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ORIGINAL ARTICLE

Circulating adiponectin levels and risk of type 2 diabetes in the Japanese

S Yamamoto[1], Y Matsushita[2], T Nakagawa[1], T Hayashi[1], M Noda[3] and T Mizoue[2]

BACKGROUND: Adiponectin has anti-inflammatory and insulin-sensitizing properties. Prospective studies have consistently shown a lower risk of type 2 diabetes among those with higher circulating adiponectin levels.
OBJECTIVE: We examined prospectively the association between serum adiponectin levels and type 2 diabetes risk among Japanese workers, taking visceral fat mass into account.
SUBJECTS AND METHODS: Subjects were 4591 Japanese employees who attended a comprehensive health screening in 2008; had biochemical data including serum adiponectin; were free of diabetes at baseline; and received health screening in 2011. Multiple logistic regression analysis was used to examine the association between adiponectin and incidence of diabetes among overall subjects, as well as subgroups. Stratified analyses were carried out according to variables including visceral fat area (VFA).
RESULTS: During 3 years of follow-up, 217 diabetic cases were newly identified. Of these, 87% had a prediabetes at baseline. Serum adiponectin level was significantly, inversely associated with incidence of diabetes, with odds ratios (95% confidence interval) adjusted for age, sex, family history, smoking, alcohol drinking, physical activity and body mass index (BMI) for the lowest through highest quartile of adiponectin of 1 (reference), 0.79 (0.55–1.12), 0.60 (0.41–0.88) and 0.40 (0.25–0.64), respectively (*P*-value for trend < 0.01). This association was materially unchanged with adjustment for VFA instead of BMI. After further adjustment for both homeostasis model assessment of insulin resistance and hemoglobin A1c, however, the association became statistically nonsignificant (*P*-value for trend = 0.18). Risk reduction associated with higher adiponectin levels was observed in both participants with and without obesity or insulin resistance at baseline.
CONCLUSIONS: Results suggest that higher levels of circulating adiponectin are associated with a lower risk of type 2 diabetes, independently of overall and intra-abdominal fat deposition, and that adiponectin may confer a benefit in both persons with and without insulin resistance.

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INTRODUCTION

The number of diabetic patients has greatly increased in the past few decades in the world including Asia.[1,2] Diabetes requires long-term medical care for glycemic control and decreases quality of life owing to complications such as retinopathy, neuropathy and nephropathy, leading to a large increase in medical expenditure.[3] Additionally, diabetes increases risk of life-threatening diseases including cardiovascular disease and cancer.[4] The prevention of diabetes is thus one of the priority issues.

Experimental and epidemiologic evidence has accumulated that supports a beneficial role of adiponectin, a major cytokine secreted from adipocyte, in glucose metabolism. Mechanistic studies show that adiponectin improves insulin sensitivity and inflammation,[5,6] important mechanisms in the development of type 2 diabetes. In humans, several prospective studies have consistently shown a lower risk of type 2 diabetes among those with higher baseline levels of circulating adiponectin.[7] However, some important issues remain to be solved. Data are conflicting as to the attenuation of adiponectin–type 2 diabetes association after adjusting for baseline levels of glucose[8–16] and insulin resistance,[12,17–19] and few studies adjusted for precisely measured visceral fat mass.[18,19] Such information would be useful when inferring the major underlying conditions linking adiponectin to type 2 diabetes or selecting variables in the prediction of diabetes risk. Further, data are limited and conflicting whether the association between adiponectin and type 2 diabetes risk is modified by levels of obesity[11,17,20] and insulin resistance;[18,19] to our knowledge, no data are available for visceral fat.

To address these issues, we examined prospectively the association between serum adiponectin levels and risk of type 2 diabetes among employees of a large company in Japan while adjusting for a range of obesity and glucose metabolism markers, including visceral fat area (VFA), measured using a computed tomography (CT), and homeostasis model assessment of insulin resistance (HOMA-IR). We also assessed the above associations with stratification by these variables.

