Different Associations of Diabetes With β-Cell Dysfunction and Insulin Resistance Among Obese and Nonobese Chinese Women With Prior Gestational Diabetes Mellitus

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Diabetes Care 2014;37:2533–2539 | DOI: 10.2337/dc14-0573

OBJECTIVE

To examine the relative contributions of β-cell dysfunction and insulin resistance to postpartum diabetes risk among obese and nonobese women with prior gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

We performed a cross-sectional survey 1–5 years after 1,263 women who had GDM gave birth. Polytomous logistic regression models were used to assess the associations of β-cell dysfunction (the lower quartile of HOMA-%β), insulin resistance (the upper quartile of HOMA-IR), decreased insulin sensitivity (the lower quartile of HOMA-%S), and different categories of BMI with prediabetes and diabetes risk.

RESULTS

β-Cell dysfunction, insulin resistance, and decreased insulin sensitivity all were significantly associated with hyperglycemic status across normal weight, overweight, and obese groups, and the patterns of insulin resistance and decreased insulin sensitivity were similar. BMI was inversely associated with β-cell dysfunction and positively associated with insulin resistance across normal glucose, prediabetes, and diabetes categories. Compared with women with normal glucose and weight, obese women with normal glucose had increased β-cell secretory function (odds ratio [OR] 0.09 [95% CI 0.02–0.37]) and insulin resistance (OR 17.4 [95% CI 9.47–31.9]). Normal weight diabetic women displayed the most β-cell dysfunction (OR 13.6 [95% CI 4.06–45.3]), whereas obese diabetic women displayed the highest insulin resistance (OR 45.8 [95% CI 18.5–113]).

CONCLUSIONS

For women with prior GDM, β-cell dysfunction had more pronounced contribution to postpartum diabetes among nonobese subjects, whereas insulin resistance contributed more to postpartum hyperglycemia among obese subjects.

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset of or first recognition during pregnancy (1). GDM occurs in about 2–10% of all pregnancies in the United States (2). In urban China, the prevalence of GDM has increased from 2.4% in 1999 to 8.2% in 2012 (3). Studies identified that women

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Received 6 March 2014 and accepted 30 April 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0573/-/DC1.

with GDM are at higher risk of developing type 2 diabetes after delivery, and a recent meta-analysis showed that women with prior GDM had a 7.43-fold risk of diabetes compared with those who had a normoglycemic pregnancy (4).

Obesity, impaired insulin secretion, and insulin resistance are three major factors for the development of diabetes. The fundamental pathological sequence leading to diabetes is presumed to be the development of obesity-induced insulin resistance followed by hyperglycemia when the β-cell can no longer compensate (5). This model of the pathogenesis of diabetes is mainly based on studies of obese subjects, and it is unclear whether diabetes in nonobese subjects is caused by impaired insulin secretion, insulin resistance, or both. Some studies suggested that among a white population, obese diabetic patients displayed peripheral insulin resistance in combination with defective insulin secretion, whereas nonobese diabetic patients showed only a secretory defect (6). Yet because Asians and Asian emigrants generally have lower BMI, similar or even higher prevalence of diabetes (7–9), and decreased insulin sensitivity and β-cell dysfunction (10) compared to whites, an ethnic difference underlying the pathogenesis of diabetes seems to exist. Moreover, few studies have focused on β-cell dysfunction and insulin resistance among women with a history of GDM. The aim of this study was to evaluate the effects of β-cell dysfunction and insulin resistance on postpartum diabetes risk based on different levels of BMI among women with a history of GDM.

RESEARCH DESIGN AND METHODS

Tianjin GDM Screening Project

Tianjin is the fourth largest city in Northern China. In 2010, among the 13 million residents in the 16 county-level administrative districts there were 4.3 million people living in 6 central urban districts. Since 1999, all pregnant women living in those six urban districts have participated in universal screening for GDM, and the average proportion of screened pregnancies was >91% from 1999 to 2008 (3). All pregnant women at 26–30 weeks' gestation participated in a 1-h 50-g glucose screening test (GCT), and those who had a glucose reading ≥7.8 mmol/L were invited to undergo a 75-g 2-h oral glucose tolerance test (OGTT) at Tianjin Women's and Children's Health Center (3). GDM is defined using the World Health Organization criteria (11). Women with a 75-g 2-h OGTT result confirming either diabetes (fasting glucose ≥7 mmol/L or 2-h glucose ≥11.1 mmol/L) or impaired glucose tolerance (IGT) (2-h glucose ≥7.8 and <11.1 mmol/L) were regarded as having GDM. From December 1998 to December 2009 a total of 128,125 pregnant women participated in the GDM screening program, and 6,247 were diagnosed with GDM (12,13).

