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Adiponectin, C-reactive protein, fibrinogen and tissue plasminogen activator antigen levels among glucose-intolerant women with and without histories of gestational diabetes

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Abstract

Aim—To examine concentrations of biomarkers (adiponectin, C-reactive protein, fibrinogen and tissue plasminogen-activator antigen) associated with glucose homeostasis and diabetes risk by history of gestational diabetes.

Methods—We conducted a secondary analysis of the Diabetes Prevention Program, a randomized trial of lifestyle intervention or metformin for diabetes prevention. At baseline, participants were overweight and had impaired glucose tolerance. Biomarkers at baseline and 1 year after enrolment were compared between parous women with ($n=350$) and without a history of gestational diabetes ($n=1466$). Cox proportional hazard models evaluated whether history of gestational diabetes was associated with diabetes risk, after adjustment for baseline biomarker levels as well as for change in biomarker levels, demographic factors and anthropometrics.

Results—At baseline, women with histories of gestational diabetes had lower adiponectin (7.5 $\mu\text{g/ml}$ vs. 8.7 $\mu\text{g/ml}$; $p<0.0001$) and greater log C-reactive protein (-0.90 mg/l vs. -0.78 mg/l , $p=0.04$) levels than women without histories of gestational diabetes, but these associations did not

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Competing interests

None declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:
Appendix S1 Diabetes Prevention Program research group investigators.

persist after adjustment for demographic factors. Fibrinogen and tissue plasminogen-activator antigen were similar between women with and without histories of gestational diabetes. Women with and without histories of gestational diabetes had a similar pattern of changes in biomarkers within randomization arm. Adjustment for age, race/ethnicity, baseline weight, change in weight, baseline biomarker level and change in biomarker level did not significantly alter the association between history of gestational diabetes and diabetes risk.

Conclusions—Among women with impaired glucose tolerance, biomarkers in women with and without histories of gestational diabetes are similar and respond similarly to lifestyle changes and metformin. Adjustment for biomarker levels did not explain the higher risk of diabetes observed in women with histories of gestational diabetes.

Introduction

Women with a history of gestational diabetes mellitus have a greater diabetes risk than women without, even among women with impaired glucose tolerance [1]. In the Diabetes Prevention Program (DPP), a randomized trial of lifestyle or metformin for diabetes prevention, women with histories of gestational diabetes had a greater diabetes hazard than women without, despite the younger age of women with gestational diabetes and the similarities in race/ethnicity, weight and glucose levels in the two groups [1].

The more rapid progression to diabetes among women with histories of gestational diabetes could potentially be linked to inflammatory or prothrombotic activity. Lower adiponectin [2] and greater C-reactive protein (CRP) levels [3] have been associated with incident diabetes in populations with non-gestational diabetes, and tissue plasminogen-activator antigen and fibrinogen have been cross-sectionally associated with insulin resistance [4]. Cross-sectional comparisons have suggested that women with histories of gestational diabetes have lower levels of favourable adipocytokines, such as adiponectin, than women without histories of gestational diabetes [5–9]. Other cross-sectional studies have noted that women with histories of gestational diabetes may also have less favourable inflammatory profiles, as suggested by their greater CRP and fibrinogen levels [9–14].

It is not known if these biomarkers differ by gestational diabetes status among women with impaired glucose tolerance, nor if these markers change after interventions in women with histories of gestational diabetes. Finally, it is unknown if these markers or their changes predict diabetes among women with histories of gestational diabetes. In the DPP, randomization to intensive lifestyle changes or metformin compared with placebo was associated with favourable changes in adiponectin [15], CRP [16] and fibrinogen [16] levels, but these biomarkers were not examined in the subgroup of women with histories of gestational diabetes.

We evaluated biomarkers by gestational diabetes status among parous women enrolled in the DPP, which required that participants had impaired glucose tolerance upon study entry. We hypothesized that women with histories of gestational diabetes would have less favourable adiponectin, CRP, fibrinogen and tissue plasminogen-activator antigen levels than women without histories of gestational diabetes, and such differences would persist after adjustment for confounders. We also hypothesized that adjustment for baseline

biomarker levels and changes in these biomarker levels would reduce the association between gestational diabetes status and diabetes risk.

