Adiponectin, Change in Adiponectin, and Progression to Diabetes in the Diabetes Prevention Program

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OBJECTIVE—To determine whether baseline adiponectin levels or intervention-associated change in adiponectin levels were independently associated with progression to diabetes in the Diabetes Prevention Program (DPP).

RESEARCH DESIGN AND METHODS—Cox proportional hazards analysis was used to evaluate the contribution of adiponectin and treatment-related change in adiponectin to risk of progression to diabetes.

RESULTS—Baseline adiponectin was a strong independent predictor of incident diabetes in all treatment groups (hazard ratio per ~3 μg/ml higher level; 0.61 in the lifestyle , 0.76 in the metformin, and the 0.79 in placebo groups; all $P < 0.001$, $P = 0.13$ comparing groups). Baseline differences in adiponectin between sexes and race/ethnicity groups were not reflected in differences in diabetes risk. DPP interventions increased adiponectin levels ([means ± SE] 0.83 ± 0.05 μg/ml in the lifestyle group, 0.23 ± 0.05 μg/ml in the metformin group, and 0.10 ± 0.05 μg/ml in the placebo group; $P < 0.001$ for increases versus baseline, $P < 0.01$ comparing groups). These increases were associated with reductions in diabetes incidence independent of baseline adiponectin levels in the lifestyle and placebo groups but not in the metformin subjects (hazard ratio 0.72 in the lifestyle group ($P < 0.001$), 0.92 in the metformin group ($P = 0.18$), and 0.89 in the placebo group; $P = 0.02$ per ~1 μg/ml increase, $P = 0.02$ comparing groups). In the lifestyle group, adjusting for change in weight reduced, but did not remove, the effect of increased adiponectin.

CONCLUSIONS—Adiponectin is a powerful marker of diabetes risk in subjects at high risk for diabetes, even after adjustment for weight. An increase in adiponectin in the lifestyle and placebo groups was associated with a reduction in diabetes risk. However, these changes in adiponectin were comparatively small and less strongly related to diabetes outcome than baseline adiponectin levels. ***Diabetes*** **57:980–986, 2008**

Adiponectin, the dominant secretory product of adipocytes, is a marker and perhaps a mediator of metabolic and cardiovascular disease risk (1–4). In a number of case-control and cohort studies (1,5–15), adiponectin levels have been found to be inversely associated with insulin sensitivity, conversion to diabetes, and risk of myocardial infarction. These associations remain significant after adjustment for baseline measures of obesity, suggesting that adiponectin reflects components of metabolic and vascular risk beyond those encompassed in obesity alone. The measurement of adiponectin may therefore carry additional prognostic value for diabetes and heart disease beyond the currently recognized set of risk factors.

Furthermore, in experimental studies in animal models exogenous adiponectin reversed insulin resistance (16) and protected against diet-induced insulin resistance (17). Impairing adiponectin production or adiponectin receptor function predisposed to impairments in metabolism (18–20). These observations, together with the epidemiologic observation that lower levels of adiponectin reflect greater diabetes risk, suggest the hypothesis that this risk can be mitigated by interventions that augment adiponectin levels. Although isolated changes in adiponectin levels cannot be readily achieved, an alternative approach is to evaluate the contribution of changes in adiponectin levels to reductions in diabetes risk in intervention studies targeting diabetes prevention.

The Diabetes Prevention Program (DPP) was a multicenter, randomized, clinical trial of the effect of intensive lifestyle changes (exercise and diet program targeting a weight loss of at least 7% total body weight) or 850 mg metformin twice daily versus placebo on the rate of developing diabetes. Subjects who qualified for this study were by definition at increased risk of future diabetes, on the basis of elevated fasting glucose, impaired glucose tolerance, and obesity. Also, because of historical data suggesting increased risk for diabetes among members of minority communities, subjects from ethnic and racial minorities were oversampled and comprised 45% of all subjects enrolled. Here, we have tested the hypothesis that higher adiponectin levels at baseline, and intervention-associated increases in adiponectin levels, are associated with decreased rates of progression to diabetes.

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DPP, Diabetes Prevention Program.

RESEARCH DESIGN AND METHODS

DPP interventions. In the DPP, subjects with elevated fasting glucose (5.3–6.9 mmol/l or <6.9 mmol/l for American Indians), impaired glucose tolerance (glucose 7.8–11.0 mmol/l 2 h after a 75-g oral glucose tolerance test), and overweight or obesity (BMI ≥24 kg/m^2, except Asian Americans where the cut point used was ≥22 kg/m^2) were randomly assigned to one of three treatments: Intensive lifestyle intervention, treatment with metformin, or treatment with placebo (21–23). A fourth intervention arm, in which subjects were randomized to receive e troglitazone, was prematurely terminated (24). The maximal measurable effectiveness of the DPP interventions, and the greatest compliance with assigned treatments, was seen at the end of the first year of intervention (23). Changes over this first-year interval have since proven to relate strongly to progression to diabetes (25–28).