Study Samples

We used the baseline data of the participants enrolled in the Tianjin Gestational Diabetes Mellitus Prevention Program, which was described previously (12). Briefly, all pregnant women who were diagnosed with GDM between 2005 and 2009 in six urban districts (N = 4,644) were recruited 1–5 years after delivery based on a good health care registration system providing health and contact information for mothers with GDM in Tianjin. Of those, 1,263 women with GDM (participation rate 27%) more than 24 years old returned and finished the baseline survey. There were no differences in the OGTT at 26–30 weeks' gestation with regard to age (28.9 vs. 28.7 years), fasting glucose (5.34 vs. 5.34 mmol/L), 2-h glucose (9.23 vs. 9.16 mmol/L), and the prevalence of IGT (90.9% vs. 91.8%) and diabetes (9.1% vs. 8.2%) between the returned and unreturned women with GDM. The study was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center, and informed consent was obtained from each participant.

Questionnaires and Measurements

All study participants filled in a questionnaire about their sociodemographics (age, marital status, education, income, and occupation); history of GDM; family history (diabetes, coronary heart disease, stroke, cancer, and hypertension); medical history (hypertension, diabetes, and hypercholesterolemia); pregnancy outcomes (prepregnancy weight, weight gain during pregnancy, and number of children); dietary habits (a self-administered food frequency questionnaire to measure the frequency and quantity of intake of 33 major food groups and beverages during the past year) (14); alcohol intake; smoking habits; passive smoking; and physical activity (the frequency and duration of leisure-time and sedentary activities) at the postpartum baseline survey. The women also completed the 3-day 24-h food records using methods for dietary record collection taught to them by a dietitian. The performance of 3-day 24-h food records (14), the food frequency questionnaire (14), and the above-mentioned questionnaire assessing physical activity (15,16) were validated in the China National Nutrition and Health Survey in 2002.

Body weight and height of all women were measured by specially trained research doctors using a standardized protocol. Height (without shoes) was measured to the nearest 0.1 cm, and weight was rounded to the nearest half kilogram. BMI was calculated by dividing current weight in kilograms by the square of height in meters. Using the Chinese BMI classification standard (17), BMI was divided into three categories: normal weight (<24 kg/m^2), overweight (24–27.9 kg/m^2), and obese (≥28 kg/m^2).

Blood samples were collected from all participants after an overnight fast of at least 12 h. Participants without a self-reported history of diabetes were given a standard 2-h 75-g glucose solution. Plasma glucose was measured using an automatic analyzer (TBA-120FR; Toshiba, Japan), and insulin was measured with chemiluminescence using a Siemens ADVIA Centaur CP Immunossay System.

HOMA was used to estimate β-cell secretory function (HOMA-%β), insulin resistance (HOMA-IR), and insulin sensitivity (HOMA-%S) (18,19). The HOMA2 calculator was updated by the University of Oxford in 2004 (20), and plasma glucose and insulin were used in the calculation. β-Cell dysfunction (impaired insulin secretion), insulin resistance, and decreased insulin sensitivity were defined as the lower quartile of HOMA-%β, the upper quartile of HOMA-IR, and the lower quartile of HOMA-%S, respectively.

Definition of Postpartum Diabetes and Prediabetes

After a 75-g 2-h OGTT at the baseline survey 1–5 years postpartum, women were classified according to the American Diabetes Association 2005 criteria

(21): diabetes (fasting glucose ≥7.0 mmol/L and/or 2-h glucose ≥11.1 mmol/L), prediabetes (either impaired fasting glucose [IFG] or fasting glucose ≥5.6 and <7.0 mmol/L), and/or IGT [2-h glucose ≥7.8 and <11.1 mmol/L]) and normal glucose (fasting glucose <5.6 mmol/L and 2-h glucose <7.8 mmol/L).

