Low Serum Levels of High–Molecular Weight Adiponectin in Indo-Asian Women During Pregnancy

Evidence of ethnic variation in adiponectin isoform distribution

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Indo-Asian ethnicity is associated with an increased risk of type 2 diabetes and cardiovascular disease (CVD) that is not reconciled by conventional risk factors (1,2). In a recent study (3), we found that pregnant Indo-Asian women exhibited strikingly low serum levels of adiponectin, a protein with putative insulin-sensitizing and antiatherogenic activity. Hypoadiponectinemia has since been demonstrated in both Indo-Asian male and nonpregnant female subjects (4–6). Thus, hypoadiponectinemia may be a generalized phenomenon in people of Indo-Asian descent that could contribute to their increased risk of type 2 diabetes and CVD.

It has recently emerged that adiponectin circulates in oligomeric complexes, with its high–molecular weight (HMW) isoform mediating insulin-sensitizing and vasculature-protective effects (7,8). Accordingly, Scherer and colleagues (7) have proposed the ratio of the HMW isoform to total adiponectin (S_A) (expressed as a percentage) as a measure of the biological activity of adiponectin. Given the risk of type 2 diabetes and CVD in Indo-Asians, we hypothesized that hypoadiponectinemia in this ethnic group may reflect selective deficiency of the HMW isoform (i.e., low S_A). Therefore, to test this hypothesis, we sought to assess the relationship between S_A and ethnicity within our earlier study of pregnant women.

RESEARCH DESIGN AND METHODS

— Study protocol and methods have been described previously (9,10). The research ethics board at Mount Sinai Hospital approved the protocol, and all participants gave written informed consent. Briefly, participants consisted of 180 healthy pregnant women attending outpatient obstetrics clinics, who had been referred for a 3-h, 100-g oral glucose tolerance test (OGTT) following an abnormal result on a screening 50-g glucose challenge (plasma glucose ≥7.8 mmol/l at 1-h postchallenge). Demographic/historical information was obtained by the interviewer-administered questionnaire at the OGTT. Indo-Asians were defined as having ancestry from India, Pakistan, Sri Lanka, or Bangladesh. As described previously (9), the OGTT stratified participants into three glycemic tolerance groups: normal glucose tolerance, impaired glucose tolerance, and gestational diabetes mellitus (GDM). The current analysis was performed in 95 participants, in whom adiponectin isoform distribution was measured. These 95 participants consisted of 65 Caucasians and 30 Indo-Asians randomly selected in a 2:1 ratio within each glucose tolerance group (normal glucose tolerance: 27 Caucasians, 13 Indo-Asians; impaired glucose tolerance: 10 Caucasians, 4 Indo-Asians; and GDM: 28 Caucasians, 13 Indo-Asians).

Venous blood samples for measurement of glucose and insulin were drawn at fasting and hourly during the OGTT. Glucose, insulin, C-reactive protein (CRP) and total adiponectin were measured as previously described (9,10). Adiponectin isoform distribution was determined from fasting serum by modification of the method described by Pajvani et al. (7), adapted to use an SW60 rotor (Beckman Coulter, Mississauga, ON, Canada) and infrared Western blot analysis (Doc#988-07737; LI-COR, Lincoln, NE).

Statistical analyses were conducted using the Statistical Analysis System (SAS version 8.02; SAS Institute, Cary, NC). The area under the glucose curve ($AUC_{glucose}$), insulin sensitivity index (IS_{OGTT}), and S_A were determined as previously described (7,9,11). The distributions of weeks' gestation, prepregnancy BMI, fasting glucose, fasting insulin, IS_{OGTT}, CRP, and total adiponectin were skewed, and thus natural logarithmic transformations of these variables were used in multivariate analyses. Ethnic variation in S_A after adjustment for covariates was tested by ANCOVA. Univariate correlates of S_A were assessed by Spearman correlation analysis. The following variables of known or potential biological relevance to adiponectin were considered in forward stepwise multiple linear regression analysis: age, ethnicity, prepregnancy BMI, weight gain in pregnancy, family history of diabetes, previous GDM, smoking history, $AUC_{glucose}$, and IS_{OGTT}.

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Received for publication 21 February 2006 and accepted 27 February 2006.