Stored plasma samples were analyzed for levels of total circulating adiponectin. Of 3,234 subjects who participated in the three main study arms, samples were retrieved from 2,842 subjects who had both baseline and year 1 samples available and from an additional 281 subjects with only baseline samples available. Samples from both time points were analyzed at the same time, with paired samples from each subject run in the same batch. Samples from subjects who participated in the troglitazone treatment arm were not analyzed. A total of 127 subjects were excluded due to insufficient available stored plasma. The excluded subjects were on average slightly younger than subjects whose samples were used in the current analyses (aged 48.8 ± 11.3 vs. 50.7 ± 10.7 years; $P = 0.06$) but otherwise were not different by weight, fasting or postload glucose levels at baseline, sex, race, treatment assignment, or in the rate of conversion to diabetes. Therefore, excluding these subjects did not bias the current analyses, and the sampled group remained representative of the overall study population.

Total circulating adiponectin was measured 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 ($r = 0.99$) (29). Other analytes were measured at a central laboratory as previously reported (24). β-Cell function was assessed using the change in insulin divided by change in glucose over the first 30 min of the oral glucose tolerance test (i.e., insulinogenic index) (28). Insulin sensitivity was assessed using inverse fasting insulin levels, as in our prior publications (28).

Statistical methods. Descriptive statistics of baseline measurements were computed by sex-specific quartiles of baseline adiponectin levels. Pearson correlation coefficients were computed for baseline measurements with baseline adiponectin level separately for men and women. Treatment group–specific linear regression models were used to assess factors measured at baseline and change over 1 year on the change in adiponectin from baseline to year 1. Cox regression models were used to assess effect of change in adiponectin on development of diabetes (30). Variables without relationship with diabetes outcome were excluded from modeling. Variables were added sequentially to each model to assess the change in the hazard ratio for adiponectin change with each subsequent covariate. To facilitate comparisons of effects across variables, hazard ratios are reported for convenient increments, approximating 1 SD of measure. Cox models were run separately for each treatment group adjusted for sex, age, and self-reported race/ethnicity, and a test of heterogeneity was used to see if the effect of variables differed across treatment groups. Nominal P values are presented. The SAS analysis system was used for all analyses (SAS Institute, Cary, NC).

RESULTS

Cohort description. Baseline levels of adiponectin were widely distributed among DPP participants, ranging from 1.8 to 35.0 μg/ml in a skewed distribution. The median value was 7.30 and the mean was 7.93. Women comprised 67.7% of the DPP population. The previously described sex difference in adiponectin levels was seen, with 26% higher levels in women than men ($P < 0.00001$) (Table 1) (Fig. 1). Distributions of standard anthropomorphic, hemodynamic, and metabolic variables across the observed range of adiponectin levels, divided into quartiles, are presented in Table 1. We observed significant univariate relationships of baseline adiponectin with many of these variables in both men and women. The strongest associations with baseline adiponectin (correlation coefficients >0.25; $P < 0.001$) were with age and HDL cholesterol (directly correlated) and fasting insulin and homeostasis model assessment of insulin resistance (inversely correlated). Triglyceride levels and β-cell function (insulinogenic index) were the next most strongly related to baseline adiponectin levels, with correlation coefficients on the order of 0.2. In this obese cohort, obesity measures were less tightly correlated; although weight and BMI were both significantly related to adiponectin levels, waist circumference was not.

Baseline adiponectin levels across the five ethnic groups are presented in Fig. 1. Adiponectin levels differed by ethnicity ($P < 0.00001$). The highest levels were seen in non-Hispanic white participants, with these trends unaffected by adjustment for group differences in age and adiposity. The smallest subgroups, Asian/Pacific Islanders and American Indians, are disproportionately represented by men and women, respectively. Differences in baseline adiponectin levels across groups remain significant after adjusting for sex distributions.

Baseline adiponectin and progression to diabetes. Cox proportional hazards models were used to predict progression to diabetes in relation to baseline levels of adiponectin adjusted for baseline demographics (age, sex, and race/ethnicity) (Fig. 2) (Table 2, *model 1*). Adiponectin levels were inversely associated with progression to diabetes in all three intervention groups. Among subjects randomized to receive lifestyle and placebo interventions, adiponectin-associated diabetes risk remained significant after adjustment for baseline adiposity (Table 2, *model 2*). This was seen whether weight or waist circumference was included as the measure of adiposity.

