Grand Multiparity Is Associated With Type 2 Diabetes in Filipino American Women, Independent of Visceral Fat and Adiponectin

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OBJECTIVE — To determine whether multiparity is associated with type 2 diabetes, independent of visceral adipose tissue (VAT) and adipokines.

RESEARCH DESIGN AND METHODS — Participants were from the University of California San Diego Filipino Women's Health Study with at least one live birth. A 2-h 75-g oral glucose tolerance test was administered; adiponectin, leptin, ghrelin, reproductive history, family history of diabetes, VAT, and lifestyle behaviors were measured between 1995 and 2002.

RESULTS — Among 152 women, mean age was 59.5 years (range 48–73 years) and mean parity was 4.3 (range 1–12 births). Type 2 diabetes prevalence increased by parity group (low parity, 1–2 births, 25%; medium parity, 3–5 births, 30.3%; and grand multiparity: 6–12 births, 50%; $P = 0.048$). Family history of diabetes, exercise, insulin resistance, and leptin and ghrelin levels did not differ by parity group. Compared with women in the low parity group, women with ≥6 births were significantly older (62 vs. 57 years), had lower college completion (22 vs. 58%, $P = 0.006$), more hypertension (72 vs. 55%), higher VAT (74.9 vs. 58.4 cm^3), and lower adiponectin concentration (5.79 vs. 7.61 μg/ml). In multivariate analysis adjusting for adiponectin, VAT, family history of diabetes, age, education, hypertension, and estrogen use, grand multiparous women had a threefold higher odds of type 2 diabetes (adjusted odds ratio 3.40 [95% CI 1.13–10.2]) compared with low parity women. No differences were observed in the odds of diabetes between women in the medium (1.10 [0.41–2.91]) and low parity groups.

CONCLUSIONS — Having ≥6 children was associated with type 2 diabetes, independent of adiponectin, VAT, family history, and other measured diabetes risk factors.

Diabetes Care **33:385–389, 2010**

Prior studies have reported elevated type 2 diabetes prevalence among multiparous women (1–5); however, the elevated risk has been attributed to postpartum weight retention (1,2). Other studies have shown that the excess diabetes risk in multiparous women persisted after adjustment for anthropometric factors (3–5) as well as lifestyle, reproductive, and inflammatory factors (3,4).

Visceral adipose tissue (VAT) is an active endocrine organ and is an important determinant of type 2 diabetes. Estimates of obesity including BMI, waist girth, waist-to-hip ratio, and truncal fat by dual energy x-ray absorptiometry do not distinguish VAT from subcutaneous adipose tissue (SAT), whereas computed tomography provides a direct estimate of VAT and SAT. Excess VAT accumulation contributes to changes in the production or action of adipocytokines, including adiponectin, resistin, leptin, tumor necrosis factor-α, and C-reactive protein (6). Adiponectin, an adipocyte-secreted protein with insulin-sensitizing effects, is inversely associated with VAT, and low levels are predictive of type 2 diabetes even among populations without generalized obesity, such as Japanese and Asian Indians (7–10). Leptin regulates appetite control and energy metabolism, is strongly correlated with obesity, and may play a major role in islet cell growth and insulin secretion (11,12). Ghrelin, a peptide hormone secreted by the stomach, regulates hunger and long-term weight gain or loss and is thought to play a role in glucose homeostasis and insulin resistance (13). Plasma ghrelin concentrations are lower in persons with obesity, hypertension, and type 2 diabetes (14,15).

Prior studies have reported VAT increases with higher parity, independent of percent body fat among women without diabetes, endocrine disorders, or cardiovascular disease (16), but whether VAT or adipocyte-derived proteins mediate the association between multiparity and type 2 diabetes has not been evaluated.

Filipinos in the Philippines, Hawaii, and California have an elevated prevalence of type 2 diabetes, despite the absence of general obesity (17–19). In addition, Filipino American women in San Diego had excess VAT despite having BMI, waist girth, and percent total body and truncal fat similar to those of Caucasian women, and significantly lower anthropometric markers than African American women (20). Type 2 diabetes prevalence was 32.1% among Filipinas compared with 5.8% among Caucasian women with similar BMI, waist girth and percentage of truncal fat; when limited to women in the lowest VAT category, the excess diabetes prevalence among Filipinas (22.8%) persisted compared with that in Caucasian (1.7%) and African American women (12.1%) (20). Among normoglycemic women, Filipinas had significantly lower concentrations of adiponectin and ghrelin compared with those in normoglycemic Caucasian women, even after adjustment for anthropometric markers and insulin resistance (21).

