Low Plasma Adiponectin Concentrations Predict Increases in Visceral Adiposity and Insulin Resistance

Seung Jin Han,[1,2,3] Edward J. Boyko,[2,3] Wilfred Y. Fujimoto,[3] Steven E. Kahn,[3,4] and Donna L. Leonetti[5]

[1]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Republic of Korea 16499; [2]Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Seattle, Washington 98108; [3]Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195; [4]Hospital and Specialty Medicine Service, VA Puget Sound Health Care System, Seattle, Washington 98108; and [5]Department of Anthropology, University of Washington, Seattle, Washington 98105

Context: Plasma adiponectin concentration has been shown to be inversely associated with body mass index (BMI) and insulin resistance in cross-sectional research. However, it is unclear whether adiponectin predicts future body composition and insulin resistance.

Objective: We aimed to investigate the potential relationship between adiponectin concentration and future regional body fat distribution and insulin resistance.

Design and Setting: This was a community-based prospective cohort study with 5 years of follow-up.

Participants: A total of 218 Japanese Americans without diabetes (79 men, 139 women, mean age 51.7 ± 10.1 years) were assessed at baseline and after 5 years of follow-up.

Main Outcome Measures: Abdominal visceral and subcutaneous fat area and thigh subcutaneous fat area were measured by computed tomography (CT). Insulin resistance was evaluated by homeostasis model assessment 2 of insulin resistance (HOMA2-IR). Plasma total adiponectin was measured by radioimmunoassay.

Results: Baseline adiponectin was inversely associated with abdominal visceral fat area ($P = 0.037$) and HOMA2-IR ($P = 0.002$) at 5 years in a multiple linear regression model after adjustment for baseline traits (including age, sex, BMI, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area, HOMA2-IR) and weight change. However, no association was seen between baseline adiponectin concentration and BMI or other CT-measured regional fat depots at 5 years.

Conclusions: Low plasma adiponectin concentration independently predicted future abdominal visceral fat accumulation and increased insulin resistance in Japanese Americans. (***J Clin Endocrinol Metab*** **102: 4626–4633, 2017)**

Adipose tissue is an energy storage organ but also has been more recognized as an important component of the endocrine system by regulating metabolism through the secretion of various hormone-like substances known as adipokines (1). Adiponectin is the adipokine with the highest plasma concentration and is associated with glucose and lipid homeostasis as well as insulin sensitivity (1–3). In humans, plasma adiponectin concentration was inversely correlated with body weight, body mass index (BMI), and insulin resistance in cross-sectional research (2, 4). On the other hand, weight reduction through calorie-restricted diet or bariatric surgery was associated with an increase in plasma adiponectin (5, 6). This finding suggests that plasma adiponectin concentration is a

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA
Received 31 July 2017. Accepted 20 September 2017.
First Published Online 28 September 2017

Abbreviations: BMI, body mass index; CT, computed tomography; HOMA2, homeostasis model assessment 2; HOMA2%B, homeostasis model assessment 2 of insulin secretion; HOMA2-IR, homeostasis model assessment 2 of insulin resistance.

consequence of body fat mass. In animal research, however, administration of adiponectin resulted in weight loss and increased fatty acid oxidation in muscle in high-fat/sucrose diet fed mice (7). These animal findings suggest that adiponectin may be involved in energy homeostasis and have weight-regulating functions. However, the causal relationship of plasma adiponectin with body weight in humans is not clear from existing cross-sectional observational research. A few prospective human studies have investigated the association between adiponectin concentration and body weight, but were inconclusive (8–11). Low adiponectin concentration was not associated with the development of obesity in Pima Indians, elderly Caucasians, or Afro-Jamaicans (8–10). However, higher adiponectin concentrations were associated with greater weight gain in healthy women in the Nurses' Health Study (11).

As for the relationship between adiponectin and specific fat depots, controversy exists from previous cross-sectional studies on whether abdominal visceral fat or abdominal subcutaneous fat is more closely associated with plasma adiponectin concentration. Several studies have shown that abdominal visceral fat is inversely associated with adiponectin concentration (2, 12, 13), but other studies reported that abdominal subcutaneous fat rather than abdominal visceral fat correlated inversely with adiponectin (14, 15). On the contrary, lower extremity fat depots were positively associated with adiponectin (14, 16). To our knowledge, there is no prospective research on the association of adiponectin concentration with future body composition directly measured by computed tomography (CT).

