Adipokines and Incident Type 2 Diabetes in an Aboriginal Canadian Population

The Sandy Lake Health and Diabetes Project

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OBJECTIVE — The aim of this study was to investigate associations of adiponectin, leptin, C-reactive protein (CRP), interleukin (IL)-6, and serum amyloid A (SAA), individually or in combinations, with risk of incident type 2 diabetes in an Aboriginal Canadian population.

RESEARCH DESIGN AND METHODS — Of the 606 Sandy Lake Health and Diabetes Project cohort subjects who were free of diabetes at baseline, 540 (89.1%) participated in 10-year follow-up assessments. Concentrations of fasting adiponectin, leptin, CRP, IL-6, SAA, and covariates were measured at baseline. Fasting glucose and a 75-g oral glucose tolerance test were obtained at baseline and follow-up to determine incident type 2 diabetes, defined as clinically diagnosed type 2 diabetes or as fasting plasma glucose ≥7.0 mmol/l or 2-h postload plasma glucose ≥11.1 mmol/l at follow-up.

RESULTS — Low adiponectin, high leptin, and low adiponectin-to-leptin ratio at baseline were associated with increased risk of incident type 2 diabetes after adjustment for age, sex, triglycerides, HDL cholesterol, hypertension, and impaired glucose tolerance (odds ratio 0.63 [95% CI 0.48–0.83], 1.50 [1.02–2.21], and 0.54 [0.37–0.77], respectively). When the models were additionally adjusted for waist circumference or BMI, however, only low adiponectin remained significantly associated with increased incident diabetes (0.68 [0.51–0.90]). Combinations of leptin, CRP, IL-6, and/or SAA with adiponectin, assessed using either the ratio or joint effects, did not improve diabetes prediction.

CONCLUSIONS — Low baseline adiponectin is associated with increased risk of incident type 2 diabetes independent of leptin, CRP, IL-6, SAA, and metabolic syndrome variables including obesity.

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Obesity is a major risk factor for insulin resistance and type 2 diabetes (1). The recent focus on adipose tissue as an endocrine organ secreting signaling proteins, collectively termed adipokines, has prompted current interests in associations of adipokines with insulin resistance and diabetes (1–2). Although underlying mechanisms have not been completely explained, adipokines have been linked with obesity-induced inflammation and signaling pathways that contribute to type 2 diabetes (1). Prospectively, adiponectin, an anti-inflammatory, anti-atherogenic, and insulin-sensitizing adipokine (2,3), has been inversely associated with the development of type 2 diabetes (4–7). Several studies associated increased baseline levels of inflammatory markers, including interleukin (IL)-6 (8,9) and C-reactive protein (CRP) (9), with incident type 2 diabetes, while others reported no association of IL-6 (4) and CRP (4,8) with the development of type 2 diabetes after adjustment for adiposity measures. In another prospective study, the association between leptin and diabetes risk was attenuated after adjustment for intra-abdominal fat (10).

Recent studies have suggested that adipokines may interact in regulating metabolic homeostasis (11–12). In a cross-sectional study, evidence was presented for CRP inhibiting the binding of leptin to its receptors and leptin stimulating expression of CRP (11). Others identified the adiponectin-to-leptin (A/L) ratio as a reliable marker of insulin resistance (12).

Nonetheless, limited population-based data are available on how adipokines in combinations may contribute to the etiology of diabetes. In addition, previous prospective investigations on associations of adipokines with diabetes provide inconsistent findings (4–10). Among those, only a few have reported data from studies of North American Aboriginal people (4,5), while no studies have been conducted among Aboriginal Canadians in whom diabetes is increasingly prevalent (13). The objective of this study was to investigate associations of baseline adiponectin, leptin, CRP, IL-6, and serum amyloid A (SAA), individually and/or in combinations, with the development of type 2 diabetes in an Aboriginal Canadian population undergoing rapid cultural transition.

RESEARCH DESIGN AND METHODS

— The Sandy Lake Health and Diabetes Project (SLHDP) is an ongoing population-based cohort study de-

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signed to determine the incidence of type 2 diabetes and its associated risk factors in an Aboriginal Canadian population. The research partnership and methodology of the SLHDP baseline survey have been described in detail in a previous publication (13). Briefly, baseline data were obtained from 728 of 1,018 (72%) eligible residents of Sandy Lake First Nation aged 10–79 years between 1993 and 1995 (13). Signed informed consent was obtained from all participants, and the study was approved by the Sandy Lake First Nation Band Council and University of Toronto Ethics Review Committee (13).