SUBJECTS AND METHODS

Study design and participants

The Hitachi Health Study is an ongoing study among employees and their spouses who participated in a comprehensive health examination at Hitachi Health Care Center (Hitachi, Japan).[21] Of 17 606 screening examinees between April 2008 and March 2009 (baseline of the present analysis), 6996 participants underwent a CT and agreed to donate blood specimen for the study. Of these, 6612 subjects received health examination in fasting condition (fasted at least 12 h) and had data on

[1]Occupational Health Section, Hitachi Ltd., Hitachi Health Care Center, Hitachi City, Ibaraki, Japan; [2]Center for Clinical Sciences, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan and [3]Department of Diabetes and Metabolic Medicine and Diabetes Research Center, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan. Correspondence: Dr S Yamamoto, Occupational Health Section, Hitachi Ltd., Hitachi Health Care Center, 4-3-16, Ouse-cho, Hitachi City 317-0076, Ibaraki, Japan. E-mail: shuichiro.yamamoto.sr@hitachi.com
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all variables used in the present analysis. Of these, we excluded 445 patients with diabetes under treatment and another 363 who met the diagnostic criteria for diabetes at baseline (fasting plasma glucose (FPG) $\geqslant 126$ mg dl^{-1} (7.0 mmol l^{-1}) and/or hemoglobin A1c (HbA1c) $\geqslant 6.5\%$ (48 mmol mol^{-1})). Of the remaining 5804 participants free of diabetes at baseline, 4591 participated in the 3-year follow-up examination between April 2011 and March 2012 (aged 25–73 years, 4124 men and 467 women) and formed a cohort of this present analysis. According to the report of American Diabetes Association,[22] we defined the incidence of diabetes if a participant had either of the following conditions at the follow-up examination: FPG $\geqslant 126$ mg dl^{-1} (7.0 mmol l^{-1}), HbA1c $\geqslant 6.5\%$ (48 mmol mol^{-1}) or being under medical treatment for diabetes.

Health-related lifestyles including smoking, alcohol drinking, and leisure time and commuting physical activity, as well as own and family history of disease were ascertained via a questionnaire. Height and weight were measured using an automated scale (BF-220; Tanita, Tokyo, Japan). Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m^2). The VFA at the umbilical level was measured using a CT scanner (Radix turbo; Hitachi Medico, Tokyo, Japan) while the examinee was in a supine position and calculated using a software application (fatPointer; Hitachi Medico). The imaging conditions were 120 kV and 50 mA, using a 5-mm-thick slice. The glucose level was measured using glucose oxidase enzyme electrode method (A&T, Tokyo, Japan). Fasting serum immunoreactive insulin (μU ml^{-1}) was determined by an immunoenzymatic method using the AxSYM insulin assay (Abbott Laboratories, Tokyo, Japan). Adiponectin levels were measured using an immunoturbidimetric method (Adiponectin Latex Kit for humans; Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan). HOMA-IR, an index of insulin resistance, was calculated as fasting glucose (mg dl^{-1}) multiplied by fasting insulin (μU ml^{-1}) divided by 405. Homeostasis model assessment of β-cell function (HOMA-β), an index of insulin secretion, was calculated as 360 multiplied by fasting insulin (μU ml^{-1}) divided by (fasting glucose (mg dl^{-1}) − 63). HbA1c level was measured using a high-performance liquid chromatography method (HLC723-G9; Tosoh, Tokyo, Japan). The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%)+0.4%.[23] This study was approved by the ethics review committee of the Hitachi Health Care Center and the National Center for Global Health and Medicine. Written informed consent was obtained from all subjects.