Likewise, although insulin-sensitizing effects of adiponectin are well established in rodent models (17, 18), it remains unclear whether adiponectin causes changes in insulin sensitivity in humans (19). Reverse causation has also been postulated because the inverse association between adiponectin and insulin resistance may reflect suppression of adiponectin production by compensatory hyperinsulinemia (19), but this can be addressed by prospective research.

Therefore, the purpose of the current study was to investigate the association of baseline plasma concentration of adiponectin with future regional body fat distribution and BMI over a 5-year follow-up in a Japanese American cohort of men and women. We also examined whether adiponectin concentration can predict future insulin sensitivity independent of directly measured fat depots in this population.

Subjects and Methods

Study population

The study population consisted of third-generation (Sansei) Japanese Americans of 100% Japanese ancestry enrolled in the Japanese-American Community Diabetes Study. Methods for selection and recruitment of participants have been described previously (20). The Japanese-American Community Diabetes Study population is representative of Japanese American residents of King County, WA, which includes the Seattle-Tacoma-Bellevue metropolitan statistical area. For the current analysis, eligible subjects had a fasting plasma glucose <126 mg/dL, a 2-hour plasma glucose after a 75-g oral glucose tolerance test <200 mg/dL, and were not taking glucose-lowering agents (n = 253). The study received approval from the University of Washington Human Subjects Division and all subjects provided written informed consent (institutional review board number: 34469).

Clinical and laboratory examination

Blood samples were obtained after an overnight fast of 10 hours. A 75-g oral glucose tolerance test was used to define prediabetes and diabetes mellitus using American Diabetes Association criteria (21). Diabetes was defined as fasting plasma glucose ≥126 mg/dL, 2-hour postload plasma glucose ≥200 mg/dL, or current treatment with oral antidiabetes drugs or insulin. Prediabetes was defined as diagnosed as fasting plasma glucose from 100 to 125 mg/dL or 2-hour plasma glucose levels between 140 and 199 mg/dL and no diagnosis of diabetes.

Plasma glucose was measured by the hexokinase method using an autoanalyzer (Department of Laboratory Medicine, University of Washington, Seattle, WA). Plasma insulin was measured by radioimmunoassay (Diabetes Research Center, University of Washington). Updated computer models for homeostasis model assessment 2 (HOMA2) were used to calculate the indices of insulin resistance (HOMA2-IR) and insulin secretion (HOMA2%B) (https://www.dtu.ox.ac.uk/homacalculator/) (22).

Plasma total adiponectin concentrations were determined in duplicate using a commercially available radioimmunoassay kit (Linco Research, St. Charles, MO). Intra-assay and interassay coefficients of variation were <6.21% and <9.25%, respectively. Plasma was stored at −70°C until assays were performed.

BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). Single (1-cm) CT scan slices of the thorax on inspiration at the level of the nipples, the abdomen at the level of the umbilicus, and the midthigh at a level halfway between the greater trochanter and the superior margin of the patella were analyzed for cross-sectional area of adipose tissue (centimeters squared), defined as ranging from −250 to −50 Hounsfield units using density contour software (standard GE 8800, Milwaukee, WI) (23). In addition to subcutaneous fat at each of these sites, abdominal visceral adiposity was measured as intra-abdominal fat area within the transversalis fascia in centimeters squared at the level of the umbilicus. Total fat area was calculated as the sum of intra-abdominal fat area and subcutaneous abdominal fat area, thorax subcutaneous fat area, and twice the left thigh subcutaneous fat area. Total subcutaneous fat area was defined as total fat area minus the intra-abdominal fat area.

Statistical analysis

Continuous variables are expressed as means ± standard deviation and categorical variables expressed as numerals. Continuous variable distributions were assessed for skewness, and, when found in the case of fasting insulin, HOMA2-IR, and HOMA2%B, were logarithmically transformed for all analyses.

An independent *t* test was used to compare differences between means. Within-person change from baseline to 5-year follow-up measurements was analyzed by paired *t* tests. We estimated unadjusted Pearson correlation coefficients between baseline plasma adiponectin and metabolic variables, anthropometric variables, or body composition measures at 5 years; we also performed these analyses while adjusting for the baseline level of the dependent variables to estimate associations with change over 5 years as reflected by the partial correlation coefficients. Multiple linear regression analysis was used to determine independent associations between BMI, regional fat depots, and insulin resistance at 5 years in relation to baseline plasma adiponectin concentrations. The presence of multicollinearity in multivariate models was evaluated using the variance inflation factor, with a value >5 suggesting its presence (24). The data were analyzed using IBM Statistical Package for the Social Sciences Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). A two-sided *P* value <0.05 was considered to indicate statistical significance.