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Received 7 August 2009 and accepted 4 November 2009. Published ahead of print at http://care.diabetesjournals.org on 16 November 2009. DOI: 10.2337/dc09-1477.

Multiparity has been associated with type 2 diabetes, primarily though postpartum weight retention; however, the association with VAT and adipokines has not been elucidated, particularly in nonobese, highly parous populations. The objective of this study was to determine whether multiparity is associated with type 2 diabetes, independent of visceral fat, adipokines, and other measured diabetes risk factors.

RESEARCH DESIGN AND METHODS

— The Rancho Bernardo Study, a San Diego community-based longitudinal study of multiple health outcomes since 1972, includes participants who are predominantly non-Hispanic Caucasians. Between 1995 and 1999, an ethnic comparison cohort of Filipino women was enrolled (19). Population-based sampling was not possible because Filipinos were not identified separately from Asians in the 1990 census; consequently, a convenience sample was recruited, as described elsewhere (19). Clinical evaluations were performed at the University of California San Diego Rancho Bernardo Clinic between 1995 and 1999. Participants without known cardiovascular disease (by history, electrocardiogram abnormalities, or angina pectoris by Rose questionnaire) or coronary revascularization surgery were invited between 2001 and 2002 to measure coronary artery calcium as well as VAT and SAT. The study was approved by the University of California San Diego Human Research Protections Program, and all women provided written informed consent.

Clinical evaluation

Demographic characteristics, lifestyle (cigarette smoking, alcohol use, and physical activity), physician-diagnosed conditions, and menopausal status were determined using structured questionnaires. Reproductive history was assessed by a self-administered questionnaire. Participants who were using prescription or nonprescription medications in the month before the clinic visit brought pills and prescriptions to the clinic to be verified and recorded by a nurse. None of the participants were taking thiazolidinediones, which have been shown to alter adiponectin concentration.

Height and weight were measured in participants wearing lightweight clothing without shoes. BMI (weight in kilograms divided by the square of height in meters) was computed as an estimate of general obesity. Waist circumference was measured at the natural bending point; hip circumference was measured at the iliac crest. VAT and SAT were measured by electron beam computed tomography (Imatron C-150 scanner; GE Healthcare) with three slices between L4 and L5.

A 75-g oral glucose tolerance test was administered after a minimum 8-h overnight fast; blood samples were obtained by venipuncture at 0 and 2 h. Plasma glucose was measured by the glucose oxidase method, and insulin was determined by radioimmunoassay in a diabetes research laboratory. Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) and β-cell function (HOMA-β). Type 2 diabetes was defined using the 1999 World Health Organization criteria: fasting plasma glucose level ≥126 mg/dl, or 2-h postchallenge glucose level ≥200 mg/dl, or a history of type 2 diabetes diagnosed by a physician, or treatment with an oral hypoglycemic agent or insulin. Two morning blood pressure readings were recorded with a mercury sphygmomanometer using the Hypertension Detection and Follow-up Program protocol. Hypertension was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mmHg or use of antihypertensive medication. Fasting adiponectin, leptin, and ghrelin concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO) in 2004 using archived samples that had been stored frozen at −70°C and not previously thawed.

Statistical analysis

Nulliparous women were excluded to exclude those who might have had polycystic ovary disease, a known risk factor for diabetes. Parity, defined as live births, was analyzed as a continuous variable and further classified into low parity (1–2 births), medium parity (3–5 births), and grand multiparity (6–12 births) groups. Data were analyzed using SAS (version 9.1, SAS Institute, Cary, NC). Analysis of variance, general linear models, and χ^2 tests were used for descriptive statistics. General linear models were used to compare mean levels of each anthropometric marker, while adjusting for age and diabetes. The distributions of adiponectin, leptin, and ghrelin were skewed and consequently were log-transformed for statistical analysis; geometric mean levels of these proteins are reported. Univariate analysis was performed to identify covariates associated with diabetes. Multivariable logistic regression was performed to identify covariates associated with type 2 diabetes and to compare the odds of type 2 diabetes by parity category, using the low parity category as the referent group. Covariates included in the multivariable models consisted of variables that differed by parity group and those associated with diabetes in univariate analysis. Statistical significance was designated at $P < 0.05$ and 95% confidence intervals that excluded 1.