Between 2003 and 2005, subjects who were free of diabetes at baseline (n = 606) were contacted to participate in a 10-year follow-up study, and 540 (89.1%) residents were contacted. Residents who did not return for follow-up (n = 66), compared with respondents, were slightly younger but were not different regarding sex, BMI, or any nontraditional risk factors at baseline, except for slightly higher adiponectin. Of 540 responses, 27 (5.0%) deaths were reported due to cancer (n = 6), pneumonia (n = 5), liver cirrhosis (n = 3), cardiovascular disease (n = 2), brain tumor or aneurysm (n = 2), suicide (n = 2), and other including accidents (n = 7). In the present study, we excluded nine subjects with diabetes at baseline defined by the revised 1999 World Health Organization diagnostic criteria of fasting plasma glucose (FPG) ≥7.0 mmol/l or 2-h postload plasma glucose ≥11.1 mmol/l. In addition, subjects who died during follow-up (n = 27, described above) or who had missing baseline fasting and 2-h postload glucose values (n = 12) were excluded. After exclusions, 492 men and women remained in the present study.

Baseline data collection and laboratory procedures

At baseline, blood samples were collected after an 8- to 12-h overnight fast to determine glucose, insulin, lipid profile, adiponectin, leptin, CRP, IL-6, and SAA concentrations. A 75-g oral glucose tolerance test (OGTT) was administered, and a second blood sample for glucose was drawn after 120 min. Individuals were excluded from the OGTT if they had physician-diagnosed diabetes and were currently receiving medication for diabetes or if they had an FPG level >11.1 mmol/l.

Detailed baseline biochemical analyses have been described in previous publications (13–16). Glucose concentration was determined using the glucose oxidase method. Fasting plasma insulin concentration was analyzed by radioimmunoassay. Triglycerides and HDL and LDL cholesterol were determined using standard methods described in the Lipid Research Clinics manual of operations (17). Serum leptin (interassay coefficient of variation [CV] 4.7% at 10.4 μg/l) and adiponectin (interassay CV 9.3% at 7.5 μg/l) were measured using radioimmunoassay (Linco Research, St. Louis, MO). SAA and IL-6 were determined using the enzyme-linked immunosorbent assay (interassay CV 11% at 81 mg/l and 10% at 2 ng/l, respectively) (BioSource International, Camarillo, CA). CRP concentration was assessed using the Behring BN 100 and the N high-sensitivity CRP reagent (interassay CV 5.0% at 12.8 mg/l) (Dade-Behring, Mississauga, ON).

Anthropometric data including height, body weight, waist circumference at the iliac crest, and percent body fat were collected as described previously (13). The percentage of body fat was estimated by bioelectrical impedance analysis using the Tanita TBF-201 Body Fat Analyzer (Tanita, Tokyo, Japan). Systolic and diastolic blood pressure was measured with the subject seated at the appearance of first and fifth Korotkoff sounds, respectively. Hypertension was defined as a systolic blood pressure ≥130 mmHg, a diastolic blood pressure ≥85 mmHg, or receiving antihypertensive medication therapy. Each anthropometric and blood pressure measurement was performed twice, and the average was used in analyses. An interviewer-administered questionnaire indicating medical history was collected.

Follow-up data collection and outcome assessment

Incident type 2 diabetes at follow-up was defined as the presence of any one of the following: *1*) FPG ≥7.0 mmol/l or 2-h postload plasma glucose ≥11.1 mmol/l, 2) current use of insulin or oral hypoglycemic agents, or 3) a positive response to the question, "Have you ever been diagnosed with diabetes by a nurse (practitioner) or a doctor?"

Statistical analyses

Distributions of continuous variables were assessed for normality, and natural log transformations of skewed variables were used in subsequent analyses. Descriptive statistics for continuous variables were summarized as the mean ± SD or median (25^{th}–75th percentile) for variables with a skewed distribution. Categorical variables were summarized using proportions. Baseline characteristics of subjects with and without incident type 2 diabetes were compared using Welch's modified t test or χ^2 test as appropriate. To assess baseline cross-sectional associations between adipokines and potential covariates, Spearman's rank correlation analysis was performed with adjustment for age and sex.

Multivariate logistic regression analysis was conducted to evaluate independent associations of baseline adipokines with incident type 2 diabetes. Each adipokine was tested separately in three models: model 1, adjusted for age and sex; model 2, adjusted for the model 1 variables in addition to triglycerides, HDL cholesterol, hypertension, and impaired glucose tolerance (IGT); and model 3, adjusted for the model 2 variables in addition to waist circumference or BMI. The OR per 1-SD increase in the corresponding adipokine and 95% CI were calculated.