Results

Of the 253 nondiabetic participants, we excluded 35 subjects with missing CT adiposity data at baseline or 5-year follow-up. The clinical and laboratory characteristics of the subjects are summarized in Table 1. There were 218 subjects included in this study with mean age of 51.7 ± 10.1 years, mean BMI 24.7 ± 3.6 kg/m^2, and 36.2% men. Adiponectin concentrations were significantly higher for women than men. Over the 5-year follow-up period, there were statistically significant changes in weight and BMI.

The cross-sectional analysis of baseline measurements revealed that adiponectin concentration was negatively associated with fasting plasma glucose, fasting insulin, HOMA2-IR, HOMA2%B weight, BMI, abdominal visceral fat area, and abdominal subcutaneous fat area, and was positively associated with thigh subcutaneous fat area (Table 2).

In prospective analysis, the patterns of association between baseline adiponectin concentration and 5-year values of parameters were similar to the cross-sectional analysis except for a nonsignificant correlation with abdominal subcutaneous fat area in unadjusted analysis, although the magnitude of the correlation coefficient was similar to the cross-sectional result (Table 2). We further analyzed 5-year levels while adjusting for baseline levels to permit estimation of the association between adiponectin concentration and change over 5 years. In these adjusted analyses, baseline adiponectin concentration was negatively associated with 5-year change in fasting plasma glucose, fasting insulin, HOMA2-IR, HOMA2% B, and abdominal visceral fat area at 5 years, but no important association was seen with weight, BMI, or thigh subcutaneous fat area.

We next performed multivariate analyses to determine whether baseline adiponectin concentration independently predicted 5-year BMI and abdominal visceral fat area. Baseline adiponectin concentration was not significantly associated with future BMI (Table 3). Age and baseline BMI were independent predictors of 5-year BMI. Baseline adiponectin concentration was significantly and inversely associated with 5-year abdominal visceral fat area after adjusting for baseline traits (including age, sex, BMI, HOMA2-IR, abdominal visceral fat

Table 1. Clinical Characteristics of Study Subjects

	Baseline		5-y Follow-Up	
Characteristics	**Men (n = 79)**	**Women (n = 139)**	**Men (n = 79)**	**Women (n = 139)**
Age (y)	45.9 ± 3.5[a]	55.0 ± 11.1	50.8 ± 3.9[a,b]	60.6 ± 11.1[b]
Weight (kg)	73.7 ± 9.8[a]	57.6 ± 9.6	75.4 ± 10.9[a,b]	58.6 ± 9.8[b]
BMI (kg/m^2)	25.7 ± 3.2[a]	24.1 ± 3.8	26.3 ± 3.5[a,b]	24.6 ± 3.8[b]
Fasting plasma glucose (mg/dL)	100.1 ± 8.0[a]	96.3 ± 9.0	96.5 ± 9.4[b]	95.1 ± 11.3
2-h plasma glucose (mg/dL)	131.6 ± 26.7[a]	142.8 ± 27.9	134.0 ± 36.2[a]	147.2 ± 34.6
Fasting insulin (μU/mL)	16.7 ± 14.1	14.3 ± 7.9	15.4 ± 9.8	14.5 ± 8.3
HOMA2-IR	2.2 ± 1.7	1.9 ± 1.0	2.0 ± 1.2	1.9 ± 1.1
HOMA2%B	127.0 ± 68.6	123.2 ± 38.1	128.4 ± 47.5	127.5 ± 41.8
Adiponectin (μg/mL)	7.3 ± 3.3[a]	11.9 ± 4.7	—	—
Total fat area (cm^2)	417.0 ± 166.3[a]	611.9 ± 246.9	455.7 ± 161.2[a,b]	635.1 ± 236.5
Total subcutaneous fat area (cm^2)	338.1 ± 139.6[a]	538.0 ± 219.1	363.1 ± 134.4[a,b]	557.9 ± 211.2[b]
Abdominal visceral fat area (cm^2)	78.9 ± 38.6	74.9 ± 39.8	91.7 ± 41.2[a,b]	77.0 ± 38.6
Abdominal subcutaneous fat area (cm^2)	154.5 ± 68.8[a]	210.6 ± 98.6	169.2 ± 69.6[a,b]	219.0 ± 93.5
Thigh subcutaneous fat area (cm^2)	47.5 ± 18.9[a]	93.8 ± 35.6	46.7 ± 18.3[a]	89.7 ± 33.6
NGT/prediabetes/diabetes (n)	31/48/0	48/91/0	37/35/7	61/63/15

Data are presented as means ± standard deviation.

