Circulating Prolactin Associates With Diabetes and Impaired Glucose Regulation

A population-based study

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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 0.33–0.89) 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.

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

Diabetes Care 36:1974–1980, 2013

Prolactin is a polypeptide originally known as a pituitary hormone and named for its ability to promote lactation in response to the suckling stimulus of hungry young mammals (1). Besides its well-known lactogenic properties, prolactin is also a highly versatile hormone whose functions are related to reproduction, growth and development, metabolism, immune regulation, brain function, and behavior (2,3). Maternal prolactin increases concurrently to insulin during the second half pregnancy and stimulates β-cell proliferation, insulin production, and insulin secretion (4,5). Moreover, it is recognized that the glucose metabolic regulation effect of prolactin is not confined to the period of pregnancy (3,6,7).

Animal studies clarify the in vivo effect of prolactin levels on glucose and insulin levels in nonpregnant rodent models, suggesting the ability of prolactin to protect from diabetes (8–10). However, epidemiological studies investigating the association between circulating prolactin and glucose metabolic regulation are not available. We hypothesize that in nonpregnant individuals, the variation of serum prolactin may also be associated with glucose metabolism regulation, and in the current study, we explored this association in community-based middle-aged and elderly Chinese men and postmenopausal women.

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

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Received 17 September 2012 and accepted 19 December 2012.
DOI: 10.2337/dc12-1893
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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 autoanalyser (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 A_{1c} (HbA_{1c}) 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

Table 1—*Characteristics of participants*

	Men				Women			
	NGR $n = 426$	IGR $n = 235$	Diabetes $n = 373$	*P*	NGR $n = 631$	IGR $n = 304$	Diabetes $n = 408$	*P*
Age (years)	59.7 ± 9.1	61.9 ± 9.5	62.2 ± 9.7	<0.001	60.1 ± 8.6	63.6 ± 9.2	65.6 ± 9.0	<0.001
BMI (kg/m^2)	24.5 ± 3.3	25.4 ± 2.9	25.7 ± 3.4	<0.001	24.7 ± 3.6	26.1 ± 3.9	26.5 ± 4.4	<0.001
Current smoker	251 (58.9)	110 (46.8)	156 (41.8)	<0.001	13 (2.1)	5 (1.6)	9 (2.2)	0.91
Current drinker	152 (35.7)	94 (40.0)	121 (32.4)	0.42	22 (3.5)	12 (4.0)	11 (2.7)	0.36
Family history of diabetes	55 (12.9)	20 (8.5)	106 (28.4)	<0.001	69 (10.9)	65 (21.4)	121 (30.0)	<0.001
FPG (mmol/L)	4.9 ± 0.5	5.3 ± 0.6	7.5 ± 2.5	<0.001	4.9 ± 0.5	5.3 ± 0.7	7.6 ± 2.6	<0.001
PPG (mmol/L)	6.0 ± 1.2	8.9 ± 1.1	16.4 ± 4.4	<0.001	6.1 ± 1.0	8.9 ± 1.0	17.1 ± 6.2	<0.001
HbA_{1c} (%)	5.8 ± 0.4	6.0 ± 0.5	8.0 ± 1.8	<0.001	5.9 ± 0.4	6.2 ± 0.4	7.8 ± 1.8	<0.001
HbA_{1c} (mmol/mol)	40 ± 4	43 ± 5	64 ± 19	<0.001	41 ± 4	44 ± 5	62 ± 19	<0.001
HOMA-IR	1.2 (0.7–1.7)	1.7 (1.0–2.5)	2.4 (1.4–3.8)	<0.001	1.4 (0.9–2.0)	2.1 (1.4–3.0)	3.3 (2.1–5.3)	<0.001
HOMA-B	80.5 (52.5–129.7)	82.8 (54.8–126.9)	44.2 (26.9–84.0)	<0.001	90.9 (63.9–133.4)	102.3 (68.9–163.7)	62.3 (36.3–102.9)	<0.001
Prolactin (ng/mL)	9.08 ± 3.25	8.74 ± 3.18	8.59 ± 3.36	0.038	10.06 ± 4.15	9.56 ± 4.23	9.48 ± 4.49	0.003

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 χ^2 test for categorical data.

