Reduced Adiponectin Concentration in Women With Gestational Diabetes

A potential factor in progression to type 2 diabetes

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Adiponectin, a novel protein secreted exclusively by adipocytes, has emerged as an important potential mediator of the insulin resistance that is so characteristic of obesity, type 2 diabetes, and atherosclerotic cardiovascular disease (1,2). Consistent with the established inverse relationship between plasma adiponectin concentration and insulin resistance, hypoadiponectinemia has been documented in patients with each of these pathologic conditions (3–7). Moreover, in the Pima Indian population, low baseline adiponectin concentration predicts the subsequent development of insulin resistance (8), whereas conversely, elevated baseline adiponectin levels have been shown to be protective against the future development of type 2 diabetes (9). Taken together, these observations suggest that hypoadiponectinemia may be an important factor in the development of insulin resistance and the pathophysiology of type 2 diabetes. Gestational diabetes mellitus (GDM) identifies a population of young women at high risk of developing type 2 diabetes (10), representing an early stage in the natural history of the disease. Thus, we hypothesized that hypoadiponectinemia may be associated with GDM. The present study investigated the relationship between adiponectin and glucose tolerance in pregnancy.

RESEARCH DESIGN AND METHODS

The study design, protocol, and laboratory methods have been fully described previously (11). The study protocol was approved by the research ethics board at Mount Sinai Hospital, and all subjects gave written informed consent. In brief, participants consisted of 180 healthy pregnant women attending outpatient obstetrics clinics who had been referred for a 100-g oral glucose tolerance test (OGTT) following an abnormal result on a screening 50-g glucose challenge test (plasma glucose ≥ 7.8 mmol/l at 1 h postchallenge). As previously described (11), the OGTT stratified participants into three glycemic tolerance groups, 1) GDM, 2) impaired glucose tolerance (IGT), and 3) normal glucose tolerance (NGT). Venous blood samples for laboratory measurement of adiponectin and fasting insulin were drawn during the OGTT. Plasma adiponectin concentration was measured at 180 min (adiponectin level is not affected by food intake [5]) by radioimmunoassay (Linco Research) with a coefficient of variation of 9.3%. Specific insulin was measured using the Roche Elecsys 1010 immunoassay analyzer and the electrochemiluminescence immunoassay kit. This assay shows 0.05% cross-reactivity to intact human proinsulin and the primary circulating split form (Des 31,32). Demographic and historical information was collected by interviewer administered questionnaire.

Statistical analysis

All analyses were conducted using the Statistical Analysis System (SAS version 8.02; SAS Institute, Cary, NC). ANOVA and χ^2 tests were used to assess univariate differences between continuous and categorical variables, respectively. Since the distribution of adiponectin was substantially skewed, the natural logarithmic transformation was used in univariate and multivariate analyses with back-transformed results presented. Parity and smoking exposure were previously defined (11). Univariate associations of adiponectin with continuous measures of adiposity, glucose, and insulin were assessed with Spearman correlation analysis. ANCOVA was used to test differences in adiponectin concentration across categories of glucose tolerance after adjustment for covariates, including prepregnancy BMI, weight gain in pregnancy, parity, ethnicity, smoking history, previous GDM or delivery of an infant ≥ 10 lb, family history of GDM or type 2 diabetes, and fasting insulin. Finally, multiple linear regression analysis was used to determine which factors were significantly and independently associated with variation in log adiponectin concentration.

RESULTS

There were no significant differences between the glycemic tolerance groups in age, weeks gestation, prepregnancy BMI, weight gain during pregnancy, parity, smoking exposure, ethnicity, or family history of type 2 diabetes or GDM (data not shown). Of GDM patients, 18.8% had a previous history of GDM or delivery of a macrosomic infant compared with 10.3% of IGT subjects and 4.3% of NGT subjects (overall $P = 0.0206$). GDM patients also had the highest median fasting insulin level (74.0 pmol/l, interquartile range [IQR] 53.5–104) followed, in turn, by IGT (63.0 pmol/l, IQR 47–81) and NGT subjects (58.0 pmol/l, IQR 39.5–77) (overall P value from ANOVA = 0.0036).
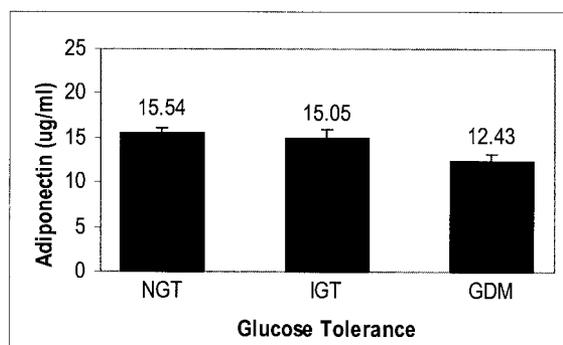
Figure 1—*Adjusted mean adiponectin by glucose tolerance group. Trend P = 0.0018; GDM vs. NGT, P = 0.0011; GDM vs. IGT, P = 0.0144; IGT vs. NGT, P = 0.6443. Adjusted for age, prepregnancy BMI, weight gain in pregnancy, ethnicity, previous GDM, family history, smoking, parity, and fasting insulin.*

Median adiponectin concentration was highest in the NGT group (16.2 µg/ml, IQR 12.4–19.3), followed by IGT (15.3 µg/ml, IQR 11.7–19.8) and GDM (12.3 µg/ml, IQR 7.9–16.6) (overall $P = 0.0004$). Adjustment for age, prepregnancy BMI, weight gain, parity, smoking, previous GDM, ethnicity, family history, and fasting insulin did not significantly attenuate the trend of decreasing adiponectin levels with worsening glycemic tolerance status (trend $P = 0.0018$, Fig. 1).

On univariate Spearman correlation analysis, adiponectin concentration was most strongly, and inversely, associated with fasting insulin ($r = -0.41$, $P < 0.0001$). Adiponectin was also inversely associated with glucose measurements (from the OGTT and glucose challenge test) (all $|r| \geq 0.2$, $P < 0.01$) and prepregnancy BMI ($r = -0.19$, $P = 0.0126$). There was no significant correlation between adiponectin and weight gain during pregnancy.

On multiple linear regression analysis, a model consisting of age, prepregnancy BMI, weight gain during pregnancy, parity, ethnicity, history of previous GDM, family history of GDM or type 2 diabetes, fasting insulin, and glucose intolerance (IGT or GDM) reconciled 32.8% of the variance in logarithmically transformed adiponectin. South Asian ethnicity emerged as an independent and negative predictor of adiponectin concentration, indicating significantly lower levels of adiponectin in this ethnic group after adjustment for other variables ($t = -4.97$, $P < 0.0001$). Log fasting insulin ($t = -4.24$, $P < 0.0001$) and GDM ($t = -2.92$, $P = 0.004$) were also independently and in-

versely related to adiponectin. Restriction of the same multiple linear regression model (without ethnicity) to only Caucasian subjects, the predominant ethnic group in the study population, produced similar results, with log fasting insulin and GDM again emerging as significant independent predictors of adiponectin (data not shown).

CONCLUSIONS — In this report, we demonstrate that GDM is associated with decreased adiponectin levels compared with IGT or NGT in pregnancy. Consistent with previous observations in nonpregnant individuals (4), adiponectin in pregnancy is more strongly correlated with insulin resistance than with measures of adiposity. These data suggest that hypoadiponectinemia in GDM may be an early event in the natural history of type 2 diabetes, with potential implications for the pathophysiology, screening, and prevention of this disease.

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