NGT, normal glucose tolerance.

[a] $P < 0.05$, significant difference between men and women.

[b] $P < 0.05$, significant difference between baseline examinations values and 5-y follow-up examination values.

Table 2. Correlations Between Baseline Plasma Adiponectin and Measures of Body Fat or Metabolic Characteristics at Baseline and 5-y Follow-Up

Cross-Sectional Analysis			Prospective Analysis				
Baseline Variables	**Unadjusted**	***P* Value**	**5-y Variables**	**Unadjusted**	***P* Value**	**Baseline Level Adjusted**	***P* Value**
Fasting plasma glucose	−0.233	0.001	Fasting plasma glucose	−0.251	<0.001	−0.134	0.048
2-h plasma glucose	0.035	0.603	2-h plasma glucose	−0.033	0.625	−0.072	0.289
Fasting insulin	−0.315	<0.001	Fasting insulin	−0.340	<0.001	−0.249	0.002
HOMA2-IR	−0.318	<0.001	HOMA2-IR	−0.345	<0.001	−0.250	<0.001
HOMA2%B	−0.226	0.001	HOMA2%B	−0.219	0.001	−0.165	0.015
Weight	−0.525	<0.001	Weight	−0.518	<0.001	−0.068	0.316
BMI	−0.366	<0.001	BMI	−0.363	<0.001	−0.069	0.312
Total fat area	−0.085	0.216	Total fat area	−0.108	0.116	−0.044	0.524
Total subcutaneous fat area	−0.045	0.508	Total subcutaneous fat area	−0.053	0.441	0.001	0.983
Abdominal visceral fat area	−0.273	<0.001	Abdominal visceral fat area	−0.324	<0.001	−0.194	0.004
Abdominal subcutaneous fat area	−0.137	0.043	Abdominal subcutaneous fat area	−0.120	0.078	0.008	0.903
Thigh subcutaneous fat area	0.164	0.016	Thigh subcutaneous fat area	0.173	0.011	0.087	0.207

Results are expressed as correlation coefficients.

Partial correlation coefficients for variables at 5-y follow-up are adjusted for the baseline levels.

area, abdominal subcutaneous fat area, thigh subcutaneous fat area) and 5-year weight change (Table 4). We examined the first-order interaction term between adiponectin and sex in the prediction of abdominal visceral fat area in model of Table 4, but found it to not be statistically significant (interaction term coefficient, 0.122; $P = 0.620$). In addition, no significant relationships between baseline adiponectin concentration and future abdominal or thigh subcutaneous fat area were observed when using the same covariates shown in model of Table 4 (data not shown).

As shown in Table 5, baseline adiponectin was significantly associated with greater 5-year HOMA2-IR after adjustment for baseline traits (age, sex, BMI, HOMA2-IR, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area) and weight change. Female sex, BMI, weight change, and abdominal visceral fat area at baseline were also predictors of future HOMA2-IR. No significant interaction was seen between baseline adiponectin and 5-year HOMA2-IR by sex (interaction term coefficient, −0.243; $P = 0.517$) when this interaction term was inserted into the regression model in Table 5.

In addition, when we performed multivariable linear regression analysis of the prediction of change in abdominal visceral fat area and HOMA2-IR over 5 years instead of abdominal visceral fat area and HOMA2-IR at 5 years, we obtained nearly identical results with baseline adiponectin remaining an independent predictor of both outcomes (Supplemental Table 1). As for HOMA2%B, there was no important association between baseline adiponectin and HOMA2%B after adjustment for demographics, overall and regional body composition, and weight change (Supplemental Table 2).