RESULTS

— The study population included 152 parous Filipino American women with a mean age of 59.5 years (range 48–73 years); the majority were immigrants (99%), were well educated (44% were college graduates), and engaged in healthy behaviors. Only 14% had ever smoked, 1% had ≥3 alcoholic drinks per week, and 71% reported exercising at least three times per week. Mean BMI was 25.4 kg/m^2 and mean waist girth was 81.4 cm, and one-third (33.6%) had type 2 diabetes. One fourth ($n = 39$, 25.7%) had at least one biological parent with type 2 diabetes; of these, 18 had both a biological parent and sibling with type 2 diabetes. An additional 14 women (9.2%) had a sibling (diagnosed after age 45) with type 2 diabetes but did not have an affected biological parent, for a total of 34.9% who had a family history of type 2 diabetes. The number of live births ranged from 1 to 12 births (mean 4.3 live births), and one-fourth had grand multiparity (≥6 live births; mean 8.1 births).

When stratified by parity group, mean age increased with increasing parity, where women with ≥6 children were significantly older (mean age 62.4 years compared with 57.1 years for those who bore one or two children ($P < 0.001$) (Table 1). Women with grand multiparity had lower college completion and estrogen use (22.2% and 2.8%, respectively) compared with women with medium (47.4% completed college and 26.3% used estrogen) or low parity (57.5% and 32.5%). Grand multiparous women had significantly higher fasting and 2-h glucose levels; however, fasting and 2-h insulin levels, HOMA-IR, and HOMA-β levels, family history of type 2 diabetes, and exercise (≥3 times/week) frequency did not vary by parity category (Table 1). The prevalence of hypertension and type 2 diabetes increased significantly by parity category; diabetes prevalence was 25% in the low parity group, 30.3% in the me-

Table 1—*Age-adjusted demographic and clinical characteristics, by parity category, Filipino American women, San Diego, California, 1995–2002*

	Number of live births			
	1–2	3–5	6–12	*P* value
n	40	76	36	
Age (years)	57.1	59.5	62.4	0.001
College graduate (%)	57.5	47.4	22.2	0.006
Family history diabetes (%)	40.0	35.5	27.8	0.528
Exercise (≥3 times/week, %)	70.0	72.4	69.4	0.940
Estrogen use (current, %)	32.5	26.3	2.8	0.004
Fasting glucose (mmol/l)	5.41	5.93	6.79	0.046
2-h glucose (mmol/l)	8.69	10.09	12.09	0.029
Fasting insulin (pmol/l)	80.94	74.59	76.24	0.947
2-h insulin (pmol/l)	435.63	576.36	542.39	0.157
HOMA-IR	2.98	3.03	3.25	0.929
HOMA-β index	119.71	113.27	96.85	0.438
Hypertension (%)	55.0	64.5	72.2	0.029
Type 2 diabetes (%)	25.0	30.3	50.0	0.048

Data are means or frequency distribution.

dium parity group, and 50% among women with ≥6 births ($P = 0.048$).

Age-adjusted mean BMI, waist girth, and VAT were significantly lower in women in the low parity group compared with women in either the medium parity or grand multiparity group, but did not differ between the medium parity and grand multiparity group (Table 2). Waist-to-hip ratio was significantly smaller in women with one to two children than in those with ≥6 children but did not differ from that for the medium parity group. Subcutaneous fat was significantly lower in the low parity group than in women with three to five children but did not differ from that in grand multiparous women. Adiponectin was inversely associated with obesity and was significantly lower in the medium parity and grand multiparity groups than that in women with lower parity. Age-adjusted ghrelin and leptin levels did not differ by parity category.

These observations persisted after adjustment for both age and diabetes with the exception of BMI and adiponectin. BMI did not differ by parity group after adjustment for age and diabetes, whereas adiponectin was significantly lower in the medium parity group but did not differ between the low parity and grand multiparity categories. Neither ghrelin nor leptin levels varied by parity category after adjustment for age and diabetes.