Statistical analyses

Baseline characteristics were compared between participants with and without incident diabetes by using either *t*-test (continuous variables) or χ^2 test (categorical variables). Multiple logistic regression analysis was used to assess the association of serum adiponectin levels and incidence of diabetes. Odds ratios (ORs) and 95% confidence interval (95% CIs) for the incidence of diabetes were calculated for each quartile of adiponectin levels, with the lowest quartile as reference, while adjusting for sex, age (years, continuous), family history of diabetes (parent or sibling, yes or no), smoking (never, past or current), alcohol use (nondrinker, drinker consuming <1, 1–1.9 or $\geqslant 2$ *go* (1 *go* contains 23 g ethanol) per day) and leisure time and commuting physical activity ($\geqslant 400$ and <400 METs-min per week, respectively; Model 1). Moreover, we created various models with additional adjustment for either of the following obesity and glucose metabolism markers: BMI (kg m^{-2}, continuous; Model 2), VFA (cm^2, continuous; Model 3), BMI and HOMA-IR (continuous; Model 4), BMI and HbA1c (continuous, Model 5) and BMI, HbA1c and HOMA-IR (Model 6). To examine whether the association differs by the level of obesity, insulin resistance and insulin secretary function, we repeated the above analyses (Model 1) using tertile of adiponectin instead of quartile with stratification by BMI (<25 or $\geqslant 25$ kg m^{-2}), VFA (lower two-thirds or higher third), HOMA-IR (lower two-thirds or higher third) and HOMA-β (lower third or higher two-thirds). To test the interaction, a term was generated by multiplying a stratified variable (dichotomized) and adiponectin (with 1 to 3 being assigned to increasing tertile of adiponectin and treated as continuous) and added (together with the stratified variable) to the Model 1. All tests were two-sided and *P*-values <0.05 were considered statistically significant. All the analyses were performed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the 3-year follow-up, a total of 214 patients were newly identified as having diabetes. Of these, 87% of patients were in a prediabetic condition at baseline (FPG $\geqslant 110$ mg dl^{-1} (6.1 mmol l^{-1}) and/or HbA1c $\geqslant 6.0$ (42 mmol mol^{-1})). Table 1 compares the baseline characteristics of study participants between those who developed diabetes and those who did not. Compared with participants who had been free of diabetes through the study period, patients who developed diabetes were older, had a higher mean of BMI, VFA, waist circumference, fasting plasma glucose, HbA1c, fasting insulin and HOMA-IR, but had a lower mean of serum adiponectin levels.

Table 2 shows association between adiponectin concentrations and 3-year incidence of type 2 diabetes. In the basic model with adjustment for sex, age, family history of diabetes, smoking, alcohol use and physical activity (Model 1), higher adiponectin at baseline was significantly associated with lower risk of type 2 diabetes; OR (95% CI) of type 2 diabetes for the lowest through highest quartiles of adiponectin levels was 1 (reference), 0.76 (0.53–1.08), 0.54 (0.37–0.79) and 0.33 (0.21–0.52), respectively (*P*-values for trend <0.01). The association was only slightly attenuated after further adjusting for BMI (Model 2) or VFA (Model 3); ORs for the highest quartile were around 0.4. The odds of diabetes in the highest quartile of adiponectin was somewhat elevated after additional adjustment for either baseline HOMA-IR (Model 4: OR = 0.53) or HbA1c (Model 5: OR = 0.56), but remained statistically significant. In the full model adjusting for all variables including HOMA-IR and HbA1c (Model 6), there was a sizable attenuation in association, which became statistically nonsignificant (OR for the highest quartile = 0.69; *P*-value for trend = 0.18).

Table 3 shows results of analyses stratified by BMI, VFA, HOMA-IR and HOMA-β. A statistically significant, inverse association between adiponectin and type 2 diabetes risk was observed in all subgroups. The inverse association seems to be stronger in obese than non-obese participants (*P*-value for interaction by BMI

Table 1. Characteristics of study subjects at baseline

	Subjects without diabetes incidence	*Subjects with diabetes incidence*
Number	4377	214
Sex (% women)	10.3	7.9
Age (years)	52.2 (9.6)	55.9 (8.7)**
Family history of diabetes (%)	16.7	22.9*
Smoking (%)		
Never	35.2	32.2
Past	31.8	35.0
Current	32.9	32.7
Alcohol use (%)		
Nondrinker	28.5	26.6
Drinking <1 *go* per day	39.8	38.8
Drinking 1–1.9 *go* per day	22.1	22.9
Drinking $\geqslant 2$ *go* per day	9.6	11.7
Physical activity, % $\geqslant 400$ MET-min per week[a]	49.2	51.4
Body mass index (kg m^{-2})	23.8 (2.9)	24.8 (3.4)**
Waist circumference (cm)	86.0 (12.9)	88.4 (8.8)**
Visceral fat areas (cm^2)	115 (52)	137 (53)**
Fasting glucose (mg dl^{-1})	99.7 (7.9)	112.5 (7.9)**
Hemoglobin A1c (%, mmol mol^{-1})	5.7 (0.3), 39 (2.8)	6.0 (0.3)**, 42 (2.8)**
Fasting insulin (μU ml^{-1})	5.8 (3.5)	8.1 (6.1)**
HOMA-IR	1.46 (0.94)	2.26 (1.71)**
HOMA-β	57.6 (32.6)	59.3 (45.8)
Adiponectin (μg ml^{-1})	7.93 (4.09)	6.82 (3.57)**

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function, HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent. Values are mean (s.d.), unless stated otherwise; *$P<0.05$ and **$P<0.01$. [a]Physical activity during leisure time and on commuting to work.