Interactions between adipokines and independent variables including sex, fasting insulin, fasting and 2-h postload glucose, IGT, waist circumference, and BMI were assessed by adding an interaction term into a model adjusted for age, sex, triglycerides, HDL cholesterol, hypertension, and waist circumference in addition to main effects. The A/L ratio was used to assess the previously proposed combination effect of adipokines (12). Adipokine combinations were added into the full model (model 3) to assess joint effects. To compare different logistic models in their capability to discriminate subjects with and without incident diabetes, the C statistic, which is analogous to the area under the receiver operating characteristic curve, was calculated with the significance determined using the DeLong algorithm (18). Data analyses were performed with the use of SAS software, version 9.1 (SAS Institute, Cary, NC), and with the consideration of two-sided $P < 0.05$ as statistically significant for all analyses.

RESULTS — Baseline characteristics of subjects with and without incident type 2 diabetes at follow-up are presented in Table 1. Of 492 subjects, 86 (17.5%) developed type 2 diabetes by follow-up: 72 of 383 subjects (18.8%) were ascertained using fasting and/or 2-h postload glucose at follow-up assessments, and 14 of 109

Table 1—*Baseline characteristics of the Sandy Lake Health and Diabetes Project participants according to incident type 2 diabetes at follow-up*

	No diabetes	Incident diabetes	*P*
n (%)	406 (82.5)	86 (17.5)	
Age (years)*	25.4 ± 13.0	31.5 ± 12.4	<0.001
Sex (male/female)†	173/233 (42.6/57.4)	34/52 (39.5/60.5)	0.60
Anthropometry*			
Height (cm)	165.3 ± 10.4	166.8 ± 9.1	0.16
Weight (kg)	69.8 ± 18.1	82.0 ± 15.9	<0.001
BMI (kg/m^2)	25.4 ± 5.5	29.4 ± 5.3	<0.001
Percent body fat (%)	33.0 ± 13.2	40.1 ± 10.3	<0.001
Waist circumference (cm)	94.4 ± 14.1	104.7 ± 12.1	<0.001
Blood pressure			
Systolic blood pressure (mmHg)‡	113.0 (103.5–120.0)	118.0 (110.0–130.0)	<0.001
Diastolic blood pressure (mmHg)*	64.0 ± 11.5	69.9 ± 12.3	<0.001
Hypertension†§	54 (13.3)	29 (33.7)	<0.001
Lipid profile			
HDL cholesterol (mmol/l)*	1.26 ± 0.28	1.19 ± 0.25	0.02
LDL cholesterol (mmol/l)*	2.42 ± 0.74	2.74 ± 0.66	<0.001
Triglycerides (mmol/l)‡	1.10 (0.81–1.53)	1.48 (1.16–1.82)	<0.001
Glucose homeostasis			
Fasting glucose (mmol/l)*	5.3 ± 0.46	5.6 ± 0.58	<0.001
2-h glucose (mmol/l)*	5.4 ± 1.62	6.5 ± 2.08	<0.001
Fasting insulin (pmol/l)‡	94 (66–131)	123 (91–187)	<0.001
IGT†‖	36 (8.9)	23 (26.7)	<0.001
Impaired fasting glucose†¶	22 (5.4)	10 (11.6)	0.005
Adipokines‡			
CRP (mg/l)	1.45 (0.40–4.28)	2.82 (1.24–7.48)	<0.001
IL-6 (ng/l)	0.67 (0.33–1.23)	0.83 (0.52–1.38)	0.01
Serum amyloid A (mg/l)	7.04 (4.43–11.1)	8.61 (5.52–14.5)	0.03
Leptin (ng/ml)	10.6 (5.20–19.4)	15.0 (9.40–25.7)	<0.001
Adiponectin (μg/ml)	14.5 (11.0–19.6)	11.0 (8.01–15.1)	<0.001
Adiponectin-to-leptin ratio	1.36 (0.65–3.25)	0.73 (0.36–1.44)	<0.001

Data are *n* (%), mean ± SD, and median (25th–75th percentile). Number of subjects (*n*) for each characteristic varies slightly due to occasional missing values. *Welch's *t* test performed. †χ^2 test performed. ‡Welch's *t* test performed on log transformation. §Hypertension is defined as a systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or receiving antihypertensive medication therapy. ‖IGT is defined as fasting plasma glucose <7.0 mmol/l and 2-h postload glucose ≥7.8 and <11.1 mmol/l. ¶Impaired fasting glucose is defined as fasting plasma glucose 6.1–6.9 mmol/l and 2-h postload glucose <7.8 mmol/l.