Patients and methods

Study population

The characteristics of participants in the DPP by gestational diabetes status have been previously described [17]. Briefly, inclusion criteria included age ≥ 25 years, a fasting plasma glucose value of 5.3–6.9 mmol/l (≥ 6.9 mmol/l for Native Americans) and a 2-h plasma glucose of 7.8–11.1 mmol/l after a 75-g glucose load, and BMI ≥ 24 kg/m² (≥ 22 kg/m² for Asian Americans). Written informed consent was obtained from all participants before screening, consistent with the guidelines of each centre's institutional review board.

Data collection

Eligible participants were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily or intensive lifestyle changes. The goals of intensive lifestyle changes were to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet, and to engage in moderate physical activity for at least 150 min/week [17]. Diabetes was diagnosed on the basis of an annual oral glucose tolerance test or a semi-annual fasting plasma glucose test according to American Diabetes Association criteria [18]. The diagnosis required confirmation by a second test, usually within 6 weeks. Participants were followed for an average of 3.2 years [17].

At the time of randomization, all women completed a simple questionnaire relating to their number of pregnancies and live births and whether their pregnancies were complicated by gestational diabetes. No further information on the index pregnancies was available because of the time that had passed between the pregnancy and study recruitment. Of 2190 women in the DPP, 350 reported a history of gestational diabetes and 1840 did not. Of the 1840 women without histories of gestational diabetes, 321 had never been pregnant. Of the 1519 with pregnancies, 1416 had at least one live birth. In this report, we restricted analyses to the 1416 women without histories of gestational diabetes reporting at least one live birth, and to all 350 women with histories of gestational diabetes because all reported at least one live birth. Of the 350 women with histories of gestational diabetes, 122 were assigned to placebo, 111 to metformin and 117 to intensive lifestyle changes, whereas among the 1416 women without histories of gestational diabetes, 487 were assigned to placebo, 464 to metformin and 465 to intensive lifestyle changes. Those women with histories of gestational diabetes enrolled in the DPP had a mean 12-year interval ($n = 207$ as a result of incomplete data) since the delivery of their first pregnancy.

Total circulating adiponectin level was measured in each participant using a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical, Tokyo, Japan). The within-run and total coefficient of variation for this assay are 0.8–1.9% and 1.1–2.0%, respectively, and results are highly correlated with enzyme-linked immunosorbent assay-based methods ($r = 0.99$) [15]. Other analytes were measured at the DPP central laboratory, as previously

reported [15]. Adiponectin measures were performed at baseline and at 1 year after randomization. High-sensitivity CRP and fibrinogen levels in plasma were measured immunochemically using Dade–Behring reagent on the Behring Nephelometer autoanalyser, which uses polystyrene particles coated with monoclonal antibodies specific to the ligand. The intra- and interassay coefficients of variation for CRP were 4 and 5%, respectively. The intra- and interassay coefficients of variation for fibrinogen were 3 and 5%, respectively [19]. Concentrations of total tissue plasminogen-activator antigen were measured in citrated plasma using an enzyme-linked immunosorbent assay (Asserachrom tPA kit; Diagnostica Stago, Asnières sur Seine, France) [20]. As a result of a lack of adequate stored plasma, adiponectin measures were not available for 20 women with histories of gestational diabetes and 41 without, CRP measures were not available for three women without histories of gestational diabetes, fibrinogen measures were not available for three women without histories of gestational diabetes, and tissue plasminogen-activator antigen measures were not available for nine women without histories of gestational diabetes and three women with histories of gestational diabetes. These women did not differ from the women included in the present analysis.

Other analytes such as glucose and insulin were measured as previously reported [21]. β -cell function was assessed using corrected insulin response = $(100 \times 30\text{-min insulin}) / (30\text{-min glucose} \times [30\text{-min glucose} - 70 \text{ mg/dl}])$ [21]. Insulin sensitivity was assessed using inverse fasting insulin levels [21]. Age, race/ethnicity, family history of diabetes, smoking history, parity, polycystic ovarian syndrome and menopausal status were obtained by self-report.

