-Rad, Hercules, CA). Serum prolactin was determined using chemiluminescent microparticle immunoassay by the Architect assay (Abbott

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**Table 1—Characteristics of Participants**

|               | NGR | IGR | Diabetes | Men | Women |<sup>P</sup> |<sup>n</sup> |
|---------------|-----|-----|----------|-----|-------|-----------|--------|
| Age (years)   | 59.7±9.1 | 61.9±9.5 | 25.4±2.9 | 55.3±1.4 | 56 ± 1.4 | 0.001 | 426 |
| BMI (kg/m²)   | 24.7±2.9 | 27.6±2.5 | 29.8±2.7 | 26.3±1.0 | 27.8±2.0 | 0.001 | 375 |
| HOMA-IR       | 1.2 (0.7–2.4) | 1.2 (0.7–2.4) | 1.8 (1.1–2.5) | 1.4 (0.9–2.5) | 1.2 (0.9–2.0) | 0.001 | 373 |
| HOMA-B       | 80.5 (52.5–131) | 84.7 (53.8–157) | 95.8 (65.9–159) | 89.4 (57.8–148) | 82.1 (52.1–139) | 0.001 | 373 |
| FPG (mmol/L)  | 4.9±0.4 | 5.6±0.4 | 6.4±0.6 | 5.2±0.3 | 5.4±0.3 | 0.001 | 373 |
| PPG (mmol/L)  | 6.0±0.4 | 7.4±0.8 | 9.0±1.2 | 6.6±0.4 | 7.4±0.6 | 0.001 | 373 |
| HbA1c (mmol/mol) | 7.8±0.5 | 8.0±0.5 | 11.5±1.9 | 7.9±0.9 | 8.0±0.9 | 0.001 | 373 |
| HbA1c (%)     | 5.8 ± 1.8 | 6.0 ± 1.8 | 8.9 ± 1.8 | 6.1 ± 1.8 | 6.0 ± 1.8 | 0.001 | 373 |
| Family history of diabetes | 55 (12.9) | 20 (4.8) | 110 (30.0) | 156 (41.8) | 126 (38.0) | 0.001 | 373 |
| Current drinker | 152 (35.7) | 94 (40.0) | 121 (32.4) | 0.42 | 22 (3.5) | 12 (4.0) | 11 (2.7) | 0.36 | 373 |
| Current smoker | 251 (59.1) | 110 (46.8) | 156 (41.8) | 0.001 | 41 (10.9) | 22 (5.2) | 19 (4.6) | 0.001 | 373 |

*NGR = Normoglycemia; IGR = Impaired Glucose Regulation*
Statistical analysis

Table 2—Demographic and laboratory characteristics of the study population according to serum prolactin quartiles