Statistical Analyses

Differences in risk factors among the five groups of women with different glucose status (normal glucose, isolated IGT, isolated IFG, both IGT and IFG, and diabetes) 1–5 years postpartum were tested using one-way ANOVA (continuous variables) or χ^2 tests (categorical variables). Fasting and 2-h insulin, HOMA-%β, HOMA-IR, and HOMA-%S were nonnormally distributed and were performed on a logarithmic scale in the analyses.

A score test was conducted to evaluate the possible use of ordinal logistic regression; the proportional odds could not be assumed as required (i.e., the null hypothesis that the model was constrained by the proportional odds assumption was rejected [χ^2 = 55.47; degrees of freedom = 3; $P < 0.0001$]). Therefore, polytomous logistic regression, rather than ordinal logistic regression, was determined to be appropriate and used to obtain odds ratios (ORs) of β-cell dysfunction, insulin resistance, and decreased insulin sensitivity for abnormal glucose status, that is, diabetes and prediabetes (independent variable) among women with different BMI levels before pregnancy and at the baseline survey 1–5 years postpartum. A structured adjustment scheme was used to consider confounding effects of other covariables. Four models were used: model 1 adjusted for age; model 2 adjusted for age, time postpartum, sitting time, dietary fiber, and intakes of monounsaturated fat, polyunsaturated fat, and saturated fat (continuous variables for above all variables) and education, family history of diabetes, smoking, passive smoking, alcohol drinking, leisure-time physical activity (categorical variables for above all variables); model 3 adjusted for variables in model 2 as well as BMI; and model 4 adjusted for variables in model 3 as well as insulin resistance and decreased insulin sensitivity (in β-cell dysfunction analysis), β-cell dysfunction and decreased insulin sensitivity (in insulin resistance analysis), and β-cell dysfunction and insulin resistance (in decreased insulin sensitivity analysis). All statistical analyses were performed using SAS for Windows, version 9.3 (SAS Institute, Cary, NC). $P \leq 0.05$ was considered statistically significant.

RESULTS

General characteristics of the study population are presented in Table 1 and Supplementary Table 1. Among the 1,263 women with a history of GDM, 83 were diagnosed as having diabetes, and 401 were diagnosed as having prediabetes (128 via isolated IGT, 171 via isolated IFG, and 102 via both IGT and IFG) 1–5 years postpartum. Among women with GDM 1–5 years postpartum, 682 were normal weight, 383 were overweight, and 198 were obese. Compared with women with GDM and normal glucose after delivery, women with GDM who were diagnosed as having prediabetes or diabetes after delivery had significantly higher BMI before pregnancy and at baseline survey,

Table 1—General characteristics of women with GDM

		Prediabetes (n = 401)				
	Normal glucose (n = 779)	Isolated IGT (n = 128)	Isolated IFG (n = 171)	IGT and IFG (n = 102)	Diabetes (n = 83)	P value
Age (years)	32.3 ± 3.5	32.4 ± 3.3	32.5 ± 3.6	32.4 ± 3.6	32.7 ± 3.8	0.864
Time postpartum (months)	27.0 ± 10	27.3 ± 11	27.8 ± 10	26.5 ± 9.7	31.6 ± 11	0.005
BMI (kg/m^2)						
Before pregnancy	22.4 ± 3.0	24.2 ± 3.4	23.2 ± 3.1	24.6 ± 3.7	25.6 ± 3.7	<0.001
At baseline survey	23.2 ± 3.4	25.9 ± 4.1	24.5 ± 3.9	26.3 ± 4.3	27.3 ± 4.0	<0.001
β-Cell dysfunction[a]	18.4 (143)	10.9 (14)	43.9 (75)	33.3 (34)	59.0 (49)	<0.001
Insulin resistance[b]	16.8 (131)	32.8 (42)	34.5 (59)	53.9 (55)	61.4 (51)	<0.001
Decreased insulin sensitivity[c]	15.5 (121)	31.3 (40)	31.6 (54)	50.0 (51)	57.8 (48)	<0.001
Family history of diabetes	31.7 (247)	39.8 (51)	36.7 (63)	42.6 (43)	59.0 (49)	<0.001
BMI categories (kg/m^2)						
Before pregnancy						<0.001
<24	71.9 (560)	57.8 (74)	63.2 (108)	50.0 (51)	36.1 (30)	
24–27.9	23.2 (181)	29.7 (38)	29.8 (51)	32.4 (33)	38.6 (32)	
≥28	4.88 (38)	12.5 (16)	7.02 (12)	17.6 (18)	25.3 (21)	
At baseline survey						<0.001
<24	63.3 (493)	39.1 (50)	52.6 (90)	30.4 (31)	21.7 (18)	
24–27.9	27.6 (215)	31.3 (40)	29.8 (51)	44.1 (45)	38.6 (32)	
≥28	9.11 (71)	29.7 (38)	17.5 (30)	25.5 (26)	39.8 (33)	
Combined categories						<0.001
<28 both before pregnancy and at baseline survey	89.5 (697)	68.8 (88)	80.7 (138)	72.5 (74)	56.6 (47)	
<28 before pregnancy and ≥28 at baseline survey	5.65 (44)	18.8 (24)	12.3 (21)	9.80 (10)	18.1 (15)	
≥28 before pregnancy and <28 at baseline survey	1.41 (11)	1.56 (2)	1.75 (3)	1.96 (2)	3.61 (3)	
≥28 both before pregnancy and at baseline survey	3.47 (27)	10.9 (14)	5.26 (9)	15.7 (16)	21.7 (18)	