subjects without follow-up blood samples (12.8%) were ascertained based on self-reported clinical diagnosis only. Subjects without blood samples at follow-up compared with those with blood samples were younger and had lower CRP and higher adiponectin (all $P \leq 0.02$) but were not different according to sex, BMI, or other nontraditional risk factors (all $P > 0.05$). Subjects who developed diabetes were older ($P < 0.001$) and had higher adiposity measures including body weight, BMI, percent body fat, and waist circumference (all $P < 0.001$); lower HDL cholesterol ($P = 0.02$); higher LDL cholesterol, triglyceride, fasting and 2-h postload glucose, and fasting insulin (all $P < 0.001$); higher systolic and diastolic blood pressure (both $P < 0.001$); and were more likely to have had IGT or impaired fasting glucose at baseline (both $P \leq 0.005$). Higher baseline concentrations of CRP, IL-6, SAA, and leptin were observed among subjects with incident type 2 diabetes than those without diabetes (all $P \leq 0.03$), while adiponectin and the A/L ratio were lower at baseline among those with incident diabetes (both $P < 0.001$).

Using Spearman correlation, adiponectin was significantly inversely correlated with leptin, CRP, and IL-6 ($r = -0.26$, -0.25, and -0.16, respectively; all $P < 0.001$) but not with SAA (online appendix Table 1 [available at http://dx.doi.org/10.2337/dc08-0036]). Adiposity measures including BMI, percent body fat, and waist circumference were inversely correlated with adiponectin ($r = -0.36$, -0.37, and -0.32, respectively; all $P < 0.001$) and A/L ratio ($r = -0.73$, -0.75, and -0.70, respectively; all $P < 0.001$). Adiposity measurements were positively correlated with leptin, CRP, IL-6, and SAA ($r = 0.18–0.77$, all $P < 0.001$). Correlation coefficients of metabolic measurements with the A/L ratio were stronger than with individual adiponectin (online appendix Table 1), except for HDL cholesterol (both $r = 0.39$, $P < 0.001$).

Multivariate models were constructed to determine whether adipokine variables were independently associated with incident type 2 diabetes (Table 2). In the first model adjusted for age and sex, baseline adiponectin and the A/L ratio were inversely associated with incident type 2 diabetes (OR 0.57 [95% CI 0.44–0.73] and 0.43 [0.31–0.59] per 1-SD increase, respectively; both $P < 0.001$), while high leptin and CRP at baseline predicted incident diabetes (2.05 [1.44–2.90] and 1.48 [1.13–1.95], respectively; both $P \leq 0.005$). When the models were further adjusted for triglycerides, HDL cholesterol, hypertension, and IGT (model 2), the associations of adiponectin, the A/L ratio, and leptin with diabetes were attenuated but remained significant (0.63 [0.48–0.83], 0.54 [0.37–0.77], and 1.50 [1.02–2.21], respectively; all $P \leq 0.04$). In full models additionally adjusted for waist circumference (model 3), however, only low adiponectin remained significantly associated with incident diabetes (0.68 [0.51–0.90], $P = 0.007$). Results for full models adjusted for BMI were similar to those adjusted for waist circumference and are thus not presented here. IL-6 and SAA were not significantly associated with incident diabetes in any model assessed (Table 2).

There were no statistically significant interactions between sex and adipokines in predicting diabetes (all interaction $P > 0.05$) (data not shown). Similarly, there were no significant interactions of fasting insulin, fasting and 2-h postload glucose, IGT, or waist circumference with adipokines in predicting diabetes (all interaction $P > 0.05$) (data not shown).