| Men | | | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|---|
| Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P |
| Prolactin (ng/mL) | ≤6.40 | 6.41–8.16 | 8.17–10.62 | ≥10.63 | <0.001 | 61.6 ± 8.2 | 62.7 ± 8.4 | 62.6 ± 9.7 | 63.5 ± 10.0 | 0.065 |
| Age (years) | 58.3 ± 8.8 | 59.7 ± 9.0 | 62.5 ± 9.1 | 64.0 ± 9.8 | 0.050 | 25.6 ± 3.4 | 25.1 ± 3.7 | 25.6 ± 4.5 | 25.9 ± 4.2 | 0.071 |
| BMI (kg/m²) | 24.8 ± 3.0 | 25.0 ± 3.4 | 25.5 ± 3.2 | 25.3 ± 3.5 | <0.001 | 9.2 (7.0) | 6 (1.8) | 3 (0.9) | 9 (2.7) | 0.49 |
| Current smoker | 173 (65.9) | 145 (56.4) | 105 (40.5) | 94 (36.4) | 0.001 | 12 (3.6) | 12 (3.6) | 11 (3.3) | 10 (3.0) | 0.78 |
| Current drinker | 115 (44.2) | 96 (37.4) | 89 (34.4) | 67 (26.0) | <0.001 | 79 (23.4) | 70 (20.9) | 54 (16.1) | 52 (15.5) | 0.024 |
| Family history of diabetes | 53 (20.4) | 47 (18.3) | 44 (17.0) | 37 (14.3) | 0.33 | 6 (1.8) | 6 (1.8) | 5 (1.7) | 5 (1.7) | 0.011 |
| FPG (mmol/L) | 6.2 ± 2.3 | 5.9 ± 2.0 | 5.7 ± 1.9 | 5.7 ± 1.7 | 0.011 | 6.2 ± 2.2 | 5.7 ± 1.8 | 5.7 ± 1.7 | 5.6 ± 1.9 | <0.001 |
| HbA1c (%) | 6.8 ± 1.6 | 6.7 ± 1.6 | 6.5 ± 1.4 | 6.5 ± 1.3 | 0.038 | 6.7 ± 1.4 | 6.6 ± 1.3 | 6.5 ± 1.3 | 6.4 ± 1.2 | 0.042 |
| HOMA-IR | 1.6 (1.0–2.6) | 1.6 (0.9–2.5) | 1.6 (1.0–2.6) | 1.6 (1.0–2.8) | 0.20 | 2.1 (1.3–3.3) | 1.9 (1.1–3.1) | 1.8 (1.1–2.9) | 1.8 (1.1–2.9) | 0.011 |
| HOMA-B | 65.1 (32.8–100.5) | 61.0 (32.2–112.9) | 72.2 (45.3–114.7) | 76.5 (44.8–123.5) | <0.001 | 79.3 (50.7–126.4) | 87.5 (57.8–124.9) | 83.5 (55.8–124.0) | 92.9 (58.9–142.8) | 0.037 |

Continuous data are shown as mean ± SD or median (IQR) and categorical data as n (%). P values are based on ANOVA for continuous data or the χ² test for categorical data.
including age, BMI, smoking and alcohol drinking status (never, former or current), and family history of diabetes (yes or no) in men and women. Hosmer-Lemeshow goodness-of-fit was used to examine the fitness of the multivariable adjusted model, and a P value > 0.05 indicates good calibration. For prevalence of IGR and diabetes, P values were estimated for linear trend across serum prolactin quartiles. Finally, stratified analyses were conducted to determine the ORs of IGR and diabetes with each 1-SD increment in log-serum prolactin concentration.

**RESULTS**—General demographic and laboratory characteristics of the study population are summarized in Table 1. The current study included 1,034 men and 1,343 postmenopausal women. Median (IQR) ages were 60.0 years (54.0–67.8) for men and 60.5 years (55.3–70.1) for women. Medians (IQR) of serum prolactin concentration were 8.16 ng/mL (6.40–10.62) for men and 8.86 ng/mL (6.74–11.49) for women. Among all participants, 781 (32.9%) had diabetes, 539 (22.7%) had IGR, and 1,057 (44.5%) had NGR. Compared with the participants in the lowest quartile, those in the highest quartile were older and less likely to be smokers or drinkers and had lower levels of FPG, PPG, and HbA1c, but had higher levels of HOMA-B. There was no significant difference across the quartiles for family history of diabetes and HOMA-IR in men. Similarly, lower levels of FPG, PPG, and HbA1c, and higher levels of HOMA-B were found in those in the highest quartile in women. However, women in the highest quartile were less likely to have a family history of diabetes and had lower HOMA-IR.

Multinomial logit regression analyses (Table 3) show that the risk for prevalent IGR and diabetes decreased across prolactin quartiles. In multivariate-adjusted models, the ORs (95% CIs) for IGR and diabetes in the highest compared with the lowest quartile of serum prolactin were 0.54 (0.33–0.89) and 0.38 (0.24–0.59) in men, and 0.54 (0.36–0.81) and 0.47 (0.32–0.70) in women, respectively.