Statistical analyses

Comparisons between groups at baseline in biomarkers were made using the *t*-test for quantitative variables and the chi-squared test for categorical variables. Nominal *P* values are listed with no adjustment for multiple comparisons. For variables with highly skewed distributions, such as CRP, a logarithmic transformation was carried out first, and the mean of the transformed values is reported instead. To determine if associations between biomarker levels and history of gestational diabetes persisted after adjustment for confounders, we conducted a series of multivariable linear regression analyses where covariates were added sequentially to each model to assess the change in the regression coefficient with each subsequent covariate. Cox proportional hazards models were used to assess diabetes risk according to history of gestational diabetes, after adjustment for the baseline marker and the change in the marker. Modelling strategies for biomarkers were similar to those performed for previous DPP analyses [15,22]. Analyses were stratified by treatment arm. A heterogeneity test was used to determine whether the effect of the treatment varied between study arms. To determine if the strength of association between particular biomarkers and diabetes differed by history of gestational diabetes, we examined the interaction effect associated with history of gestational diabetes and the baseline biomarker levels and change in biomarker levels. Finally, we examined whether fitting of penalized regression splines altered the analyses, but we did not observe a significant impact on the results (results not shown). SAS analysis software was used for all analyses (SAS Institute, Cary, NC, USA).

Results

The characteristics of the women stratified by history of gestational diabetes are shown in Table 1. Women with and without histories of gestational diabetes were similar, except that women with histories of gestational diabetes were ~8 years younger and less commonly postmenopausal. Baseline adiponectin levels were lower and log CRP levels were higher among women with histories of gestational diabetes, although differences in fibrinogen and tissue plasminogen-activator antigen between the groups did not reach significance.

Women with and without histories of gestational diabetes had similar patterns in biomarker changes between baseline and year 1 (Fig. 1). Women with and without histories of gestational diabetes randomized to intensive lifestyle changes had significant declines in adiponectin, log CRP, fibrinogen and tissue plasminogen-activator antigen levels, both before and after adjustment for age, race/ethnicity and weight changes. Women with histories of gestational diabetes randomized to metformin had significant declines in log CRP and tissue plasminogen-activator antigen, but not adiponectin and fibrinogen, whereas women without histories of gestational diabetes randomized to metformin had significant declines in all biomarkers except for fibrinogen.

Table 2 shows the associations between gestational diabetes history and baseline biomarker levels, before and after adjustment for age, race/ethnicity, menopause and weight. After adjustment for age and race/ethnicity, history of gestational diabetes was no longer significantly associated with lower levels of adiponectin. Further adjustment for additional demographic factors, including menopause, did not significantly alter the direction or the magnitude of the association. After additional adjustment for baseline weight, the association between history of gestational diabetes and log CRP levels was no longer significant. Gestational diabetes was not significantly associated with baseline levels of fibrinogen or tissue plasminogen-activator antigen before or after adjustment for covariates (Table 2).

Table 3 shows associations between history of gestational diabetes and diabetes risk, before and after adjustment for baseline biomarker levels. The association between history of gestational diabetes and diabetes risk was only significant among women in the placebo arm because of the higher cumulative incidence of diabetes in the placebo arm, although tests for heterogeneity did not indicate that associations between history of gestational diabetes and diabetes risk differed significantly between treatment arms (results not shown). After adjustment for age, race/ethnicity, baseline weight and baseline biomarker levels, the risk of diabetes associated with history of gestational diabetes was similar to that before adjustment, suggesting that baseline biomarker levels did not mediate the higher risk of diabetes associated with history of gestational diabetes. Similarly, the association between history of gestational diabetes and diabetes was not significantly reduced with further adjustment for change in biomarker levels (Table 4), suggesting that change in biomarker levels were also not a mediator of diabetes risk.