Discussion

These prospective data demonstrate that a low baseline adiponectin concentration was related to accumulation of abdominal visceral fat and increases in insulin resistance over 5 years in Japanese Americans. These findings were independent of age, sex, BMI, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area, HOMA2-IR at baseline, and weight change. However, baseline adiponectin concentration was not related to future weight, BMI, or other

Table 3. Multivariate Linear Regression Analysis of the Prediction of BMI at 5-y Follow-Up

	Model ($R^2 = 0.863$)	
Independent Variables	**β[a]**	***P* Value**
Adiponectin	−0.001	0.989
Age	−0.074	0.036
Female sex	−0.001	0.981
BMI	0.905	<0.001
Abdominal visceral fat area	−0.057	0.161
Abdominal subcutaneous fat area	0.020	0.709
Thigh subcutaneous fat area	0.024	0.547
HOMA2-IR	0.049	0.110

Model adjusted for baseline traits (age, sex, BMI, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area, HOMA2-IR).

[a]Data are expressed as standardized β.

Table 4. Multivariate Linear Regression Analysis of the Prediction of Abdominal Visceral Fat Area at 5-y Follow-Up

	Model (R^2 = 0.715)	
Independent Variables	**β^a**	***P* Value**
Adiponectin	−0.104	0.037
Age	0.184	<0.001
Female sex	−0.066	0.324
BMI	0.245	0.004
Weight change	0.458	<0.001
Abdominal visceral fat area	0.634	<0.001
Abdominal subcutaneous fat area	−0.119	0.123
Thigh subcutaneous fat area	0.022	0.705
HOMA2-IR	−0.020	0.661

Model adjusted for baseline traits (age, sex, BMI, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area, HOMA2-IR) and change in weight.

[a]Data are expressed as standardized β.

CT-measured regional adipose area in multivariate analyses after adjustment for potential confounding factors. This study demonstrates that baseline adiponectin predicts future change in visceral adiposity directly measured by CT.

Our results were consistent with previous epidemiologic research that reported no association between adiponectin and future body weight and BMI in obese Pima Indians, elderly Caucasians, and overweight Afro-Jamaicans (8–10). Weight or BMI is not a direct measurement of body fat and does not capture information on regional body fat distribution. Thus the same weight or BMI may reflect different fat distribution in individuals according to sex, race, and age. In all of the previously mentioned studies, direct repeated measures of regional fat mass were not available. Previous research suggests that the pattern of fat distribution has a greater influence on cardiometabolic risk than fat mass *per se* (25). In particular, visceral adiposity plays an important role in development of obesity-associated metabolic disorders. Emerging evidence indicates that visceral adiposity measured by CT scan is a more accurate predictor for cardiovascular disease and its risk factors than BMI (26, 27). Furthermore, because at any given BMI Asians have greater visceral adiposity than Caucasians, BMI may be a less accurate anthropometric measure predicting future cardiometabolic risk in this ethnic group (28).

Table 5. Multivariate Linear Regression Analysis of the Prediction of HOMA2-IR at 5-y Follow-Up

	Model (R^2 = 0.390)	
Independent Variables	**β^a**	***P* Value**
Adiponectin	−0.223	0.002
Age	−0.006	0.937
Female	0.264	0.008
BMI	0.258	0.036
Weight change	0.295	<0.001
Abdominal visceral fat area	0.296	0.001
Abdominal subcutaneous fat area	0.009	0.935
Thigh subcutaneous fat area	−0.160	0.060
HOMA2-IR	0.091	0.166

Model adjusted for baseline traits (age, sex, BMI, abdominal visceral fat area, abdominal subcutaneous fat area, thigh subcutaneous fat area, HOMA2-IR) and change in weight.

[a]Data are expressed as standardized β.

A prospective study has examined the association between waist circumference and adiponectin concentration, finding that high baseline adiponectin was associated with a lower risk of greater waist circumference as a component of metabolic syndrome in Korean women during 2.6 years of follow-up (29). Because waist circumference is a crude index of abdominal visceral fat, this result supports our findings; however, this analysis cannot distinguish between whether adiponectin was associated with fat accumulation in the visceral or abdominal subcutaneous fat depot (or both) given that a surface measurement was used and direct imaging was not (30).