Data are means ± SD or % (n). One-way ANOVA was used to assess the total differences. [a]β-Cell dysfunction is defined as the lower quartile of HOMA-%β. [b]Insulin resistance is defined as the upper quartile of HOMA-IR. [c]Decreased insulin sensitivity is defined as the lower quartile of HOMA-%S.

higher serum glucose and insulin concentrations, and lower levels of education and family income and more often had β-cell dysfunction, insulin resistance, decreased insulin sensitivity, and a family history of diabetes. Women who were diagnosed as having diabetes had the longest time after delivery, the lowest HOMA-%β and HOMA-%S, and the highest HOMA-IR.

β-Cell dysfunction, insulin resistance, and decreased insulin sensitivity all were significantly associated with hyperglycemic status (Table 2). The multivariable-adjusted (model 2) ORs among women with GDM with normal glucose (reference), isolated IGT, isolated IFG, both IGT and IFG, and diabetes 1–5 years postpartum were 1.00, 0.55, 3.64, 2.51, and 7.37 for β-cell dysfunction (*P* for differences < 0.0001); 1.00, 2.58, 2.70, 5.48, and 8.08 for insulin resistance (*P* for differences < 0.0001); and 1.00, 2.62, 2.59, 5.14, and 7.55 for decreased insulin sensitivity (*P* for differences < 0.0001), respectively. After further adjustment for BMI (model 3), these positive associations were still significant and were strengthened for β-cell dysfunction but weakened for decreased insulin sensitivity and insulin resistance. When β-cell dysfunction, decreased insulin sensitivity, and insulin resistance entered a model together (model 4), the associations of hyperglycemic status with β-cell dysfunction and insulin resistance were still significant and became more pronounced, whereas the association of hyperglycemic status with decreased insulin sensitivity was no longer significant.

The associations of β-cell dysfunction and insulin resistance with the risk of diabetes and prediabetes among women with different BMI levels at the baseline survey and before pregnancy are presented in Table 3. We used three categories of BMI before pregnancy and at the baseline survey (normal weight, overweight, and obesity) and three categories of glucose status (normal glucose, prediabetes, and diabetes) in analyses. β-Cell dysfunction and insulin resistance were positively associated with the risks of prediabetes and diabetes in each BMI category (normal weight, overweight, and obesity) (all $P_{trend} < 0.05$). At baseline survey there was an inverse association between β-cell dysfunction and BMI (all $P_{trend} < 0.05$) and a positive association between insulin resistance and BMI (all $P_{trend} < 0.05$) in each glucose category (normal glucose, prediabetes, and diabetes). Compared with those with normal glucose and normal weight, women with GDM who were obese and had normal glucose 1–5 years postpartum had increased β-cell secretory function (OR 0.09 [95% CI 0.02–0.37]) and insulin resistance (OR 17.4 [95% CI 9.47–31.9]); women with GDM who were normal weight and diagnosed as having diabetes 1–5 years postpartum had the largest β-cell dysfunction (OR 13.6 [95% CI 4.06–45.3]); and women with GDM who were obese and diagnosed as having diabetes 1–5 years postpartum displayed the highest insulin resistance (OR 45.8 [95% CI 18.5–113]).