When various combinations of leptin and inflammatory markers were added to a full model (model 3) in addition to primary exposure to adiponectin, the significant association between adiponectin and incident diabetes remained unchanged (Table 3). C statistics for models assessing different combinations of joint effects ranged from 0.753 to 0.755 ($P >$

Table 2—*Multiple logistic regression analyses of the associations of adipokines with incident type 2 diabetes: the Sandy Lake Health and Diabetes Project*

		Model 1*		Model 2†		Model 3‡	
Independent variable	SD	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Adiponectin	0.49	0.57 (0.44–0.73)	<0.001	0.63 (0.48–0.83)	0.001	0.68 (0.51–0.90)	0.007
Leptin	0.92	2.05 (1.44–2.90)	<0.001	1.50 (1.02–2.21)	0.04	0.97 (0.58–1.62)	0.89
CRP	1.41	1.48 (1.13–1.95)	0.005	1.29 (0.96–1.73)	0.09	1.05 (0.76–1.46)	0.77
IL-6	1.00	1.23 (0.96–1.57)	0.10	1.11 (0.84–1.45)	0.47	1.03 (0.78–1.36)	0.84
SAA	0.88	1.17 (0.92–1.48)	0.20	1.14 (0.88–1.49)	0.33	1.07 (0.81–1.41)	0.62
A/L	1.11	0.43 (0.31–0.59)	<0.001	0.54 (0.37–0.77)	<0.001	0.66 (0.42–1.02)	0.06

Data are OR (95% CI) per 1-SD change. $n = 479$ for models including adiponectin and $n = 490$ for models including leptin, CRP, IL-6, or SAA. *Adjusted for age and sex. †Adjusted for model 1 variables + triglycerides, HDL cholesterol, hypertension, and impaired glucose tolerance. ‡Adjusted for model 2 variables + waist circumference.

0.05 for base vs. any subsequent models in Table 3), which indicated that there was no additional capacity of these models to discriminate subjects who developed diabetes from those who did not (Table 3).

CONCLUSIONS — Despite significant cross-sectional correlations of adiponectin, leptin, CRP, IL-6, SAA, and the A/L ratio with metabolic measurements at baseline, only low adiponectin, high leptin, and low A/L ratio were significantly associated with incident type 2 diabetes in our multivariate models adjusted for age, sex, triglycerides, HDL cholesterol, hypertension, and IGT. With an additional adjustment for abdominal adiposity, our results provide evidence only for the association of low baseline adiponectin with incident type 2 diabetes at 10-year follow-up. Combinations of leptin, CRP, IL-6, and/or SAA with adiponectin, assessed using either the ratio or joint effects, did not improve diabetes prediction.

Our findings are consistent with those from the Pima Indian population, another North American Aboriginal population with the high prevalence of diabetes (4,5). Using nested case-control data, Krakoff et al. (4) reported that adiponectin predicted type 2 diabetes in a multivariate model adjusted for covariates including waist circumference (incident rate ratio 0.63 [95% CI 0.41–0.98], $P = 0.04$), while CRP and IL-6 did not predict diabetes ($P = 0.88$ and 0.28, respectively). Several other prospective studies from non-Aboriginal populations have also supported the association of low adiponectin at baseline with increased diabetes risk (6–7). In the Health, Aging, Body Composition Study of white and black adults aged 70–79 years, however, adiponectin was not an independent predictor of incident type 2 diabetes after controlling for metabolic syndrome variables (19). It is possible that this inconsistent finding may be related to reduced renal function in these older subjects, which has been demonstrated to result in paradoxically elevated adiponectin levels (20).

Similar to our results, leptin predicted type 2 diabetes risk among Japanese men in a univariate logistic regression model (relative risk 1.78 [95% CI 1.28–2.48]), but the significance was attenuated with additional adjustment for baseline intra-abdominal fat ($P = 0.05$) (10). Previous prospective studies evaluating associations of inflammatory adipokine markers with diabetes risk have been inconsistent. Several studies supported the association of increased inflammatory marker levels with the development of type 2 diabetes, including IL-6 (8,9) and CRP (9), while others reported no associations of IL-6 (4) and CRP (4,8) with incident type 2 diabetes after adjusting for adiposity measures. Sex differences in the prediction of type 2 diabetes by inflammatory markers have been suggested (21). However, we did not observe a significant interaction between sex and adipokines assessed in the current study population.

Recently, an interaction between CRP and leptin was proposed as a mechanism contributing to leptin resistance (11). Evidence was presented for human CRP inhibiting the binding of leptin to its receptors in vitro and leptin stimulating expression of CRP in human primary

Table 3—*Association between adiponectin and incident type 2 diabetes with addition of leptin, CRP, IL-6, and/or SAA: the Sandy Lake Health and Diabetes Project*