Abbreviations: $AUC_{glucose}$, area under the glucose curve; CVD, cardiovascular disease; CRP, C-reactive protein; GDM, gestational diabetes mellitus; HMW, high molecular weight; OGTT, oral glucose tolerance test; S_A, ratio of HMW isoform to total adiponectin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0413

Table 1—*Baseline demographic and clinical characteristics of participants by ethnicity*

	Caucasians (n = 65)	Indo-Asians (n = 30)	P
Age (years)	33.7 ± 3.8	34.2 ± 5.2	0.5970
Weeks' gestation (weeks)	29.0 (28–30)	29.0 (28–31)	0.9758
Prepregnancy BMI (kg/m^2)	24.5 (20.8–27.1)	22.6 (20.4–24.9)	0.0627
Weight gain in pregnancy (kg)	12.0 ± 5.4	10.8 ± 4.8	0.2796
Previous GDM/macrosomia (%)	10.8	10.0	0.9101
Family history of diabetes (%)	58.5	46.7	0.2856
Parity			0.6166
Nulliparous (%)	58.5	53.3	
One (%)	30.8	33.3	
More than one (%)	10.8	13.3	
Smoking history			**0.0439**
Never (%)	63.1	86.7	
Remote (%)	23.1	6.7	
Current (%)	13.9	6.7	
Glucose tolerance status			0.9401
Normal glucose tolerance (%)	41.5	43.3	
Impaired glucose tolerance (%)	15.4	13.3	
GDM (%)	43.1	43.3	
$AUC_{glucose}$	24.1 ± 4.1	24.8 ± 4.2	0.4707
Fasting blood glucose (mmol/l)	4.5 (4.2–4.9)	4.7 (4.3–5.2)	0.1963
Fasting insulin (pmol/l)	63 (45–80)	61 (48–100)	0.3395
IS_{OGTT}	4.2 (3.2–6.7)	4.0 (2.8–5.7)	0.2780
CRP (mg/l)	5.2 (2.3–9.2)	4.5 (2.5–7.9)	0.8088
Total adiponectin (ug/ml)	15.8 (12.4–20.6)	9.7 (7.9–13.3)	**<0.0001**
S_A (%)	35.6 ± 9.5	29.9 ± 11.5	**0.0120**

Data are means ± SD or median (interquartile range) unless otherwise indicated. P values refer to overall differences between groups as derived from t test (for continuous variables) or χ^2 tests (for categorical variables). Boldface indicates $P < 0.05$

RESULTS — Table 1 shows the demographic and metabolic characteristics of the study participants. Caucasians were more likely to report a history of smoking (P = 0.0439). Otherwise, there were no significant differences between the ethnic groups in age, weeks' gestation, prepregnancy BMI, weight gain in pregnancy, previous GDM, family history of diabetes, parity, glucose tolerance status, $AUC_{glucose}$, fasting glucose, fasting insulin, IS_{OGTT}, or CRP. As expected, median total adiponectin concentration was substantially lower in Indo-Asians (9.7 μg/ml) than in Caucasians (15.8 μg/ml) ($P < 0.0001$). Mean S_A was also significantly lower in Indo-Asians (29.9%) than in Caucasian women (35.6%) (P = 0.012). After adjustment for age, weeks' gestation, prepregnancy BMI, weight gain in pregnancy, family history of diabetes, previous GDM, smoking history, and glucose intolerance, mean S_A remained significantly lower in Indo-Asians (29.6%) than in Caucasians (35.7%) (P = 0.0049).

On Spearman correlation analysis, S_A was inversely related to prepregnancy BMI in both Caucasians ($r = -0.31$, P = 0.011) and Indo-Asians ($r = -0.46$, P = 0.010). In Caucasians only, S_A was positively correlated with IS_{OGTT} (r = 0.32, P = 0.010) and CRP (r = 0.35, P = 0.0044). These relationships were not apparent in Indo-Asians (IS_{OGTT}: r = 0.18, P = 0.33; CRP: r = 0.11, P = 0.55). In both ethnic groups, S_A was unrelated to age, weeks' gestation, and weight gain in pregnancy.

On forward stepwise multiple linear regression analysis, Indo-Asian ethnicity emerged as an independent and negative determinant of S_A ($\beta = -6.21$, F = 8.37, P = 0.0048), consistent with lower S_A in this ethnic group after adjustment for covariates. Prepregnancy BMI was the only other independent and negative determinant of S_A ($\beta = -16.19$, F = 7.51, P = 0.0074), in a model reconciling 20% of the variance in S_A.

CONCLUSIONS — Women of Indo-Asian descent exhibit decreased S_A compared with Caucasian women during pregnancy. Indeed, Indo-Asian ethnicity emerged as an independent and negative determinant of S_A. These data document ethnic variation in adiponectin isoform distribution for the first time and raise the possibility that low serum levels of HMW adiponectin may contribute to the increased risk of type 2 diabetes and CVD in Indo-Asians.

Acknowledgments— This study was supported by Canadian Institutes of Health Research.

We thank Dr. Philip Scherer and Pernille Keller for guidance in the measurement of HMW adiponectin.

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