When we used the prepregnancy BMI instead of BMI at the baseline survey, the associations of β-cell dysfunction and insulin resistance with the risks of postpartum diabetes and prediabetes were almost the same among women with GDM with different levels of prepregnancy BMI compared with those with different levels of BMI at the baseline survey 1–5 years postpartum (Table 3).

When we assessed the associations of β-cell dysfunction and insulin resistance with the risks of diabetes and prediabetes among women with changes in BMI from before pregnancy to the baseline survey of the current study (1–5 years postpartum), women were divided into four groups: nonobese (BMI <28 kg/m^2) both before pregnancy and postpartum (baseline survey), nonobese before pregnancy and obese postpartum (BMI ≥ 28 kg/m^2), obese before pregnancy and nonobese postpartum, and obese both before pregnancy and

Table 2—Standardized polytomous logistic regression estimates for ORs of each glucose status group

	ORs (95% CIs)					
	Normal glucose (*n* = 779)	Isolated IGT (*n* = 128)	Isolated IFG (*n* = 171)	IGT and IFG (*n* = 102)	Diabetes (*n* = 83)	*P* for difference
β-Cell dysfunction[a]						
Model 1	1.00	0.54 (0.30–0.97)	3.46 (2.43–4.93)	2.22 (1.42–3.49)	6.37 (3.96–10.2)	<0.0001
Model 2	1.00	0.55 (0.30–0.98)	3.64 (2.54–5.22)	2.51 (1.58–4.00)	7.37 (4.43–12.2)	<0.0001
Model 3	1.00	0.83 (0.45–1.52)	5.04 (3.42–7.41)	4.54 (2.72–7.57)	19.0 (10.3–35.0)	<0.0001
Model 4	1.00	0.86 (0.46–1.59)	7.66 (4.96–11.8)	9.85 (5.29–18.3)	110 (43.2–279)	<0.0001
Insulin resistance[b]						
Model 1	1.00	2.44 (1.61–3.69)	2.64 (1.83–3.81)	5.85 (3.79–9.03)	8.05 (4.97–13.0)	<0.0001
Model 2	1.00	2.58 (1.69–3.93)	2.70 (1.86–3.94)	5.48 (3.51–8.57)	8.08 (4.87–13.4)	<0.0001
Model 3	1.00	1.36 (0.86–2.17)	2.17 (1.43–3.28)	3.37 (2.06–5.50)	4.20 (2.42–7.28)	<0.0001
Model 4	1.00	1.26 (0.26–6.22)	5.61 (1.74–18.1)	10.0 (2.69–37.6)	26.6 (3.95–180)	0.0004
Decreased insulin sensitivity[c]						
Model 1	1.00	2.50 (1.64–3.82)	2.55 (1.75–3.72)	5.53 (3.57–8.54)	7.69 (4.76–12.4)	<0.0001
Model 2	1.00	2.62 (1.70–4.02)	2.59 (1.76–3.80)	5.14 (3.28–8.05)	7.55 (4.56–12.5)	<0.0001
Model 3	1.00	1.37 (0.85–2.20)	2.04 (1.34–3.12)	3.07 (1.87–5.04)	3.90 (2.25–6.75)	<0.0001
Model 4	1.00	1.11 (0.22–5.59)	0.75 (0.23–2.42)	0.72 (0.20–2.63)	1.46 (0.23–9.20)	0.9282

Model 1 was adjusted for age. Model 2 was adjusted for age, time postpartum, sitting time, dietary fiber, and monounsaturated fat, polyunsaturated fat, and saturated fat intake (continuous variables for above all variables) and education, family history of diabetes, smoking, passive smoking, alcohol drinking, and leisure-time physical activity (categorical variables for above all variables). Model 3 was adjusted for variables in model 2 and for BMI. Model 4 was adjusted for variables in model 3 and for decreased insulin sensitivity and insulin resistance (in β-cell dysfunction analysis), β-cell dysfunction and decreased insulin sensitivity (in insulin resistance analysis), and β-cell dysfunction and insulin resistance (in decreased insulin sensitivity analysis). [a]β-Cell dysfunction is defined as the lower quartile of HOMA-%β. [b]Insulin resistance is defined as the upper quartile of HOMA-IR. [c]Decreased insulin sensitivity is defined as the lower quartile of HOMA-%S.