A ~3 μg/ml higher baseline adiponectin level corresponded to a 20–40% lower rate of progression to diabetes. The relationship between adiponectin and diabetes conversion was not different across the three treatment groups ($P = 0.13$). The graphical expression of this Cox model (Fig. 2) demonstrates that this change in risk was not linear across the range of adiponectin levels, however. At lower adiponectin levels, the diabetes risk was relatively greater. Accordingly, the change in risk was disproportionately greater at lower levels of adiponectin. Figure 2 also demonstrates that although the point estimates for average diabetes risk in each group are markedly different by group (reflecting the diabetes prevention effects of the two interventions compared with placebo), the slopes of the exponential relationship between adiponectin and diabetes risk were not statistically different across the three groups. In other words, baseline adiponectin was strongly associated with diabetes risk, with similar effects of adiponectin across the three treatment groups.

We then examined whether naturally occurring differences in baseline adiponectin levels across demographic groups were reflected in differing rates of diabetes conversion. Although we found baseline differences in adiponectin across sex and race/ethnicity group, the relationship of adiponectin with progression to diabetes was not altered by including sex or race/ethnicity in the model. There was also no significant interaction of adiponectin with either sex or race/ethnicity on progression to diabetes (hazard ratio 1.14 [95% CI 0.53–2.47], $P = 0.73$, and 1.69 [0.99–2.87], $P = 0.06$, respectively, for the interaction terms added to model 1 in the lifestyle group; 1.45 [0.78–2.68], $P = 0.24$, and 0.83 [0.54–1.26], $P = 0.37$, respectively, in the metformin group; and 0.93 [0.60–1.45] and 1.04 [0.74–1.46], $P = 0.83$ in the placebo group).

TABLE 1
Baseline variables for men and women by sex-specific quartiles of baseline adiponectin

	Q1 (low)	Q2	Q3	Q4 (high)	Correlation with adiponectin
Men					
Adiponectin (μg/ml)	3.97 ± 0.68	5.47 ± 0.40	7.00 ± 0.50	10.40 ± 2.47	—
Age (years)	49.86 ± 9.55	52.40 ± 11.25	54.02 ± 10.77	58.79 ± 10.95	0.35†
Fasting glucose (mg/dl)	109.8 ± 8.46	107.8 ± 7.50	108.9 ± 8.45	107.9 ± 8.97	−0.06
2-h glucose (mg/dl)	165.6 ± 16.84	165.0 ± 17.34	164.3 ± 16.26	163.5 ± 17.15	−0.04
Fasting insulin (μU/ml)*	3.33 ± 0.54 (27.9)	3.17 ± 0.57 (23.8)	3.11 ± 0.51 (22.4)	2.92 ± 0.52 (18.5)	−0.29†
Homeostasis model assessment of insulin resistance	8.90 ± 6.09	7.48 ± 4.81	6.85 ± 3.58	5.66 ± 3.16	−0.25†
A1C (%)	5.99 ± 0.58	5.90 ± 0.54	5.90 ± 0.49	5.90 ± 0.46	−0.03
Insulinogenic index (μU/mg)	133.6 ± 92.31	119.5 ± 99.07	116.0 ± 80.85	100.8 ± 86.99	−0.166†
Waist (cm)	108.3 ± 14.35	107.3 ± 14.37	109.7 ± 13.14	107.0 ± 11.27	−0.05
Weight (kg)	100.3 ± 20.47	97.70 ± 20.96	100.5 ± 19.42	95.75 ± 16.68	−0.11‡
Total cholesterol (mg/dl)	198.8 ± 35.37	201.1 ± 35.38	204.3 ± 34.53	204.1 ± 35.30	0.05
LDL (mg/dl)	121.2 ± 34.75	125.9 ± 34.07	129.4 ± 29.44	129.7 ± 31.85	0.09‡
HDL (mg/dl)	37.64 ± 8.69	39.09 ± 8.12	40.55 ± 8.76	43.77 ± 9.04	0.26†
Triglycerides (mg/dl)*	5.15 ± 0.58 (172.4)	5.06 ± 0.51 (157.6)	5.00 ± 0.50 (148.4)	4.89 ± 0.50 (133.0)	−0.20†
Systolic blood pressure (mmHg)	124.0 ± 11.48	126.1 ± 14.58	126.4 ± 13.56	127.0 ± 15.54	0.11‡
Diastolic blood pressure (mmHg)	80.92 ± 8.89	79.58 ± 9.18	80.30 ± 9.71	78.90 ± 9.23	−0.08§
Women					
Adiponectin (μg/ml)	4.78 ± 0.84	6.87 ± 0.52	8.91 ± 0.70	13.40 ± 3.29	—
Age (years)	44.26 ± 8.34	47.77 ± 9.41	50.21 ± 9.89	54.40 ± 9.85	0.39†
Fasting glucose (mg/dl)	106.7 ± 8.43	106.3 ± 8.00	105.2 ± 7.99	103.9 ± 7.59	−0.11†
2-h glucose (mg/dl)	165.3 ± 17.02	165.5 ± 17.42	163.9 ± 16.75	164.1 ± 17.43	−0.03
Fasting insulin (μU/ml)*	3.42 ± 0.50 (30.6)	3.23 ± 0.49 (25.3)	3.10 ± 0.49 (22.2)	2.84 ± 0.51 (17.1)	−0.41†
Homeostasis model assessment of insulin resistance	9.04 ± 4.39	7.50 ± 3.90	6.49 ± 3.50	5.01 ± 2.64	−0.37†
A1C (%)	5.97 ± 0.57	5.89 ± 0.46	5.89 ± 0.50	5.88 ± 0.44	−0.04§
Insulinogenic index (μU/mg)	152.6 ± 115.9	131.7 ± 90.11	124.2 ± 89.20	100.8 ± 66.39	−0.21†
Waist (cm)	106.8 ± 15.28	105.5 ± 15.29	103.4 ± 14.01	98.74 ± 13.19	−0.21†
Weight (kg)	96.12 ± 20.57	94.57 ± 21.13	91.87 ± 19.84	86.08 ± 18.03	−0.19†
Total cholesterol (mg/dl)	195.9 ± 36.27	199.7 ± 36.96	207.8 ± 35.81	211.2 ± 35.66	0.17†
LDL (mg/dl)	120.6 ± 33.09	120.2 ± 33.73	126.0 ± 31.54	127.7 ± 32.19	0.09†
HDL (mg/dl)	42.19 ± 9.26	45.72 ± 10.76	49.76 ± 11.51	54.99 ± 12.76	0.43†
Triglycerides (mg/dl)[1]	4.97 ± 0.52 (144.0)	4.99 ± 0.52 (146.9)	4.95 ± 0.48 (141.2)	4.83 ± 0.49 (125.2)	−0.13†
Systolic blood pressure (mmHg)	122.4 ± 14.83	122.1 ± 14.49	122.9 ± 14.68	123.6 ± 15.82	0.06‡
Diastolic blood pressure (mmHg)	78.47 ± 9.57	77.73 ± 9.08	76.95 ± 9.10	76.78 ± 9.23	−0.05§