Laboratories, Abbott Park, IL). For stability verification of prolactin measurement, we randomly selected and measured prolactin concentrations in fresh serum samples of 20 men and 20 women after serum extraction. Before the determination of this study, we retested prolactin concentrations in the same samples. The deviation of the results before and after storage was within the laboratory allowable range. 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.

Definition

Diabetes was defined as FPG ≥7.0 mmol/L, or PPG ≥11.1 mmol/L, or self-reported previous diagnosis of diabetes by physicians and use of antidiabetic medications. IGR was defined as impaired fasting glucose (FPG ≥6.1 and <7.0 mmol/L) and/or impaired glucose tolerance (PPG ≥7.8 and <11.1 mmol/L). The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum insulin (μIU/mL) × FPG (mmol/L)/22.5. The index of HOMA of β-cell function (HOMA-B) was calculated as (20 × fasting serum insulin)/(FPG − 3.5).

Statistical analysis

Statistical analysis was performed using SAS 8.1 software (SAS Institute, Cary, NC), and a two-sided P value < 0.05 indicated statistical significance. Measurements with a skewed distribution, such as HOMA-IR and HOMA-B, were logarithmically transformed to achieve a normal distribution. General demographic and laboratory characteristics are summarized as mean ± SD or median with interquartile range (IQR), depending on the normality of the continuous variables, or as number with proportion for categorical variables. To test for differences of characteristics among different glucose regulation status or quartiles of prolactin, continuous variables were compared using one-way ANOVA, and a χ^2 test was used for categorical variables.

The participants were categorized into sex-specific quartiles of serum prolactin, with the first quartile representing the lowest one and the fourth quartile representing the highest one. Multinomial logit analyses were performed to evaluate the odds ratio (OR) and 95% CI of having IGR and diabetes for each quartile of serum prolactin concentration compared with the lowest quartile with controlling for potential confounders

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

	Men					Women				
	Quartile 1 n = 260	Quartile 2 n = 257	Quartile 3 n = 259	Quartile 4 n = 258	P	Quartile 1 n = 338	Quartile 2 n = 335	Quartile 3 n = 335	Quartile 4 n = 335	P
Prolactin (ng/mL)	≤6.40	6.41–8.16	8.17–10.62	≥10.63		≤ 6.74	6.75–8.86	8.87–11.49	≥11.50	
Age (years)	58.3 ± 8.8	59.7 ± 9.0	62.5 ± 9.1	64.0 ± 9.8	<0.001	61.6 ± 8.2	62.7 ± 8.6	62.6 ± 9.7	63.5 ± 10.0	0.065
BMI (kg/m^2)	24.8 ± 3.0	25.0 ± 3.4	25.5 ± 3.2	25.3 ± 3.5	0.050	25.6 ± 3.4	25.1 ± 3.7	25.6 ± 4.5	25.9 ± 4.2	0.071
Current smoker	173 (66.5)	145 (56.4)	105 (40.5)	94 (36.4)	<0.001	9 (2.7)	6 (1.8)	3 (0.9)	9 (2.7)	0.49
Current drinker	115 (44.2)	96 (37.4)	89 (34.4)	67 (26.0)	<0.001	12 (3.6)	12 (3.6)	11 (3.3)	10 (3.0)	0.78
Family history of diabetes	53 (20.4)	47 (18.3)	44 (17.0)	37 (14.3)	0.33	79 (23.4)	70 (20.9)	54 (16.1)	52 (15.5)	0.024
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
PPG (mmol/L)	11.3 ± 5.8	10.6 ± 5.6	9.8 ± 5.2	9.9 ± 5.0	0.006	11.1 ± 6.0	10.1 ± 5.6	9.5 ± 5.5	9.6 ± 6.4	0.003
HbA_{1c} (%)	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
HbA_{1c} (mmol/mol)	51 ± 18	50 ± 17	48 ± 15	47 ± 14	0.019	50 ± 16	48 ± 15	47 ± 14	46 ± 13	0.007
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 (1.1–3.0)	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 χ^2 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 with NGR, those with diabetes and IGR had lower levels of prolactin (8.59 ± 3.36 and 8.74 ± 3.18 vs. 9.08 ± 3.25 ng/mL, $P = 0.038$ in men; 9.48 ± 4.49 and 9.56 ± 4.23 vs. 10.06 ± 4.15 ng/mL, $P = 0.003$ in women, respectively).