Table 3—Standardized polytomous logistic regression estimates for ORs of each glucose status with β-cell dysfunction and insulin resistance considering categories of BMI at the baseline survey and before pregnancy

	ORs (95% CIs)			
	Normal glucose (n = 779)	Prediabetes (IGT and/or IFG) (n = 401)	Diabetes (n = 83)	P_{trend}[a]
BMI at baseline survey (kg/m^2)				
β-Cell dysfunction[b]				
<24	1.00	3.23 (2.22–4.68)	13.6 (4.06–45.3)	<0.001
24–27.9	0.35 (0.21–0.58)	0.90 (0.56–1.44)	5.30 (2.42–11.6)	<0.001
≥28	0.09 (0.02–0.37)	0.31 (0.15–0.65)	3.02 (1.42–6.44)	<0.001
P_{trend}[c]	<0.001	<0.001	0.031	
Insulin resistance[b]				
<24	1.00	2.75 (1.58–4.77)	7.78 (2.61–23.2)	<0.001
24–27.9	5.44 (3.39–8.75)	13.6 (8.19–22.6)	26.0 (11.2–60.4)	<0.001
≥28	17.4 (9.47–31.9)	31.1 (17.5–55.4)	45.8 (18.5–113)	0.035
P_{trend}[c]	<0.001	<0.001	0.010	
BMI before pregnancy (kg/m^2)				
β-Cell dysfunction[b]				
<24	1.00	2.42 (1.73–3.40)	8.81 (3.83–20.3)	<0.001
24–27.9	0.43 (0.26–0.73)	0.90 (0.54–1.48)	5.30 (2.44–11.5)	<0.001
≥28	0.41 (0.14–1.19)	0.85 (0.39–1.85)	4.23 (1.70–10.5)	0.006
P_{trend}[c]	0.003	<0.001	0.078	
Insulin resistance[b]				
<24	1.00	2.70 (1.80–4.04)	7.07 (3.18–15.7)	<0.001
24–27.9	2.86 (1.86–4.39)	11.6 (7.29–18.3)	19.3 (8.30–44.8)	<0.001
≥28	7.50 (3.69–15.2)	10.7 (5.52–20.8)	21.6 (7.86–59.5)	0.103
P_{trend}[c]	<0.001	<0.001	0.067	

The number of subjects in each group is presented in Table 1. Adjusted for age, time postpartum, sitting time, dietary fiber, and monounsaturated fat, polyunsaturated fat, and saturated fat intake (continuous variables for above all variables) and education, family history of diabetes, smoking, passive smoking, drinking alcohol, and leisure-time physical activity (categorical variables for above all variables). [a]Testing trend for differences from normal glucose to prediabetes to diabetes in each BMI category. [b]β-Cell dysfunction is defined as the lower quartile of HOMA-%β, and insulin resistance is defined as the upper quartile of HOMA-IR. [c]Testing trend for differences from BMI <24 to 24–27.9 to ≥28 kg/m^2 in each glucose category.

postpartum (Table 4). β-Cell dysfunction and insulin resistance were positively associated with the risks of prediabetes and diabetes among women within each of the four groups, with only a few exceptions due to the small sample size in several groups. Compared with women who had normal glucose at the baseline survey and were nonobese both before pregnancy and postpartum, women who had normal glucose at the baseline survey and were nonobese before pregnancy and obese postpartum and women who had normal glucose at the baseline survey and were obese both before pregnancy and postpartum had increased β-cell secretory function and insulin resistance; women who were diagnosed as having diabetes at the baseline survey and were nonobese both before pregnancy and postpartum had the largest β-cell dysfunction (OR 9.58 [95% CI 4.84–19.0]), and women who were diagnosed as having diabetes at the baseline survey and were nonobese before pregnancy and obese postpartum had the highest insulin resistance (OR 26.7 [95% CI 6.88–104]).

CONCLUSIONS

This study found that, among women with a history of GDM 1–5 years postpartum, β-cell dysfunction, insulin resistance, and decreased insulin sensitivity all were significantly associated with the risks of prediabetes and diabetes, and these associations were observed among women who were normal weight, overweight, and obese. There was an inverse association between β-cell dysfunction and BMI and a positive association between insulin resistance and BMI across all glucose categories. β-Cell dysfunction had more pronounced contribution to diabetes risk among normal weight subjects, whereas insulin resistance contributed more to postpartum hyperglycemia among obese subjects.