Data are means ± SD, within each sex-specific quartile. Correlations represent the sex-specific Pearson correlation of each variable with adiponectin. *These variables were log transformed for these analyses. Values in parentheses show the reexponentiated means. †$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$.

Change in adiponectin and progression to diabetes. Significant increases in adiponectin were observed from baseline to year 1 in all three treatment groups, with mean increases in the lifestyle, metformin, and placebo groups of 0.83 ± 0.05, 0.23 ± 0.05, and 0.10 ± 0.05 μg/ml, respectively ($P < 0.001$ comparing the increases across groups) (Fig. 3). The magnitude of these changes, and the differences across treatment groups, were essentially unchanged following adjustment for baseline adiponectin, weight, age, sex, and ethnicity (mean increases 0.83 ± 0.05, 0.22 ± 0.05, and 0.10 ± 0.05, respectively, after adjustment).

Cox proportional hazards models were used to predict progression to diabetes in relation to change in levels of adiponectin adjusted for baseline adiponectin and demographics (age, sex, and race/ethnicity adjusted) (Table 2). Added to the effects of baseline weight, baseline adiponectin, and change in weight, change in adiponectin was a significant predictor of future diabetes conversion only in subjects randomized to receive the lifestyle intervention, where a ~1 μg/ml increase in adiponectin was associated with a 16% (95% CI 1.0–28) reduction in the rate of progression to diabetes (Table 2, *model 3*). Among subjects randomized to placebo, the overall relationships were similar, but neither change in weight nor change in adiponectin was statistically significant. These relationships differed among metformin-treated subjects, where weight and adiponectin effects were dissociated: baseline adiponectin but not baseline weight, and change in weight but not change in adiponectin, were significant determinants of progression to diabetes (Table 2, *model 3*).

In the DPP, the most powerful determinants of progression to diabetes evaluated to date were change in weight, change in β-cell function, and change in insulin sensitivity

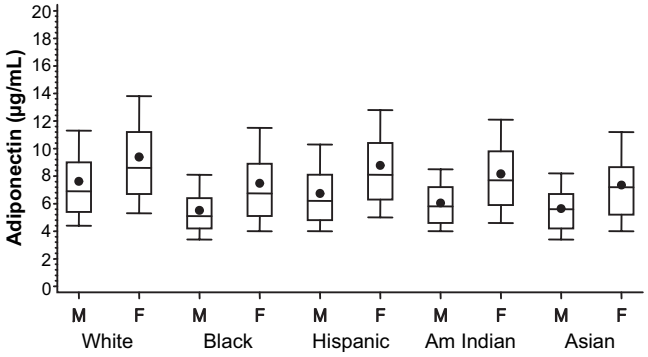

FIG. 1. Box-and-whisker plot showing the distribution of adiponectin at baseline by sex and self-described race/ethnicity. The box indicates the 25th through 75th percentile of the distribution, the whiskers show the 10th to 90th percentiles, the large dot shows the mean, and the line dissecting the box shows the median. Women had significantly higher levels of baseline adiponectin within each race/ethnic group ($P < 0.00001$), and white participants had significantly higher baseline adiponectin than all other race/ethnicity groups ($P < 0.00001$).

