



# Impact of Changes Over Time in Adipokines and Inflammatory Proteins on Changes in Insulin Sensitivity, $\beta$ -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  $\beta$ -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,  $\beta$ -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  $\beta$ -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  $\beta$ -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	$\beta$	<i>t</i>	<i>P</i>
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
D. HOMA-IR	Change in PAI-1 from 1 to 3 years	−0.000138	−2.87	0.005
	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
E. Fasting glucose	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
	Fasting glucose at 1 year	0.617208	10.99	<0.0001
	BMI at 1 year	0.029007	4.43	<0.0001
F. 2-h glucose	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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