Furthermore, we conducted stratified analyses to determine the ORs of IGR and diabetes with each 1-SD increment in log-serum prolactin concentration in total population and in subgroups of the strata variables (Fig. 1). According to the stratified analyses, the associations between each 1-SD increment of serum prolactin and the prevalence of diabetes were significant in the total population, both sex strata (men and women), both age strata (<60 and ≥60 years), both current smoking status (yes and no), both current drinking status (yes and no), and both BMI strata (<25 and ≥25 kg/m²). The associations between each 1-SD increment in serum prolactin and the prevalence of IGR were significant in all stratified analyses except for in individuals who were aged 60 years or older (n = 1,190 among total 2,377). Tests for the interactions between serum prolactin and the risk factors were not significant (all P > 0.05).

**CONCLUSIONS**—In the current study, we found that a high circulating prolactin level was significantly associated with a lower risk of prevalent diabetes and IGR in men and postmenopausal women. To the best of our knowledge, this is the first study to investigate the association between circulating prolactin and glucose regulation in a large sample of community-based men and women.

The current results are in accordance with previous experimental findings. During pregnancy, levels of prolactin and prolactin receptors elevate in parallel with the increase of β-cell mass and glucose-stimulated insulin secretion to upregulate islet cell function and maintain normal glucose homeostasis (14–16). In nonpregnant models, prolactin also takes a crucial part in regulating whole-body insulin sensitivity and glucose metabolism by increasing

**Table 3—Associations of circulating prolactin level with diabetes and IGR**

| Prolactin quartiles | 1          | 2                      | 3               | 4               | P value for trend |
|---------------------|------------|------------------------|-----------------|-----------------|-----------------|

| Sex | IGR | Age-adjusted | 1.00 | 0.74 (0.46–1.18) | 0.69 (0.44–1.10) | 0.62 (0.39–0.98) | 0.054 |

| Diabetes | Multivariate-adjusted | 1.00 | 0.72 (0.45–1.15) | 0.61 (0.38–0.98) | 0.54 (0.33–0.89) | 0.014 |

| Sex | IGR | Age-adjusted | 1.00 | 0.64 (0.42–0.98) | 0.35 (0.23–0.54) | 0.38 (0.24–0.59) | <0.001 |

| Diabetes | Multivariate-adjusted | 1.00 | 0.64 (0.42–0.98) | 0.35 (0.23–0.54) | 0.38 (0.24–0.59) | <0.001 |

Data are OR (95% CI) unless otherwise indicated. *OR with corresponding 95% CI has been adjusted for age, BMI, smoking status, alcohol drinking status, and family history of diabetes.
-cell proliferation, promoting cumulative
insulin secretion, inhibiting key caspases of
the extrinsic and intrinsic pathways leading
to islets apoptosis, and modulating immune
function (6,17–19). Interestingly, recent
studies discovered that human adipose tis-
sue produces prolactin and also expresses
prolactin receptors, highlighting a previ-
ously unappreciated action of prolactin
as a cytokine involved in adipose tissue
function. Prolactin directly regulates adipose
tissue function in downregulating lipopro-
tein lipase and fatty acid synthase (20,21),
which consequently suppress lipogenesis,
and regulates bioactivities of adipokines
such as adiponectin, interleukin-6, and,
possibly, leptin (8,22,23). Collectively,
these studies raise the prospect that
prolactin affects energy homeostasis
through its action as an adipokine and
is involved in the manifestation of insu-
lin resistance (24).

In fact, the role of prolactin on glu-
cose metabolism and insulin resistance
depends on its circulating concentration.
Prolactin knockout or prolactin receptor
deficiency is accompanied by
hypoplasia, a reduced pancreatic insulin
mRNA level, a blunted insulin secretory
response to glucose, and mild glucose in-
tolerance (10,25). Physiologically ele-
vated prolactin levels induce normal
adaptive increases in glucose-stimulated
insulin secretion through expanding
-cell mass and improving hepatic insulin
sensitivity (26,27) and have an indirect
action by increasing hypothalamic dopa-
mine synthesis to contribute to the im-
proved energy and glucose homeostasis
(27–29).