Previous studies researched the etiology of diabetes risk among obese and nonobese individuals. Several studies suggested that in white people, obese diabetic patients displayed peripheral insulin resistance in combination with β-cell dysfunction, whereas nonobese diabetic patients showed only a secretory defect (6). It has been shown that Asians and Asian Americans are more likely to develop GDM and diabetes, although they generally have lower BMI levels than whites (7,9). Two good explanations might be that Asians have higher adiposity per unit BMI (22) and have decreased insulin sensitivity and especially increased β-cell dysfunction compared with whites (10). Therefore, the etiology of diabetes risk among obese and nonobese Asians is different from that in white people. Some studies suggested that a loss of β-cell secretory function occurred before the development of obesity-induced insulin resistance among Japanese and Japanese Americans (23), and β-cell dysfunction may play a relatively more important role in the development of diabetes among both nonobese and obese subjects in Asian populations (24,25).

The current study, focusing on Chinese women living in mainland China who have a history of GDM, shows results different from previous results of studies of the general population. For normal weight women with GDM, the

Table 4—Standardized polytomous logistic regression estimates for ORs of each glucose status with β-cell dysfunction and insulin resistance considering changes in BMI (kg/m^2) from prepregnancy to baseline survey of the current study (1–5 years postpartum)

	ORs (95% CIs)			
	Normal glucose (n = 779)	Prediabetes (IGT and/or IFG) (n = 401)	Diabetes (n = 83)	P_{trend}[a]
β-Cell dysfunction[b]				
BMI <28 both before pregnancy and at baseline survey	1.00	2.55 (1.88–3.46)	9.58 (4.84–19.0)	<0.001
BMI <28 before pregnancy and ≥28 at baseline survey	0.10 (0.01–0.74)	0.15 (0.03–0.61)	4.31 (1.33–14.0)	<0.001
BMI ≥28 before pregnancy and <28 at baseline survey	1.34 (0.33–5.54)	1.42 (0.25–8.17)	4.66 (0.27–80.9)	0.970
BMI ≥28 both before pregnancy and baseline survey	0.14 (0.02–1.05)	0.84 (0.35–1.98)	4.02 (1.52–10.6)	0.002
Insulin resistance[c]				
BMI <28 both before pregnancy and at baseline survey	1.00	2.83 (2.01–3.97)	7.14 (3.72–13.7)	<0.001
BMI <28 before pregnancy and ≥28 at baseline survey	5.91 (3.06–11.4)	19.6 (10.1–38.1)	26.7 (6.88–104)	0.040
BMI ≥28 before pregnancy and <28 at baseline survey	0.61 (0.08–4.97)	6.38 (1.28–31.8)	12.7 (0.72–224)	0.982
BMI ≥28 both before pregnancy and at baseline survey	13.8 (5.91–32.1)	9.86 (4.91–19.8)	18.7 (6.36–55.2)	0.630

The number of subjects in each group is presented in Table 1. Adjusted for age, time postpartum, sitting time, dietary fiber, and monounsaturated fat, polyunsaturated fat, and saturated fat intake (continuous variables for above all variables) and education, family history of diabetes, smoking, passive smoking, drinking alcohol, and leisure-time physical activity (categorical variables for above all variables). [a]Testing trend for differences from normal glucose to prediabetes to diabetes in each BMI category. [b]β-Cell dysfunction is defined as the lower quartile of HOMA-%β. [c]Insulin resistance is defined as the upper quartile of HOMA-IR.

worsening from normal glucose to prediabetes or diabetes 1–5 years postpartum was associated with both β-cell dysfunction and insulin resistance; however, normal weight women with GDM who developed diabetes 1–5 years postpartum showed the most β-cell dysfunction compared with overweight and obese women with GDM. Thus we assumed that β-cell dysfunction and insulin resistance were two major risk factors for the development of diabetes among normal weight Chinese women with GDM postpartum, but the effect of β-cell dysfunction seemed more important than the effect of insulin resistance. This finding was similar to that of studies conducted in the Asian general population (23–25).