(28,31). Adding measures of insulin sensitivity or β-cell function individually to the models predicting diabetes removed the significance of the contribution of change in adiponectin, except among placebo-treated subjects ($P = 0.02$ for change in adiponectin when modeled with change in insulinogenic index and $P = 0.15$ when modeled with change in inverse fasting insulin). In models including both of these variables, the change in adiponectin again retained borderline significance in placebo-treated subjects but was no longer significant in metformin- and lifestyle-treated subjects (Table 2, *model 4*). Figure 4 demonstrates how nearly flat the slopes are for the relationship of change in adiponectin and diabetes risk after these adjustments. The contribution of baseline adiponectin was robust to the inclusion of these variables.

The hazard ratios in model 4 provide information about the relative strengths of each of these variables as determinants of overall diabetes risk. From this we can see that β-cell function and insulin sensitivity variables dominate the model, plus persisting strong effects of change in weight and baseline adiponectin but not change in adiponectin. Including adiponectin did not appreciably change the recognized relationships of these other variables with the diabetes prevention effect.

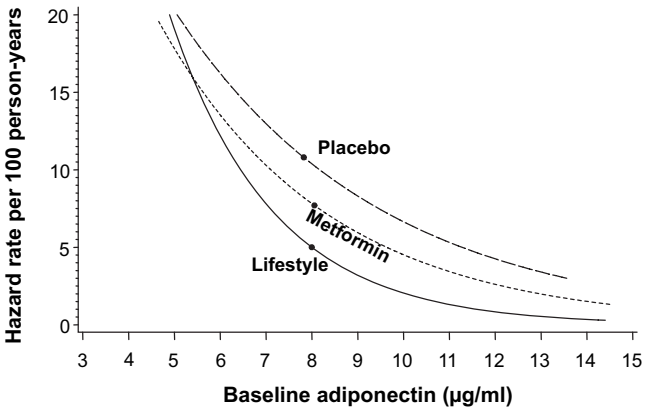

FIG. 2. Diabetes hazard rates and baseline adiponectin adjusted for sex, age, race/ethnicity, and baseline weight (Table 2, *model 2*). Cox proportional hazards models were used to estimate the risk of developing diabetes. Estimates of the absolute risk gradient associated with a given value of baseline adiponectin and adiponectin change using the range of values (5th to 95th percentiles) were used to describe the hazard rate for a participant with a value equal to the group mean. The point on each line indicates the estimated hazard rate for a subject with a value equal to the mean value for the group as estimated in the life table analysis.

Changes associated with change in adiponectin. Variables associated with the change in adiponectin were evaluated first individually then in combination in multiple regression (Table 3). In univariate analysis, the change in adiponectin was strongly inversely correlated with change in waist circumference (coefficients 0.17–0.35, $P < 0.0001$, in all treatment groups) and change in weight (coefficients 0.24–0.42, $P < 0.0001$, in all treatment groups) and also directly correlated with change in insulin sensitivity (inverse fasting insulin; coefficients 0.08–0.15, $P < 0.0001$, in all treatment groups). Change in adiponectin was not significantly related to the change in β-cell function (insulinogenic index). By multivariable regression, the main independent determinants of change in adiponectin were change in weight and baseline adiponectin concentration (Table 3), such that greater reductions in weight, and lower baseline levels, were associated with greater increases in adiponectin. In placebo- and lifestyle-treated subjects, baseline age was also significantly and independently related to change in adiponectin. The strongest of these variables in multivariable modeling was the change in weight, where overall a 5-kg weight loss was associated with an increase of 0.3 (placebo), 0.4 (metformin), and 0.5 µg/ml (lifestyle) in circulating adiponectin levels (all $P < 0.001$). There was a significant interaction of treatment and weight loss effect on adiponectin ($P = 0.03$), with lifestyle-associated changes greater than the other groups (Fig. 4). Thus, weight loss was associated with increases in adiponectin in all groups, but this effect was magnified in subjects from the lifestyle group.

DISCUSSION

In the DPP population of subjects at high risk for diabetes, baseline adiponectin levels were strongly inversely related to progression to diabetes in all treatment arms, independent of measures of adiposity. Adiponectin levels differed naturally by sex and across race/ethnicity, but these baseline differences were not reflected in sex- or ethnicity-specific rates of progression to diabetes. Adiponectin levels increased over 1 year in all three treatment groups, with the largest increase seen in lifestyle-treated subjects. Increases in adiponectin were associated with weight loss and changes in insulin sensitivity but not with changes in β-cell function. The increase in adiponectin was inversely associated with progression to diabetes among lifestyle participants independent of baseline adiponectin, baseline weight, and change in weight. However, when the predictive models were also adjusted for treatment effects on β-cell function and insulin sensitivity the independent effect of change in adiponectin was lost. Overall it appears that change in adiponectin primarily reflects changes in weight independent of treatment, and conversely the change in adiponectin contributes, at most, a modest weight-independent effect to diabetes prevention.