In a sensitivity analysis, we examined whether baseline biomarker levels or change in biomarker levels and associations with diabetes differed by history of gestational diabetes.

Associations between baseline levels of adiponectin, CRP, fibrinogen and tissue plasminogen-activator antigen and changes in these markers had similar hazards of diabetes in both women with and without history of gestational diabetes (results not shown).

Discussion

In this analysis of data from a large, racially and ethnically diverse, multicentre cohort of adults with impaired glucose tolerance, we found that biomarker profiles did not explain the higher risk of diabetes among women with histories of gestational diabetes. Although we found that women with histories of gestational diabetes had lower adiponectin levels and greater CRP levels than women without, these differences were primarily attributable to the younger age of women with histories of gestational diabetes, and differences in CRP were primarily attributable to weight and demographic profile. We also found that other markers of inflammation and thrombotic activity, namely fibrinogen and tissue plasminogen-activator antigen, were similar in women with and without histories of gestational diabetes. Interventions were associated with similar biomarker changes by gestational diabetes status, and the association between history of gestational diabetes and diabetes risk was largely unchanged after adjustment for baseline biomarkers and changes in biomarkers.

Previous studies have suggested that women with a history of gestational diabetes have a sevenfold greater risk of diabetes than women without [23]. Even among women who have already developed impaired glucose tolerance, women with a history of gestational diabetes appear to progress to diabetes more frequently than women without [1]. Potential mediators of this greater postpartum diabetes risk, specifically adipocytokines, have not been examined in longitudinal studies. Adiponectin is an adipocyte-derived cytokine that is associated with improved glycaemic control among people with diabetes [24] and degree of insulin resistance among people without diabetes [25]; thus, interventions targeting adiponectin and other adipokines for the prevention of diabetes have been developed for obese women [26]. It is unclear, however, whether adiponectin is a mediator in the pathogenesis of gestational diabetes and if targeting adiponectin would help prevent diabetes in this population. Previous studies have found women with a history of gestational diabetes have lower adiponectin levels than women without, even after consideration of weight. Retnakaran *et al.* [6] found that both total and high molecular weight adiponectin were lower in pregnant women with gestational diabetes matched for age, race/ethnicity, gestational age, weight before pregnancy and weight gain during pregnancy. Williams *et al.* [27] found that these differences were evident as early as the first trimester. Choi *et al.* [5] found that these differences in adiponectin persisted into the postpartum period. Winzer *et al.* [8] found that adiponectin levels were lower in women with a recent history of gestational diabetes, even after consideration of insulin sensitivity and weight, suggesting that adiponectin might be an independent predictor of future diabetes; however, our results suggest that adiponectin may not contribute independently to diabetes progression among women who have already developed impaired glucose tolerance.

Along similar lines, CRP and fibrinogen are inflammatory and thrombotic factors synthesized by the liver in response to factors produced by macrophages and adipokines. Like adiponectin, these factors may predict diabetes independently of weight [25],

suggesting that interventions aimed at reducing levels might aid in diabetes prevention; however, it is less clear whether CRP or fibrinogen have robust associations with diabetes incidence after consideration of insulin resistance [25], and the role of these markers in gestational diabetes is also unclear. Previous studies have found that women with histories of gestational diabetes have less favourable inflammatory and thrombotic profiles (CRP, fibrinogen) than women without [9–14], which was not the case for women in the present study, particularly after adjustment for weight. This suggests that interventions targeting these measures separately from targeting weight might have limited effectiveness. To our knowledge, tissue plasminogen-activator antigen has not been examined according to gestational diabetes status, although gestational diabetes has been associated with greater risk of cardiovascular disease [28]; the present analysis does not support an association between tissue plasminogen-activator antigen and diabetes risk among women with histories of gestational diabetes.