Stepwise logistic regression showed that parity (adjusted odds ratio [OR] 1.27 [95% CI 1.09–1.49], $P = 0.0027$) was independently associated with type 2 diabetes after adjustment for adiponectin concentration, VAT, family history of type 2 diabetes, hypertension, age, current estrogen use, and education (Table 3, model 1). Furthermore, family history of diabetes (5.03 [2.18 −11.60]), hypertension (3.16 [1.33–7.55]), and low adiponectin (log) levels (0.45 [0.22–0.94]) were also independently associated with type 2 diabetes. Age, visceral adiposity, education, and estrogen use were not associated with type 2 diabetes. These observations persisted when women were categorized by parity group. Compared with women in the low parity group, women who had ≥6 live births had a threefold higher odds (3.40 [1.13–10.2]) of having type 2 diabetes, independent of adiponectin concentration, VAT, family history of type 2 diabetes, hypertension, age, estrogen use, and education (Table 3, model 2). Similarly, family history of type 2 diabetes, hypertension, and low adiponectin concentration were independently associated with type 2 diabetes. Women in the medium parity group did not have an increased risk of type 2 diabetes (1.10 [0.41–2.91]) compared with women in the low parity group after adjustment for the above covariates. Neither ghrelin nor leptin was associated with type 2 diabetes in multivariable models that included these proteins (data not shown).

Family history of diabetes was an important correlate of type 2 diabetes; however, neither mean adiponectin, BMI, waist, nor VAT differed among those with versus those without a family history of diabetes.

Table 2—*Anthropometric characteristics, adjusted for age and type 2 diabetes, by parity category, Filipino American women, San Diego, California*

	Number of live births		
	1–2	3–5	6–12
n	40	76	36
BMI (kg/m^2)	24.55	25.71	25.85
Waist circumference (cm)	78.34	82.89*	83.04†
Waist-to-hip ratio	0.823	0.837	0.859†
VAT (cm^3)	59.39	72.12*	73.19†
SAT (cm^3)	140.73	163.03*	158.94
Adiponectin (μg/ml)	7.45	5.67*	6.02
Ghrelin (pg/ml)	1,072.0	1,084.7	1,039.6
Leptin (ng/ml)	12.38	14.72	13.63

Data are means. *$P < 0.05$, 3–5 vs. 1–2 live births. †$P < 0.05$, 6–12 vs. 1–2 live births.

Table 3—*Stepwise logistic regression: covariates associated with type 2 diabetes among parous Filipino American women*

Covariate	Adjusted OR (95% CI)	*P* value
Model 1		
Parity	1.27 (1.09–1.49)	0.0027
Adiponectin (log)	0.45 (0.22–0.94)	0.0335
Family history of diabetes	5.03 (2.18–11.6)	0.0001
Hypertension	3.16 (1.33–7.55)	0.0095
Model 2		
≥6 live births	3.40 (1.13–10.2)	0.0295
Adiponectin (log)	0.42 (0.20–0.89)	0.0234
Family history of diabetes	4.35 (1.95–9.73)	0.0003
Hypertension	2.99 (1.26–7.07)	0.0128

Data are adjusted for age, education, estrogen use, and VAT. Model 1: parity as a continuous variable; model 2: by parity category, with low parity (1–2 births) as the referent group.

When limited to the 99 women without a family history of type 2 diabetes, parity remained independently associated with type 2 diabetes (adjusted OR 1.22 [95% CI 1.03–1.44], $P = 0.021$) after adjustment for adiponectin, VAT, age, education, estrogen use, and hypertension.

CONCLUSIONS — This highly parous cohort of nonobese Filipino American women with elevated diabetes prevalence offered a unique opportunity to assess the association between multiparity and type 2 diabetes. Prior studies have identified postpartum weight retention as the primary mechanism for type 2 diabetes in multiparous women (1,2); however, to our knowledge, no studies have included computed tomography–defined VAT measures, adipokines, or ghrelin. Although anthropometric markers, including VAT, increased with parity, visceral adiposity did not explain the excess diabetes prevalence among grand multiparous women. Low adiponectin concentration and hypertension were independently associated with type 2 diabetes, as was family history of diabetes, reinforcing the important contribution of genetic factors; however, the excess diabetes prevalence in grand multiparous women persisted when the analysis was limited to those without a family history of type 2 diabetes.