Although we found that adiponectin had an inverse association with abdominal subcutaneous fat area and a positive relationship with thigh subcutaneous fat area in cross-sectional analyses similar to those previously performed, adiponectin was not associated with change in these fat depots in prospective analyses adjusted for confounding factors. Thus, our data do not support an association between adiponectin concentration and change in these fat depots, and, in the case of abdominal subcutaneous fat, suggest potential reverse causation as the underlying association seen in cross-sectional research (14, 15). That is, the inverse relationship between abdominal subcutaneous fat and adiponectin in cross-sectional research can be explained by greater abdominal subcutaneous fat–induced adiponectin suppression.

The biological mechanism linking adiponectin and visceral adipose tissue is not fully understood. Kim *et al.* (18) reported that a leptin-deficient mouse model with overexpression of adiponectin showed a decrease in visceral fat and increase in subcutaneous fat and improved insulin sensitivity. This finding implies that adiponectin might causally affect body fat distribution.

There are few prospective studies concerning the association between adiponectin and insulin sensitivity. Low baseline adiponectin concentrations were associated with greater insulin resistance over 3 to 4 years in a small sample of Pima Indians (31) and Native Canadians (32). In addition, adiponectin concentration was negatively correlated with subsequent change over 2 years in HOMA-IR in

middle-aged Japanese men (33). Because adiposity is known as a key confounder in this relationship, these studies adjusted for percent body fat, waist circumference, or BMI. Our research used directly measured abdominal visceral fat area, abdominal subcutaneous fat area, and thigh subcutaneous fat as covariates in modeling the adiponectin-insulin resistance relationship. We previously demonstrated an association between greater visceral fat area measured by CT and subsequent development of insulin resistance in Japanese Americans (26). In the current study, low adiponectin significantly predicted insulin resistance independent of BMI, abdominal visceral fat area, abdominal subcutaneous fat area, and thigh subcutaneous fat area. Thus, if causal, the insulin-sensitizing effects of adiponectin may be through pathways other than adiposity. Possible mechanisms for insulin sensitivity may include adiponectin action on skeletal muscle and liver. Previous research showed that adiponectin increased fatty acid oxidation by the activation of 5′-AMP-activated protein kinase in skeletal muscle and liver (7, 34, 35). In addition, adiponectin may enhance insulin sensitivity by modulating insulin signaling molecule insulin receptor substrate-2 or by a reduction in ceramides in liver (36, 37).

The strengths of our study include the direct and precise measurement of regional fat compartments using CT scans at two points in time over 5 years, which allowed us to explore the association between the baseline adiponectin and future change in regional body fat distribution beyond what is possible using BMI or surface measurements of adiposity. In addition, the prospective design permits assessment of temporal sequence not possible in cross-sectional research. There are, however, several limitations. Although high-molecular-weight adiponectin is a more physiologically active form, only total adiponectin was measured in this study. But the concentration of high-molecular-weight adiponectin correlates significantly with total adiponectin, and many other studies are also based on the assessment of total adiponectin concentrations, thereby permitting comparison of our results to an established literature (38). Because we measured adiponectin concentrations at baseline only, we were not able to assess whether changes in adiposity and insulin resistance were associated with longitudinal changes in adiponectin concentration. HOMA-IR is not a gold standard method of assessing insulin resistance. Because HOMA-IR is simply based on basal (*i.e.*, fasting) glucose and insulin concentrations, in contrast to clamps, it does not reflect insulin sensitivity of the stimulated state. Some research has shown that the original HOMA-IR equation compared poorly with directly measured insulin sensitivity derived from the hyperinsulinemic euglycemic clamp or intravenous glucose tolerance test (39, 40). The emerging evidence that race, sex, and insulin secretory function can affect the accuracy of HOMA-IR in estimating insulin sensitivity should also be taken into consideration (40, 41). Despite these limitations, HOMA-IR is still one of the most frequently used tools of determining insulin resistance in large population-based studies. An updated version of HOMA-IR, HOMA2-IR, was developed, and we used the computer model available for its calculation in these analyses (41). In addition, as is true for all observational research, it is possible that unknown confounding factors may be responsible for the associations noted between adiponectin concentration and adiposity or insulin resistance identified in this study. Finally, this cohort was restricted to Japanese Americans; thus, caution should be taken when generalizing our findings to other populations.

In conclusion, low plasma adiponectin concentration predicted future abdominal visceral fat accumulation and greater insulin resistance in Japanese Americans after adjustment for conventional anthropometric and metabolic variables and direct measurements of regional fat depots. The results suggest that adiponectin may play an important role not only in the regulation of body composition, but also insulin resistance. Further studies are needed to confirm our findings in other populations and enhance understanding of the pathophysiological mechanisms linking adiponectin to accrual of abdominal visceral fat and changes in insulin resistance.