Baseline adiponectin and future diabetes. The most robust and statistically powerful observation is the strong, independent inverse association of baseline adiponectin levels with future diabetes. This observation is consistent with prior reports of associations of baseline adiponectin with diabetes risk (1,5–9,11–15) and confirms that this relationship is unchanged after adjustment for baseline adiposity. Furthermore, even though baseline weight was

TABLE 2
Cox proportional hazards modeling predicting progression to diabetes

	Placebo		Metformin		Lifestyle		Groups
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	*P*
Model 1							
Baseline adiponectin (per 3 μg/ml)	0.77 (0.66–0.89)	0.0004	0.73 (0.60–0.87)	0.0005	0.56 (0.44–0.71)	<0.0001	0.13
Model 2							
Baseline adiponectin (per 3 μg/ml)	0.80 (0.70–0.92)	0.001	0.76 (0.65–0.89)	0.0005	0.64 (0.52–0.79)	<0.0001	0.22
Weight (per 10 kg)	1.12 (1.05–1.18)	0.0002	0.99 (0.92–1.07)	0.77	1.16 (1.08–1.25)	<0.0001	0.006
Model 3							
Baseline adiponectin (per 3 μg/ml)	0.79 (0.69–0.91)	0.001	0.77 (0.66–1.20)	0.001	0.60 (0.48–0.76)	<0.0001	0.12
Change in adiponectin (per 1 μg/ml)	0.91 (0.82–1.01)	0.08	0.96 (0.85–1.09)	0.54	0.84 (0.72–0.99)	0.037	0.43
Baseline weight (per 10 kg)	1.10 (1.04–1.17)	0.0009	0.99 (0.91–1.07)	0.78	1.16 (1.07–1.26)	0.0002	0.014
Change in weight (per 5 kg)	0.88 (0.77–1.01)	0.07	0.78 (0.66–0.94)	0.007	0.66 (0.57–0.77)	<0.001	0.021
Model 4							
Baseline adiponectin (per 3 μg/ml)	0.84 (0.71–0.98)	0.03	0.77 (0.65–0.92)	0.003	0.63 (0.50–0.79)	<0.0001	0.14
Change in adiponectin (per 1 μg/ml)	0.87 (0.77–0.98)	0.02	0.99 (0.87–1.11)	0.84	0.88 (0.75–1.05)	0.15	0.30
Baseline weight (per 10 kg)	1.07 (1.00–1.14)	0.06	0.99 (0.90–1.08)	0.81	1.19 (1.09–1.31)	0.0002	0.017
Change in weight (per 5 kg)	0.82 (0.69–0.97)	0.02	0.77 (0.63–0.92)	0.006	0.63 (0.53–0.74)	<0.0001	0.08
Baseline insulinogenic index (per 0.03 μU/mg)	0.44 (0.35–0.55)	<0.0001	0.31 (0.22–0.43)	<0.0001	0.41 (0.30–0.57)	<0.0001	0.20
Change in insulinogenic index (per 0.03 μU/mg)	1.68 (1.42–1.99)	<0.0001	1.88 (1.43–2.48)	<0.0001	1.72 (1.34–2.22)	<0.0001	0.79
Baseline 1/fasting insulin (per 100 μU/ml)	0.63 (0.50–0.78)	<0.0001	0.63 (0.49–0.80)	0.0001	0.76 (0.59–0.98)	0.03	0.46
Change in 1/fasting insulin (per 100 μU/ml)	1.19 (0.96–1.47)	0.11	1.34 (1.10–1.63)	0.003	1.27 (1.03–1.56)	0.02	0.72

Hazard ratios are expressed per ~SD within the population for each variable. Higher values of inverse fasting insulin correspond to greater insulin sensitivity; higher insulinogenic index values correspond to better β-cell function. Change values are defined as year 1 minus baseline. Group comparisons represent the *P* value for comparing the contribution of each variable to the model across treatment groups. All models are adjusted for sex, self-reported race/ethnicity, and age at baseline.

not a determinant of diabetes risk in the metformin-treated subjects, baseline adiponectin was inversely associated with progression to diabetes even in this group, underscoring the separate associations of weight and adiponectin with progression to diabetes.