Physical inactivity did not differ by parity group, contrary to other observations. Our observations of decreasing education and estrogen use with increasing parity is consistent with prior studies (3), but neither was independently associated with type 2 diabetes. However, this cohort was highly educated, and almost half were college graduates, including 22% of grand multiparous women. Consequently, we were unable to observe the confounding effects of education and socioeconomic status on lifestyle behaviors and diabetes risk associated with higher parity in prior studies (5).

Pregnancy is a diabetogenic state characterized by adipose tissue accretion, hyperinsulinemia, insulin resistance, lipolysis, elevated leptin and resistin levels, and reduced adiponectin secretion (22). Multiple pregnancies result in longer cumulative exposure to insulin resistance and hypoadiponectinemia. It remains unclear whether these conditions are sustained or exacerbated postpartum through middle-age. Low adiponectin was independently associated with type 2 diabetes in this analysis, and levels were significantly lower in multiparous women, but neither insulin resistance (by HOMA-IR) nor leptin concentration differed by parity group.

Gestational diabetes mellitus (GDM) is a risk factor for future incident type 2 diabetes (23), but GDM history was not ascertained in this study because the majority (88%) of women gave birth before 1979, when GDM became a clinically recognized entity. Despite the general absence of preconceptional obesity, Filipino American parturients have the third highest GDM prevalence (7.1%) in the U.S., following Asian Indians (8.6%) and Pacific Islanders (7.4%), and have higher GDM prevalence than Native American, Caucasian, African American, or Hispanic parturients (24). Women in our cohort might have had a similarly elevated prevalence of GDM during multiple pregnancies, consequently exacerbating their risk for type 2 diabetes.

Study limitations included enrollment of a volunteer sample because census data during study enrollment reported Asian-American nationalities collectively, such that population-based sampling of Filipinos was not possible. However, college completion in our cohort was identical to that in the 2000 national census data for all Filipino American women aged ≥25 years; suggesting that our sample was generalizable to all Filipino American women with regard to socioeconomic status. Additional considerations include the small sample sizes when stratified into parity categories, as reflected by the wide CIs in multivariable regression analysis. Total adiponectin, rather than the different isomers of adiponectin, was measured; the high-molecular-weight form of adiponectin is substantially reduced in GDM (25), although it remains unclear whether high-molecular-weight adiponectin accounts for the elevated diabetes risk in grand multiparity. Furthermore, we did not include fetal losses, where long gestations that terminated spontaneously or as stillbirths contributed to the cumulative diabetogenic exposure during pregnancy. Finally, the generalizability of our findings to other highly parous populations is questionable, given the elevated prevalence of type 2 diabetes, GDM, family history of type 2 diabetes, excess VAT accumulation, and low adiponectin concentration among Filipino American women (20,21,24).

The strengths of this study include use of a cohort of highly parous women of whom one-third had type 2 diabetes and one-fourth had grand multiparity. Use of computed tomography–defined VAT allows more precise enumeration of intra-abdominal obesity compared with estimates provided by BMI or waist in prior studies. To our knowledge, this is the first study to assess the role of adiponectin, leptin, and ghrelin as mechanisms for the association between multiparity and diabetes. None of the women were using thiazolidinediones, which enabled comparisons by parity group without the confounding effects of medications that can alter adiponectin or ghrelin levels.

In summary, grand multiparity was associated with type 2 diabetes, independent of visceral adiposity and adiponectin concentration. Hypertension, family history of diabetes and low adiponectin levels were also associated with type 2 diabetes but did not explain the excess diabetes prevalence in grand multiparous women. Grand multiparity may exacerbate diabetes risk through myriad mechanisms that have yet to be identified.

Acknowledgments — This work was supported by the American Heart Association (0070088Y) and by the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01-DK-31801and R03-DK-60575).

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

Parts of this study were presented in abstract form at the 68th Scientific Sessions of the American Diabetes Association, Chicago, Illinois, 22–26 June 2007.

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