The present results may differ from previous studies for several reasons: 1) all participants in the DPP had impaired glucose tolerance at baseline, whereas other studies included younger women without impaired glucose tolerance; 2) women with a history of gestational diabetes in the DPP were approximately a decade removed from pregnancy, as opposed to the intrapartum or early postpartum populations in other studies; and 3) women in the DPP with and without histories of gestational diabetes were statistically similar regarding multiple factors associated with adipocytokine levels, namely weight and insulin secretion and sensitivity. The lack of association of gestational diabetes and biomarkers in the DPP may therefore be attributable to its selection of a population that already had impaired insulin secretion and sensitivity, with resulting glucose intolerance.

To our knowledge, no studies have examined changes in biomarkers in response to interventions among women with history of gestational diabetes. In previous analyses of the DPP [1], the intensive lifestyle changes and metformin interventions had similar effectiveness among women with histories of gestational diabetes; in contrast, intensive lifestyle changes had greater effectiveness than metformin among women without histories of gestational diabetes. We did not find evidence to support the hypothesis that the differing effectiveness of interventions by gestational diabetes status was attributable to adipokine levels. Changes in adipokine levels were similar by gestational diabetes status and were relatively small in both populations; thus, biomarkers did not explain the higher diabetes risk of women with histories of gestational diabetes.

The present study has several strengths, including a well-characterized multiethnic cohort, its large sample size compared with previous studies of women with history of gestational diabetes, the prospective data collection, and the ability to examine response to interventions. Limitations include its lack of more detailed information regarding the original diagnosis of gestational diabetes, particularly the diagnostic criteria used to make the original diagnosis, conduction of multiple comparisons, and possible sample size limitations. In addition, unobserved confounders may have obscured associations between biomarkers and diabetes risk.

We conclude that among women in the DPP who have already developed impaired glucose tolerance, women with and without histories of gestational diabetes have similar adipocytokine profiles which respond similarly to interventions; therefore, baseline adipokine levels and changes in these levels do not seem to mediate the increased risk of women with history of gestational diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- This is the first study to examine whether biomarkers, including C-reactive protein, adiponectin, fibrinogen and tissue plasminogen-activating antigen, explain the higher diabetes risk of women with histories of gestational diabetes.
- This is the first study to determine whether concentrations of biomarkers associated with abnormal glucose homeostasis respond similarly to lifestyle changes and metformin among women with and without histories of gestational diabetes.
- Among women with impaired glucose tolerance, these biomarkers do not explain the higher diabetes risk observed in women with histories of gestational diabetes.

FIGURE 1.
Change in biomarkers by intervention arm and history of gestational diabetes status. CRP, C-reactive protein.

Table 1

Baseline characteristics of women with and without histories of gestational diabetes mellitus (history of gestational diabetes)

Characteristic	No history of gestational diabetes N=1416	History of gestational diabetes N=350	P
Age, years	51 (10)	43 (8)	<0.001
Race/ethnicity, %			0.11
Non-Hispanic white	50	54	
Black	23	18	
Hispanic	17	16	
Native American	3	2	
Asian	7	10	
Family history of diabetes, %	30	33	0.20
Postmenopause, %	58	18	<0.001
Current smoking, %	7	6	0.54
Polycystic ovarian syndrome, %	3	1	0.14
Parity, number	2.6 (1.5)	2.6 (1.3)	0.76
Weight, kg	91 (19)	91 (18)	0.85
Waist circumference, cm	103 (14)	102 (14)	0.22
Fasting glucose, mmol/l	5.8 (0.4)	5.9 (0.5)	0.25
2-h glucose, mmol/l	9.1 (0.9)	9.2 (1.0)	0.12
1/fasting insulin, ml/uU	0.05 (0.03)	0.05 (0.04)	0.85
Corrected insulin response, uU·dl ² /ml·mg ²	0.66 (0.42)	0.61 (0.40)	0.07
Adiponectin, ug/ml	8.7 (3.7)	7.5 (3.2)	<0.001
Log C-reactive protein, mg/dl	−0.78 (0.99)	−0.90 (0.99)	0.04
Fibrinogen, g/l	3.95 (0.81)	3.88 (0.92)	0.16
Tissue plasminogen-activator antigen, ng/dl	10.8 (3.9)	10.4 (3.2)	0.06

Data are mean (sd), unless otherwise indicated.