The general demographic and laboratory characteristics according to serum prolactin quartiles are reported in Table 2. The quartile ranges of serum prolactin were ≤6.40, 6.41–8.16, 8.17–11.62, and ≥10.63 ng/mL in men and ≤6.74, 6.75–8.86, 8.87–11.49, and ≥11.50 ng/mL in women. In men, 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 HbA_{1c}, 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 HbA_{1c}, 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/m^2). The associations between each 1-SD increased 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
Men					
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
Multivariate-adjusted*	1.00	0.72 (0.45–1.15)	0.61 (0.38–0.98)	0.54 (0.33–0.89)	0.014
Diabetes					
Age-adjusted	1.00	0.70 (0.47–1.04)	0.46 (0.30–0.69)	0.48 (0.32–0.73)	<0.001
Multivariate-adjusted*	1.00	0.64 (0.42–0.98)	0.35 (0.23–0.54)	0.38 (0.24–0.59)	<0.001
Women					
IGR					
Age-adjusted	1.00	0.57 (0.38–0.85)	0.54 (0.37–0.81)	0.53 (0.36–0.80)	0.003
Multivariate-adjusted*	1.00	0.60 (0.40–0.89)	0.56 (0.37–0.83)	0.54 (0.36–0.81)	0.004
Diabetes					
Age-adjusted	1.00	0.56 (0.39–0.80)	0.40 (0.28–0.59)	0.46 (0.32–0.67)	<0.001
Multivariate-adjusted*	1.00	0.58 (0.39–0.85)	0.41 (0.28–0.62)	0.47 (0.32–0.70)	<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.