It is worth mentioning that the effect
of a physiologically high prolactin level
and pathological hyperprolactinemia on
glucose metabolism could be different.
Excessive high levels of prolactin exacer-
bate whole-body and hepatic insulin re-
sistance and impair the insulin secretory
capacity in diabetic mice (26) and in pa-
tients with hyperprolactinemia caused by
prolactinoma (30). Patients with pituitary
prolactinoma often have a higher risk of
hyperglycemia, accompanied by obesity
and insulin resistance, and dopamine
agonist treatment, such as bromocriptine,
is used to reverse these symptoms
(28,30,31).

In the current study, we revealed that
physiologically high serum prolactin was
associated with a favorable glucose me-
tabolic profile, including lower levels of
FPG, PPG, and HbA1c. We noticed that
compared with the first quartile, the third

\[
\begin{array}{|c|c|}
\hline
\text{A} & \text{B} \\
\hline
\text{Total and subgroups} & \text{Total and subgroups} \\
\hline
\text{Total} & \text{Total} \\
\text{Sex} & \text{Sex} \\
\text{Men} & \text{Men} \\
\text{Women} & \text{Women} \\
\hline
\text{Age (years)} & \text{Age (years)} \\
< 60 & < 60 \\
\geq 60 & \geq 60 \\
\hline
\text{Current smoking} & \text{Current smoking} \\
Yes & Yes \\
No & No \\
\hline
\text{Current drinking} & \text{Current drinking} \\
Yes & Yes \\
No & No \\
\hline
\text{BMI (kg/m²)} & \text{BMI (kg/m²)} \\
< 25 & < 25 \\
\geq 25 & \geq 25 \\
\hline
\text{Adjusted ORs for each 1-SD increment of log-serum prolactin concentration associated}
\text{with IGR (A) and diabetes (B) in total population and in subgroups. The ORs with corre-
\text{sponding 95% CIs have been adjusted for age, sex, BMI, smoking status, alcohol drinking status,}
\text{and family history of diabetes.}

\text{Figure 1} — Adjusted ORs for each 1-SD increment of log-serum prolactin concentration associated
with IGR (A) and diabetes (B) in total population and in subgroups. The ORs with corre-
splying 95% CIs have been adjusted for age, sex, BMI, smoking status, alcohol drinking status,
and family history of diabetes.
and fourth quartiles of serum prolactin associates with higher levels of HOMA-B, suggesting an association between prolactin and β-cell function. However, a strict linear relationship was not observed across prolactin quartiles. Although evaluation of β-cell function using the HOMA model has been proved to be robust in epidemiological studies (32), using a gold standard such as hyperglycemic clamps or intravenous glucose tolerance test to estimate the β-cell function should provide more precise results, and further studies are warranted.

The strength of our study is the novelty, the large number of participants, and the well-characterized participants. However, several limitations must be considered. First, owing to the cross-sectional nature, no causal inference can be drawn. Prospective studies are needed to clarify their precise interrelationship. Second, because of the initial study design (11–13), individuals with IGR and diabetes were oversampled in the selection process to ensure adequate numbers. Therefore, the results in a population with oversampled IGR and diabetes may not be generalizable to the general population. Third, 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. Moreover, studies in other ethnicities are needed to confirm the finding.

Our findings lend support to the postulation that the variation of serum prolactin levels associates with glucose metabolism changes in humans outside pregnancy, suggesting that prolactin may be a mediator in the pathogenesis of impaired glucose metabolism. Future studies are warranted to clarify the potential contribution of prolactin to the development of diabetes.

T.W. conceived and designed the study, recruited subjects, undertook the statistical analysis, wrote the first draft of the manuscript, and approved the final version. J.L. conceived and designed the study, undertook the statistical analysis, wrote the first draft of the manuscript, and approved the final version. Y.X. and W.W. contributed to discussion, revised the manuscript, and approved the final version. M.L., J.S., J.Z., and B.X. recruited subjects and approved the final version of the manuscript. M.X. and Y.C. conceived and designed the study, contributed to discussion, revised the manuscript, and approved the final version. G.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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