Table 2

Association between history of gestational diabetes and baseline biomarker levels

	Regression coefficient (95% CI) [*]			
	Adiponectin	Log CRP	Fibrinogen	Tissue plasminogen-activator antigen
Adjusted for study randomization arm	-1.19[†] (-1.62, -0.76)	-0.12[†] (-0.24, -0.003)	-7.04 (-16.79, 2.71)	-0.43 (-0.87, 0.019)
Adjusted for study arm, age, and race/ethnicity	-0.074 (-0.49, 0.34)	-0.17[†] (-0.29, -0.046)	-2.24 (-12.58, 8.11)	-0.21 (-0.68, 0.26)
Adjusted for above, and menopausal status	-0.014 (-0.43, 0.41)	-0.14[†] (-0.26, -0.016)	-0.77 (-11.17, 9.64)	-0.29 (-0.76, 0.19)
Adjusted for above, and baseline weight	-0.10 (-0.52, 0.32)	-0.074 (-0.19, 0.042)	4.47 (-5.37, 14.32)	-0.16 (-0.63, 0.31)

CRP, C-reactive protein.

^{*} Referent group is women without history of gestational diabetes.[†] Significant association between history of gestational diabetes and biomarker at $P < 0.05$.

Table 3

Association between history of gestational diabetes and diabetes by randomization arm, before and after adjustment for baseline biomarker levels

	Hazard ratio (95% CI)		
	Intensive lifestyle change	Metformin	Placebo
Unadjusted association between history of gestational diabetes and diabetes	1.53 (0.95, 2.48)	1.00 (0.62, 1.61)	1.65 (1.16, 2.34)
Adjusted for baseline log CRP, age (years), race (white vs. non- white), and weight (kg)	1.42 (0.84, 2.40)	1.15 (0.69, 1.93)	1.79 (1.21, 2.63)
Adjusted for baseline fibrinogen, age (years), race (white vs. non- white), and weight (kg)	1.43 (0.85, 2.41)	1.12 (0.67, 1.88)	1.71 (1.17, 2.52)
Adjusted for baseline adiponectin, age (years), race (white vs. non- white), and weight (kg)	1.32 (0.78, 2.25)	1.06 (0.62, 1.82)	1.81 (1.23, 2.66)
Adjusted for baseline tissue plasminogen-activator antigen, age (years), race (white vs. non- white), and weight (kg)	1.46 (0.87, 2.47)	1.14 (0.68, 1.90)	1.74 (1.19, 2.56)

CRP, C-reactive protein.

Referent group is women without history of gestational diabetes.

Table 4

Association between history of gestational diabetes and diabetes by randomization arm, before and after adjustment for baseline and change in biomarker levels between baseline and year 1, hazard ratios and 95% CIs shown.

	Hazard ratio (95% CI)		
	Intensive lifestyle change	Metformin	Placebo
Unadjusted association between history of gestational diabetes and diabetes	1.53 (0.95, 2.48)	1.00 (0.62, 1.61)	1.65 (1.16, 2.34)
Adjusted for baseline log CRP, change in log CRP, age (years), race (white vs. non-white), weight (kg), and change in weight	1.26 (0.75, 2.13)	1.20 (0.71, 2.04)	1.79 (1.22, 2.64)
Adjusted for baseline fibrinogen, change in fibrinogen, age (years), race (white vs. non-white), weight (kg), and change in weight	1.26 (0.75, 2.13)	1.14 (0.67, 1.93)	1.71 (1.16, 2.51)
Adjusted for baseline adiponectin, change in adiponectin, age (years), race (white vs. non-white), weight (kg), and change in weight	1.25 (0.71, 2.23)	0.97 (0.53, 1.78)	1.95 (1.31, 2.90)
Adjusted for baseline tissue plasminogen-activator antigen, change in tissue plasminogen-activator antigen, age (years), race (white vs. non-white), weight (kg), and change in weight	1.24 (0.74, 2.09)	1.04 (0.60, 1.81)	1.77 (1.20, 2.60)

Referent group is women without history of gestational diabetes