The relationship between adiponectin and future diabetes is complex. Natural variation in adiponectin levels are seen across sex (possibly associated with proportionally increased total fat and likely also to differences in fat distribution [32]) and race/ethnicity (mechanism unknown, likely reflecting group-related differences in production and/or disposal of adiponectin). The resulting absolute differences across groups might otherwise be expected to result in measurable differences in the rates of diabetes, given the powerful relationship of adiponectin with diabetes risk. Interestingly this was not observed, suggesting that the contributions of sex and ethnicity to adiponectin levels are independent of adiponectin's relationship with progression to diabetes, at least within the time frame available with these data.

Change in adiponectin and progression to diabetes. We found that treatment-associated changes in adiponectin from baseline to year 1 were proportional to the effectiveness of diabetes prevention. The increase in adiponectin was most closely related to weight loss, but in proportional hazards modeling, changes in adiponectin remained significant determinants of progression to diabe-

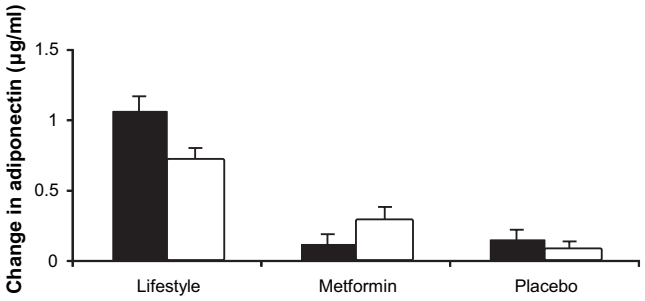

FIG. 3. Change in adiponectin by treatment group. Unadjusted values are presented. Bars represent means ± SE for change in adiponectin over 1 year of treatment. ■, men; □, women.

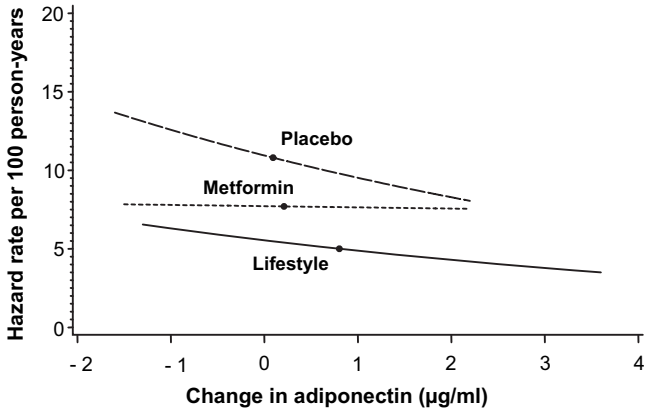

FIG. 4. Diabetes hazard rates and change in adiponectin (Table 2, *model 4*). Cox proportional hazards models were used to estimate the risk of developing diabetes. Estimates of the absolute risk gradient associated with a given value of baseline adiponectin and adiponectin change using the range of values (5th to 95th percentiles) were used to describe the hazard rate for a participant with a value equal to the group mean. The point on each line indicates the estimated hazard rate for a subject with a value equal to the mean value for the group as estimated in the life table analysis.

TABLE 3
Changes associated with change in adiponectin

	Placebo		Metformin		Lifestyle	
Univariate correlations						
Change in weight	−0.24	P <0.001	−0.29	P <0.001	−0.42	P <0.001
Change in waist	−0.17	P <0.001	−0.19	P <0.001	−0.35	P <0.001
Change in 1/FI	0.11	P = 0.0007	0.08	P = 0.02	0.15	P <0.001
Change in insulinogenic index	−0.04	P = 0.23	−0.02	P = 0.54	−0.01	P = 0.75
Multivariate modeling						
Baseline adiponectin (3 μg/ml)	−0.21 ± 0.04	P <0.001	−0.08 ± 0.05	P = 0.10	−0.15 ± 0.05	P = 0.005
Baseline 1/FI (0.03 100 μU/ml)	−0.02 ± 0.06	P = 0.78	0.04 ± 0.06	P = 0.52	0.13 ± 0.06	P = 0.03
Baseline insulinogenic index (100 μU/mg)	−0.06 ± 0.06	P = 0.26	−0.03 ± 0.06	P = 0.68	0.01 ± 0.07	P = 0.94
Baseline weight (10 kg)	−0.01 ± 0.02	P = 0.58	−0.05 ± 0.03	P = 0.10	−0.12 ± 0.03	P <0.001
Change in weight (5 kg)	−0.31 ± 0.05	P <0.001	−0.43 ± 0.05	P <0.001	−0.49 ± 0.04	P <0.001

Data are correlation coefficient of coefficient ± SE. Pearson correlation coefficients for change in adiponectin are presented for change in relevant potential univariate determinants after adjustment for baseline weight. Coefficients in multivariate modeling were derived from linear regression modeling, reported per ~SD for each variable. Higher values of inverse fasting insulin (1/FI) reflect greater insulin sensitivity; higher insulinogenic index (II) values reflect better β-cell function. Change values are year 1 minus baseline. In multivariate modeling, neither 1/FI or II contributed significantly to change in adiponectin in any treatment group.1/FI, inverse fasting insulin.

tes after adjustment for baseline weight and change in weight. This novel observation underscores the notion that adiponectin serves as a marker of metabolic status independent of weight, despite the fact that it is produced by adipocytes. There is no current literature beyond the present report addressing the question whether improvements in adiponectin levels contribute to the diabetes prevention effect of pharmacologic or lifestyle interventions.