Acknowledgments

We thank the King County Japanese-American community for support and cooperation.

***Financial Support*:** This work was supported by National Institutes of Health Grants DK-31170 and HL-49293; facilities and services were provided by the Diabetes Research Center (DK-17047), Clinical Nutrition Research Unit (DK-35816), and the General Clinical Research Center (RR-00037) at the University of Washington. E.J.B. and S.E.K. were supported in this research by the VA Puget Sound Health Care System. The funding entities had no role in the conduct of this study or interpretation of its results.

Author Contributions: S.J.H. and E.J.B. made substantial contributions to the conception and design of the study, drafted the article, and provided approval for the final version. W.Y.F., D.L.L., and S.E.K. revised the article critically for important intellectual content and provided approval for the final version. S.J.H. and E.J.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Correspondence and Reprint Requests: Seung Jin Han, PhD, MD, Department of Endocrinology & Metabolism, Ajou University School of Medicine, 164, World Cup-ro, Yeongtong-gu, Suwon 16499 Republic of Korea. E-mail: hsj@ajou.ac.kr.

Disclosure Summary: The authors have nothing to disclose.

References

1. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. 2006;**6**(10): 772–783.
2. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*. 2003;**46**(4):459–469.
3. Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis*. 2014;**233**(2): 721–728.
4. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001;**86**(5):1930–1935.
5. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab*. 2001;**86**(8):3815–3819.
6. Ma W, Huang T, Zheng Y, Wang M, Bray GA, Sacks FM, Qi L. Weight-loss diets, adiponectin, and changes in cardiometabolic risk in the 2-year POUNDS Lost Trial. *J Clin Endocrinol Metab*. 2016; **101**(6):2415–2422.
7. Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA*. 2001;**98**(4):2005–2010.
8. Vozarova B, Stefan N, Lindsay RS, Krakoff J, Knowler WC, Funahashi T, Matsuzawa Y, Stumvoll M, Weyer C, Tataranni PA. Low plasma adiponectin concentrations do not predict weight gain in humans. *Diabetes*. 2002;**51**(10):2964–2967.
9. Langenberg C, Bergstrom J, Laughlin GA, Barrett-Connor E. Ghrelin, adiponectin, and leptin do not predict long-term changes in weight and body mass index in older adults: longitudinal analysis of the Rancho Bernardo cohort. *Am J Epidemiol*. 2005;**162**(12): 1189–1197.
10. Bennett NR, Boyne MS, Cooper RS, Royal-Thomas TY, Bennett FI, Luke A, Wilks RJ, Forrester TE. Impact of adiponectin and ghrelin on incident glucose intolerance and on weight change. *Clin Endocrinol (Oxf)*. 2009;**70**(3):408–414.
11. Hivert MF, Sun Q, Shrader P, Mantzoros CS, Meigs JB, Hu FB. Higher adiponectin levels predict greater weight gain in healthy women in the Nurses' Health Study. *Obesity (Silver Spring)*. 2011; **19**(2):409–415.
12. Drolet R, Bélanger C, Fortier M, Huot C, Mailloux J, Légaré D, Tchernof A. Fat depot-specific impact of visceral obesity on adipocyte adiponectin release in women. *Obesity (Silver Spring)*. 2009; **17**(3):424–430.
13. Park KG, Park KS, Kim MJ, Kim HS, Suh YS, Ahn JD, Park KK, Chang YC, Lee IK. Relationship between serum adiponectin and leptin concentrations and body fat distribution. *Diabetes Res Clin Pract*. 2004;**63**(2):135–142.
14. Frederiksen L, Nielsen TL, Wraae K, Hagen C, Frystyk J, Flyvbjerg A, Brixen K, Andersen M. Subcutaneous rather than visceral adipose tissue is associated with adiponectin levels and insulin resistance in young men. *J Clin Endocrinol Metab*. 2009;**94**(10): 4010–4015.
15. Fujikawa R, Ito C, Nakashima R, Orita Y, Ohashi N. Is there any association between subcutaneous adipose tissue area and plasma total and high molecular weight adiponectin levels? *Metabolism*. 2008;**57**(4):506–510.
16. Borges MC, Oliveira IO, Freitas DF, Horta BL, Ong KK, Gigante DP, Barros AJ. Obesity-induced hypoadiponectinaemia: the opposite influences of central and peripheral fat compartments [published online ahead of print March 27, 2017]. *Int J Epidemiol*.
17. Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H, Rossetti L, Scherer PE. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem*. 2006;**281**(5):2654–2660.
18. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J Clin Invest*. 2007;**117**(9):2621–2637.
19. Cook JR, Semple RK. Hypoadiponectinemia–cause or consequence of human "insulin resistance"? *J Clin Endocrinol Metab*. 2010; **95**(4):1544–1554.
20. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW. Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes*. 1987;**36**(6):730–739.
21. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;**27**(Suppl 1):S5–S10.
22. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998;**21**(12):2191–2192.
23. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri VM, Moss AA, Fujimoto WY. Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol*. 1986;**21**(6): 483–487.
24. Kutner M, Nachtsheim C, Neter J. *Applied Linear Statistical Models*. 4th ed. Chicago, IL: McGraw-Hill; 2004.
25. Amato MC, Guarnotta V, Giordano C. Body composition assessment for the definition of cardiometabolic risk. *J Endocrinol Invest*. 2013;**36**(7):537–543.
26. Hayashi T, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY. Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. *Diabetes*. 2008;**57**(5):1269–1275.
27. Neeland IJ, Turer AT, Ayers CR, Berry JD, Rohatgi A, Das SR, Khera A, Vega GL, McGuire DK, Grundy SM, de Lemos JA. Body fat distribution and incident cardiovascular disease in obese adults. *J Am Coll Cardiol*. 2015;**65**(19):2150–2151.
28. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr*. 2007;**86**(2):353–359.
29. Kim JY, Ahn SV, Yoon JH, Koh SB, Yoon J, Yoo BS, Lee SH, Park JK, Choe KH, Guallar E. Prospective study of serum adiponectin and incident metabolic syndrome: the ARIRANG study. *Diabetes Care*. 2013;**36**(6):1547–1553.
30. Hanley AJ, Wagenknecht LE. Abdominal adiposity and diabetes risk: the importance of precise measures and longitudinal studies. *Diabetes*. 2008;**57**(5):1153–1155.
31. Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, Youngren JF, Havel PJ, Pratley RE, Bogardus C, Tataranni PA. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes*. 2002;**51**(6):1884–1888.
32. Hanley AJ, Connelly PW, Harris SB, Zinman B. Adiponectin in a native Canadian population experiencing rapid epidemiological transition. *Diabetes Care*. 2003;**26**(12):3219–3225.
33. Yamamoto Y, Hirose H, Saito I, Nishikai K, Saruta T. Adiponectin, an adipocyte-derived protein, predicts future insulin resistance: two-year follow-up study in Japanese population. *J Clin Endocrinol Metab*. 2004;**89**(1):87–90.
34. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB,

Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;**8**(11):1288–1295.

35. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheeseboro L, Ding YY, Russell RG, Lindemann D, Hartley A, Baker GR, Obici S, Deshaies Y, Ludgate M, Rossetti L, Scherer PE. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology*. 2004;**145**(1):367–383.
36. Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K, Kobayashi M, Iwane A, Sasako T, Okazaki Y, Ohsugi M, Takamoto I, Yamashita S, Asahara H, Akira S, Kasuga M, Kadowaki T. Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. *Cell Metab*. 2011;**13**(4):401–412.
37. Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, Wade MR, Tenorio VM, Kuo MS, Brozinick JT, Zhang BB, Birnbaum MJ, Summers SA, Scherer PE. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat Med*. 2011;**17**(1):55–63.
38. Funahashi T, Matsuzawa Y. Adiponectin and the cardiometabolic syndrome: an epidemiological perspective. *Best Pract Res Clin Endocrinol Metab*. 2014;**28**(1):93–106.
39. Kang ES, Yun YS, Park SW, Kim HJ, Ahn CW, Song YD, Cha BS, Lim SK, Kim KR, Lee HC. Limitation of the validity of the homeostasis model assessment as an index of insulin resistance in Korea. *Metabolism*. 2005;**54**(2):206–211.
40. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. *Diabetes Care*. 2013;**36**(4):845–853.
41. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;**27**(6):1487–1495.