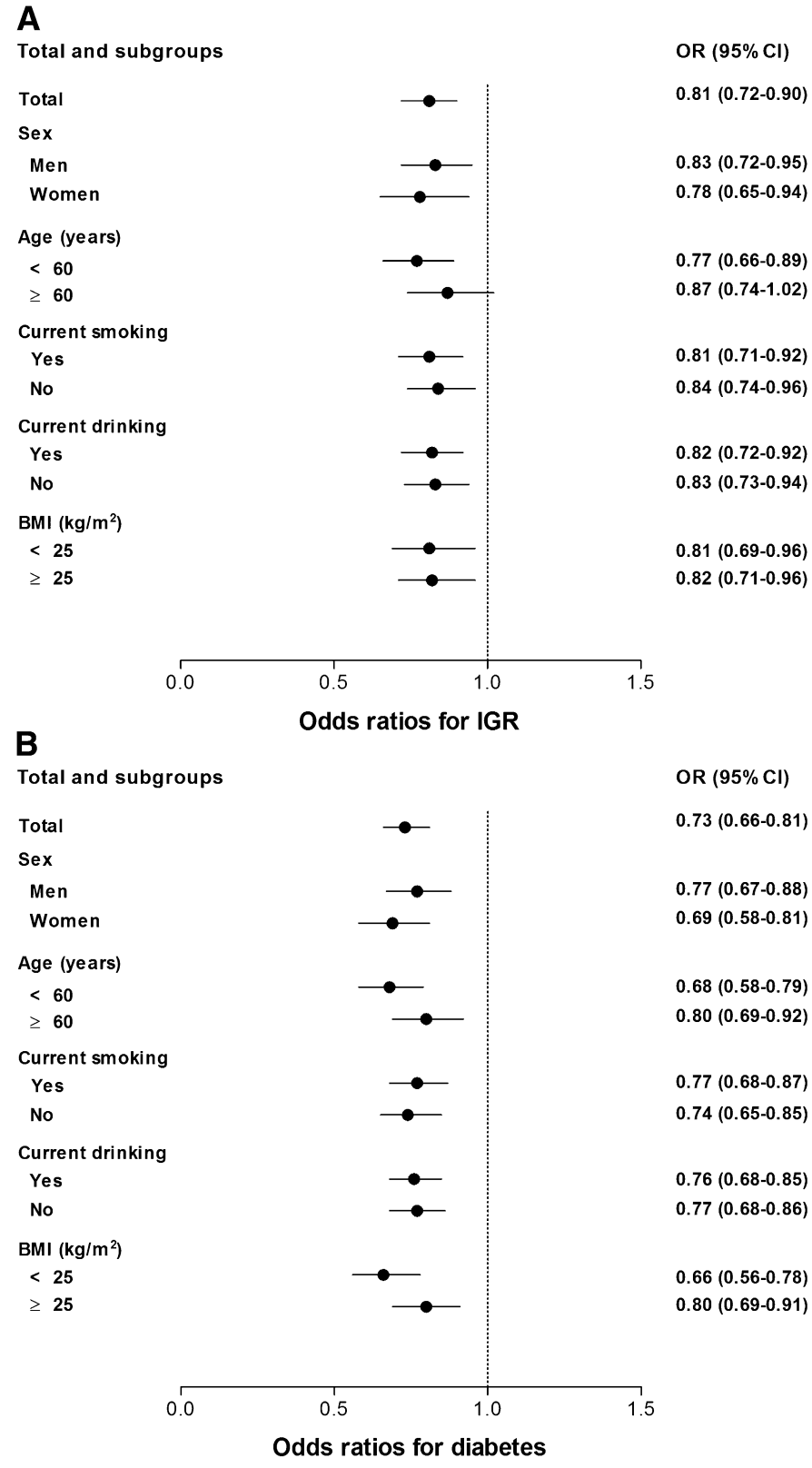

Figure 1—*Adjusted ORs for each 1-SD increment of log-serum prolactin concentration associated with IGR (A) and diabetes (B) in total population and in subgroups. The ORs with corresponding 95% CIs have been adjusted for age, sex, BMI, smoking status, alcohol drinking status, and family history of diabetes.*

β-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 tissue produces prolactin and also expresses prolactin receptors, highlighting a previously unappreciated action of prolactin as a cytokine involved in adipose tissue function. Prolactin directly regulates adipose tissue function in downregulating lipoprotein 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 insulin resistance (24).

In fact, the role of prolactin on glucose metabolism and insulin resistance depends on its circulating concentration. Prolactin knockout or prolactin receptor deficiency is accompanied by β-cell hypoplasia, a reduced pancreatic insulin mRNA level, a blunted insulin secretory response to glucose, and mild glucose intolerance (10,25). Physiologically elevated prolactin levels induce normal adaptive increases in glucose-stimulated insulin secretion through expanding β-cell mass and improving hepatic insulin sensitivity (26,27) and have an indirect action by increasing hypothalamic dopamine synthesis to contribute to the improved 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 exacerbate whole-body and hepatic insulin resistance and impair the insulin secretory capacity in diabetic mice (26) and in patients 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 metabolic profile, including lower levels of FPG, PPG, and HbA_{1c}. We noticed that compared with the first quartile, the third

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.

Acknowledgments—The current study was supported by the grants from the Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health (1994DP131044), the Sector Funds of Ministry of Health (201002002), the National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), the National Natural Science Foundation of China (81222008, 81100564), the 863 project (2012AA02A509), and the Shanghai New Excellent Youth Program (XYQ2011009).

No potential conflicts of interest relevant to this article were reported.

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. contributed to discussion, revised the manuscript, and approved the final version. Y.B. and G.N. 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.

This study was presented in poster format at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank all participants for their contributions.

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