# Impact of Changes Over Time in Adipokines and Inflammatory Proteins on Changes in Insulin Sensitivity, β-Cell Function, and Glycemia in Women With Previous Gestational Dysglycemia

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Adipokine dysregulation and subclinical inflammation are putative diabetogenic features of adiposity. However, while alterations in adipokines/inflammatory proteins can predict incident type 2 diabetes in longitudinal studies (1–3), evidence for causality is generally hindered by two limitations. First, there is a relative paucity of human data linking changes in adipokines/inflammatory proteins with changes in insulin sensitivity and β-cell function over time, as might be expected for causal mediators. Second, because obesity-induced changes in circulating proteins do not occur in isolation, the precise elucidation of causal mediators ideally requires consideration of multiple adipokines/inflammatory proteins simultaneously (as opposed to individually, as typically occurs in studies). Thus, to address these limitations, we evaluated changes over 2 years in adipokines (adiponectin, chemerin, retinol-binding protein 4 [RBP-4]) and inflammatory proteins (C-reactive protein [CRP], plasminogen activator inhibitor 1 [PAI-1]) in relation to changes in insulin sensitivity, β-cell function, and glycemia in women with varying degrees of recent gestational dysglycemia and hence a range of future risk of diabetes.

In this study, 339 women underwent a glucose challenge test (GCT) and oral glucose tolerance test (OGTT) in pregnancy, followed by repeat OGTT and measurement of adiponectin (Millipore), chemerin (Millipore), RBP-4 (ALPCO), CRP (Dade Behring), and PAI-1 (Invitrogen) at both 1 year and 3 years postpartum. The study protocol has been previously described in detail (4,5). On each OGTT, insulin sensitivity/resistance was measured by Matsuda index and HOMA of insulin resistance (HOMA-IR), and β-cell function was measured by the Insulin Secretion-Sensitivity Index-2 and insulinogenic index/HOMA-IR (4,5). The antepartum GCT/OGTT identified four gestational glucose tolerance groups (gestational diabetes mellitus, gestational impaired glucose tolerance, abnormal GCT with normal OGTT, normal GCT/OGTT), each of which predicts distinct trajectories of future risk of diabetes (5). On multiple linear regression analyses (Table 1), none of the adipokines/inflammatory proteins or their changes predicted β-cell function at 3 years (models A and B). Adiponectin at 1 year predicted insulin sensitivity (Matsuda index) at 3 years, while PAI-1 at 1 year and its change from 1 to 3 years were negative predictors (model C). The same predictors emerged for HOMA-IR, in addition to CRP at 1 year and its change from 1 to 3 years (model D). For both fasting and 2-h glucose at 3 years (models E and F), significant independent predictors were the respective glucose measurement at baseline, BMI at 1 year, and change in BMI from 1 to 3 years. Of note, although weight gain is associated with both increased CRP and insulin resistance, the change in CRP was itself independently and inversely associated with HOMA-IR and fasting glucose at 3 years, likely reflecting the impact of adjustment for concurrent change in BMI and the other adipokines/inflammatory proteins. Finally, on logistic regression analysis with the same covariates, the only predictors of prediabetes/diabetes at 3 years were glucose intolerance at 1 year (odds ratio 8.12, 95% CI 3.98–16.56), BMI at 1 year (1.09, 1.02–1.16), and change in BMI (1.30, 1.05–1.59).

Thus, in fully adjusted models simultaneously evaluating all of the adipokines/inflammatory proteins and their changes over time, the dominant independent predictors of all of the metabolic outcomes were BMI at 1 year and its change from 1 to 3 years. The impact of adiposity

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**Table 1—Significant independent predictors of six metabolic outcomes at 3 years postpartum**

| Outcome at 3 years* | Significant predictors | β | *t* | *P* |
|---|---|---|---|---|
| A. ISSI-2 | ISSI-2 at 1 year | 0.552669 | 8.36 | <0.0001 |
| | BMI at 1 year | −16.72522 | −3.32 | 0.001 |
| B. IGI/HOMA-IR | IGI/HOMA-IR at 1 year | 0.007735 | 2.88 | 0.004 |
| | BMI at 1 year | −0.028240 | −1.98 | 0.049 |
| C. Matsuda index | Matsuda index at 1 year | 0.022948 | 4.85 | <0.0001 |
| | BMI at 1 year | −0.048227 | −7.28 | <0.0001 |
| | Change in BMI from 1 to 3 years | −0.100288 | −5.79 | <0.0001 |
| | Asian ethnicity | −0.289391 | −3.37 | 0.0009 |
| | Nonwhite non-Asian ethnicity | −0.325275 | −4.12 | <0.0001 |
| | Family history of diabetes | −0.134457 | −2.56 | 0.01 |
| | Adiponectin at 1 year | 0.033599 | 4.09 | <0.0001 |
| | PAI-1 at 1 year | −0.000117 | −2.59 | 0.01 |
| | Change in PAI-1 from 1 to 3 years | −0.000138 | −2.87 | 0.005 |
| D. HOMA-IR | HOMA-IR at 1 year | 0.209465 | 5.41 | <0.0001 |
| | BMI at 1 year | 0.046018 | 6.22 | <0.0001 |
| | Change in BMI from 1 to 3 years | 0.095050 | 5.15 | <0.0001 |
| | Nonwhite non-Asian ethnicity | 0.192813 | 2.30 | 0.02 |
| | Family history of diabetes | 0.115751 | 2.07 | 0.04 |
| | Adiponectin at 1 year | −0.034484 | −4.01 | <0.0001 |
| | PAI-1 at 1 year | 0.000100 | 2.08 | 0.04 |
| | Change in PAI-1 from 1 to 3 years | 0.000112 | 2.20 | 0.03 |
| | CRP at 1 year | −0.024985 | −2.56 | 0.01 |
| | Change in CRP from 1 to 3 years | −0.019536 | −2.52 | 0.01 |
| E. Fasting glucose | Fasting glucose at 1 year | 0.617208 | 10.99 | <0.0001 |
| | BMI at 1 year | 0.029007 | 4.43 | <0.0001 |
| | Change in BMI from 1 to 3 years | 0.070800 | 4.1 | <0.0001 |
| | CRP at 1 year | −0.025304 | −2.77 | 0.006 |
| | Change in CRP from 1 to 3 years | −0.020363 | −2.79 | 0.006 |
| F. 2-h glucose | 2-h glucose at 1 year | 0.640894 | 11.45 | <0.0001 |
| | BMI at 1 year | 0.062188 | 2.61 | 0.01 |
| | Change in BMI from 1 to 3 years | 0.152248 | 2.43 | 0.02 |

*Each of these six multiple linear regression models included the covariates age, ethnicity, family history of diabetes, duration of breastfeeding, BMI at 1 year, change in BMI from 1 to 3 years, the measure of the respective outcome variable at 1 year, and both the 1-year measure and change from 1 to 3 years for all of the following: adiponectin, chemerin, RBP-4, CRP, and PAI-1. IGI, insulinogenic index; ISSI-2, Insulin Secretion-Sensitivity Index-2.

on risk of diabetes in this population does not appear to be mediated by changes in adiponectin, chemerin, RBP-4, CRP, or PAI-1.

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