For overweight or obese women with GDM who were diagnosed as having normal glucose 1–5 years postpartum, higher BMI might initially induce insulin resistance and an increase in β-cell secretory function. When an increase in β-cell secretory function can compensate for insulin resistance, obese women with GDM might maintain normal glucose or a slightly IGT. However, when the obesity-induced insulin resistance becomes worse and the increase in β-cell secretory function cannot produce the amount of hormone necessary to compensate for insulin resistance, hyperglycemia develops. This result revealed that insulin resistance might be the predominant determinant for overweight or obese diabetes, and the pattern was in consonance with numerous previous investigations of whites, which had been reviewed in detail (26,27). Thus we supposed that the effect of insulin resistance was a major risk factor for the development of diabetes among obese women with GDM postpartum.

This study also suggested for the first time that among Chinese women with a history of GDM, diabetic women who were nonobese both before pregnancy and 1–5 years postpartum had the most β-cell dysfunction, and diabetic women who were nonobese before pregnancy but obese 1–5 years postpartum had the highest insulin resistance compared with women with GDM who had normal glucose 1–5 years postpartum and were nonobese both before pregnancy and 1–5 years postpartum. This finding supported the main results that, among Chinese women with prior GDM, β-cell dysfunction made a more pronounced contribution to diabetes risk among normal weight subjects, whereas insulin resistance contributed more to postpartum hyperglycemia among obese subjects.

In the past, treatment of the typical clinical course of diabetes consisted of the sequential addition of antidiabetic drugs over time, followed ultimately by insulin therapy when functional β-cell capacity deteriorates to the point at which glycemic control can no longer be achieved without exogenous insulin supplementation. However, since residual insulin secretion not only contributes to stable glycemic control but also inhibits the occurrence of diabetes complications, the potential best therapeutic option for women with a history of GDM when they are newly diagnosed with diabetes early after delivery should aim not only to obtain good serum glucose concentration but also to better preserve residual β-cell secretory function. A recent meta-analysis concluded that 2–3 weeks of intensive insulin therapy for newly diagnosed patients can induce a so-called glycemic remission, reduce insulin resistance, and improve β-cell secretory function, whereby patients are subsequently able to maintain normal glucose concentrations without any antidiabetic medication

(28). Thus insulin therapy could be suggested as the first-line therapy for those women with GDM who are newly diagnosed with diabetes postpartum, especially for patients with normal weight, who have the most β-cell dysfunction.

There were several limitations to this study. First, the participation rate was only 27% (1,263/4,644). Although there were no differences in age, 2-h glucose, fasting glucose, and the prevalence of IGT and diabetes at 26–30 weeks' gestation (based on OGTT) between those returned and those not returned, whether there was a difference between the postpartum outcomes cannot be verified. Second, because this was a cross-sectional study, the design does not allow us to look at temporal relationships of β-cell dysfunction and insulin resistance with prediabetes and diabetes risks. Third, HOMA models were used to estimate insulin sensitivity and β-cell secretory function in this study, and these have been widely used in clinical and epidemiological studies (29). However, using fasting values for estimation, HOMA mostly describes hepatic insulin resistance and steady-state insulin secretion. Although hepatic insulin resistance is strongly correlated with muscle and fat insulin resistance, steady-state insulin secretion is a late marker of β-cell dysfunction and shows only a moderate correlation with the most sensitive measures of the first phase of insulin secretion (29,30). Thus, the results of this study should be confirmed in other longitudinal studies as well as by more sophisticated methods, such as the glucose clamp technique or intravenous glucose tolerance test. Despite these limitations, this study is the first large population-based study of Chinese subjects focusing on the etiology of obese and nonobese diabetes among women with a history of GDM.

In conclusion, among Chinese women with a history of GDM postpartum, both nonobese and obese diabetic women displayed β-cell dysfunction and insulin resistance. β-Cell dysfunction made a more pronounced contribution to diabetes risk among normal weight subjects, whereas insulin resistance might be the initial attribution of hyperglycemia among overweight and obese subjects.

Funding. This study was supported by grants from the European Foundation for the Study of Diabetes (EFSD)/Chinese Diabetes Society (CDS)/Lilly Programme for Collaborative Research between China and Europe, Tianjin Women's and Children's Health Center, and Tianjin Public Health Bureau.

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

Author Contributions. W.L., S.Z., H.L., L.W., C.Z., and J.L. researched data. W.L. wrote the manuscript. Z.Y., X.Y., H.T., and G.H. reviewed and revised the manuscript. G.H. 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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