In our dataset, the independent contribution of change in adiponectin to diabetes prevention and the magnitude of the absolute change in adiponectin levels were relatively small even in the lifestyle-treated subjects, in whom the effect on diabetes prevention was the most impressive. The relationship of progression to diabetes with change in adiponectin was not robust to adjustment for changes in β-cell function and insulin sensitivity, although relationships with baseline adiponectin were robust to these adjustments. This may imply that a treatment-induced change in adiponectin is in the same pathophysiologic pathway relating these variables with diabetes outcome. Alternatively, adiponectin may be affected in parallel with upstream determinants of these changes. Another alternative is that changes in adiponectin truly reflect a different pathway, but the magnitude of this effect is too small to be evident after accounting for other dominant determinants of diabetes outcomes. The current data do not allow us to distinguish these alternatives. Overall, though, it seems reasonable to conclude that the diabetes prevention effect of DPP treatments was not importantly mediated by improvements in circulating adiponectin levels, independent of changes in weight, changes in β-cell function, and changes in insulin sensitivity. In contrast, baseline adiponectin remained a powerful, independent predictor of diabetes progression beyond the contributions of these factors, and overall baseline adiponectin levels appear to reflect an important adipose-related setting for diabetes risk.

Metformin: an informative exception to the rule. It is well recognized that metformin's actions for diabetes prevention are different from those of exercise and weight loss. In the current analyses, baseline adiponectin was significantly related to progression to diabetes in metformin-treated subjects, and the magnitude of this relationship was not different from that seen in the other treatment groups. Change in weight was a clear contributor to the diabetes prevention effect in this group and in other analyses has been found to account for as much as 64% of the total effect of metformin (33). In all three treatment groups, change in weight was the strongest determinant of change in adiponectin, and specifically in metformin-treated subjects a modest but significant improvement in adiponectin levels was seen. However, in proportional hazards modeling within the metformin group the change in adiponectin was not an important component of the metformin effect on diabetes prevention in any model. This is perhaps unexpected, since the magnitude of the change in weight and the increase in adiponectin were both intermediate between the lifestyle- and placebo-treated groups, and change in adiponectin was significant in some models for these groups. Both the pharmacologic action of metformin and the signaling pathway of adiponectin receptors involve modification of AMP-activated protein kinase signaling in hepatocytes (34–36). This convergence of actions may preclude additional effects of adiponectin beyond that achieved with metformin and perhaps contribute to the lack of independent effects of metformin and adiponectin.

Limitations. The interpretation of our study requires the recognition of certain limitations. Most importantly, the subjects recruited represent a specifically selected subgroup of the general population, and, therefore, the results may not be fully representative of the relationships of adiponectin and diabetes incidence in all subject groups. Also, the current data represent the effects of the interventions studied and cannot be assumed to extend to the potential interrelationships of adiponectin and change in adiponectin with other diabetes prevention interventions. In the DPP dataset, fasting glucose is a uniquely powerful predictor of diabetes, such that it dominates any statistical model in which it is included. Therefore, in order to distinguish effects among other variables we have excluded fasting glucose from the current modeling. These models therefore allow an assessment of the relative contributions of the included variables to overall diabetes risk but do not allow comparison to other variables of potential interest such as fasting glucose or family history.

Summary. In the DPP population, who were at high risk for diabetes, baseline adiponectin levels were inversely related to diabetes risk, and treatment-associated increases in adiponectin were also inversely related to

diabetes risk. However, sex- and race/ethnicity- associated differences in adiponectin levels were independent of adiponectin's contributions to diabetes risk. The change in adiponectin, which was largest in those assigned to lifestyle intervention, was associated primarily with weight loss. The relationship of change in adiponectin to diabetes prevention was modest compared with that of baseline adiponectin and was overshadowed in multivariable analyses by treatment-associated changes in insulin sensitivity and β-cell function.

These observations confirm the validity and utility of adiponectin as a weight-independent baseline or cross-sectional measure of metabolic status in general and of diabetes risk in particular. However, the hypothesis that treatments which prevent diabetes act via changes in adiponectin found only modest support in our study, and the apparent effect size is much smaller than might have been anticipated. Other treatments which more powerfully increase adiponectin levels may yet prove effective at diabetes prevention via this mechanism, but the changes required may be greater than currently available approaches can produce.

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