	Adiponectin	Leptin	CRP	IL-6	SAA	C Statistic*
Base model†	0.45 (0.25–0.81)					0.753
+ Leptin	0.45 (0.25–0.81)	0.98 (0.55–1.74)				0.753
+ CRP	0.45 (0.25–0.81)		0.99 (0.77–1.26)			0.753
+ IL-6	0.45 (0.25–0.81)			0.98 (0.74–1.31)		0.753
+ SAA	0.46 (0.26–0.81)				1.07 (0.79–1.47)	0.754
+ Leptin + CRP	0.45 (0.25–0.81)	1.00 (0.97–1.03)	0.98 (0.77–1.26)			0.753
+ Leptin + CRP + IL-6	0.45 (0.25–0.81)	1.00 (0.97–1.03)	0.99 (0.76–1.28)	0.99 (0.72–1.35)		0.753
+ Leptin + CRP + IL-6 + SAA	0.45 (0.25–0.81)	1.00 (0.97–1.03)	0.95 (0.70–1.27)	0.97 (0.71–1.33)	1.13 (0.77–1.65)	0.755

Data are OR (95% CI) per 1-unit change ($n = 479$). *There were no significant differences between the C statistics of the baseline model and subsequent models adjusted with additional adipokine(s). †Outcome = incident diabetes; 1° exposure = adiponectin, with adjustment for age, sex, triglyceride, HDL cholesterol, hypertension, impaired glucose tolerance, and waist circumference.

hepatocytes (11). Based on this report, we tested the hypothesis that combinational effects of CRP and leptin would improve prediction of diabetes risk compared with individual CRP or leptin. However, we found that the combinational effect of CRP and leptin was not significantly associated with incident diabetes. In addition, other joint effect combinations assessed by adding leptin, CRP, IL-6, and/or SAA into the full model adjusted for metabolic syndrome variables in addition to primary exposure to adiponectin did not improve diabetes prediction. The A/L ratio was identified as a sensitive and reliable marker of insulin resistance in a cross-sectional study (12). Although we observed similar correlations in our baseline cross-sectional analysis, the A/L ratio was not significantly associated with incident diabetes in our multivariate model adjusted for metabolic syndrome variables including waist circumference.

The independent role of low adiponectin in predicting diabetes risk is likely explained by the role of this adipokine in mediating insulin sensitivity and secretion (2,22). While the molecular mechanism of adiponectin is not completely understood, adiponectin has been linked with multiple signaling pathways at multiple sites (22–24). Recently, evidence was provided using knockout mouse models that adiponectin receptor 1 (AdipoR1) mediated 3′ AMP-activated protein kinase activity, while adiponectin receptor 2 (AdipoR2) mediated increased peroxisome proliferator–activated receptor-α ligand activity in liver (23). The disruption of both AdipoR1/R2 abolished adiponectin binding and action, increasing inflammation and oxidative stress, and therefore leading to insulin resistance and marked glucose intolerance (23). In another mouse model study, decreased expression of AdipoR1 or AdipoR2 was associated with reduced insulin-sensitizing effects of adiponectin in hepatocytes and myocytes (24). In β-cells of insulin-resistant mice, adiponectin modulated insulin secretion (22). These proposed roles and mechanisms of multiple adiponectin-mediated pathways offer explanations for the association of low adiponectin with diabetes risk and potential for understanding the etiology of diabetes.

Limitations of our study include strategic difficulties conducting investigations in a remote Aboriginal community. We were unable to collect interim data to analyze the time to onset of diabetes. We were also unable to obtain follow-up blood samples from all subjects: diabetes outcome assessments of 109 (22.2%) subjects were by self-reported clinical diagnosis only. This 22.2% without blood samples might have caused underreporting of incident diabetes. The ratio of plasma high–molecular weight adiponectin to total adiponectin has been correlated more tightly with 2-h postload glucose than total adiponectin ($r = -0.58$ for the ratio and -0.38 for total adiponectin; both $P < 0.001$) (25). However, in this prospective cohort study, high–molecular weight adiponectin analysis was not available at the time of baseline biochemical data analysis, another limitation of our study. Nonetheless, the current study was able to retain a high 10-year follow-up rate of 89.1%. In addition, investigating the association of a number of adipokines with incident type 2 diabetes in an Aboriginal Canadian population with a high prevalence of diabetes offers a unique perspective.

In summary, low adiponectin was independently associated with increased type 2 diabetes risk, while leptin, CRP, IL-6, and SAA were not associated with incident type 2 diabetes after adjustment for metabolic syndrome variables including abdominal adiposity in this Aboriginal Canadian population. Combinational effects of leptin, CRP, IL-6, and/or SAA with adiponectin, assessed using the ratio and joint effects, did not improve diabetes prediction. The strong association between adiponectin and incident type 2 diabetes, independent of obesity, suggests that adiponectin may be involved in the etiology of diabetes.

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