Table 2. Association between adiponectin concentrations and 3-year incidence of type 2 diabetes

	Quartile of adiponectin concentrations				P-*value for trend*
	1	*2*	*3*	*4*	
Adiponectin ($\mu g\,ml^{-1}$)	<5.2	5.2–6.8	6.9–9.5	$\geqslant 9.6$	
No. of cases/total subjects	76/1145	60/1138	47/1174	31/1134	
Incidence (%)	6.6	5.3	4.0	2.7	
OR1 (95% CI)	1	0.76 (0.53, 1.08)	0.54 (0.37, 0.79)	0.33 (0.21, 0.52)	<0.01
OR2 (95% CI)	1	0.79 (0.55, 1.12)	0.60 (0.41, 0.88)	0.40 (0.25, 0.64)	<0.01
OR3 (95% CI)	1	0.80 (0.56, 1.13)	0.61 (0.41, 0.89)	0.43 (0.27, 0.70)	<0.01
OR4 (95% CI)	1	0.93 (0.65, 1.34)	0.76 (0.51, 1.13)	0.53 (0.33, 0.86)	0.01
OR5 (95% CI)	1	1.03 (0.71, 1.51)	0.80 (0.53, 1.19)	0.56 (0.35, 0.91)	0.02
OR6 (95% CI)	1	1.16 (0.79, 1.70)	0.99 (0.64, 1.46)	0.69 (0.42, 1.13)	0.18

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio. OR1: Adjusted for sex, age, family history of diabetes, smoking, alcohol drinking and physical activity OR2: Adjusted for body mass index plus variables in OR1. OR3: Adjusted for visceral fat area plus variables in OR1. OR4: Adjusted for HOMA-IR plus variables in OR2. OR5: Adjusted for hemoglobin A1c plus variables in OR2. OR6: Adjusted for HOMA-IR and hemoglobin A1c plus variables in OR2.

Table 3. Association between adiponectin concentrations and 3-year incidence of type 2 diabetes according to stratified variables

Stratified variable	*Incidence*	*Odds ratio (95% confidence interval)*[a]			P-*value for trend*	P-*value for interaction*
	%	*T1* [b]	T2	T3		
Body mass index ($kg\,m^{-2}$)						
<25	3.8	1	1.05 (0.68, 1.64)	0.53 (0.32, 0.88)	0.01	
$\geqslant 25$	6.5	1	0.66 (0.41, 1.05)	0.30 (0.15, 0.62)	<0.01	0.03
Visceral fat area[c]						
Low	3.4	1	0.99 (0.62, 1.59)	0.47 (0.28, 0.81)	<0.01	
High	7.1	1	0.78 (0.51, 1.19)	0.43 (0.22, 0.83)	0.01	>0.2
HOMA-IR[c]						
Low	3.1	1	0.83 (0.51, 1.36)	0.56 (0.33, 0.96)	0.03	
High	7.7	1	0.98 (0.65, 1.49)	0.43 (0.22, 0.81)	0.03	>0.2
HOMA-β[c]						
Low	5.4	1	0.74 (0.43, 1.29)	0.44 (0.25, 0.79)	<0.01	
High	4.3	1	0.82 (0.56, 1.20)	0.27 (0.15, 0.49)	<0.01	0.12

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function, HOMA-IR, homeostasis model assessment of insulin resistance. [a]Adjusted for sex, age, family history of diabetes, smoking, alcohol drinking and physical activity. [b]Tertile of adiponectin ($\mu g\,ml^{-1}$): T1, <5.7; T2, 5.7–8.4; T3, $\geqslant 8.5$. [c]Definition (cutoff) of 'Low' group: lower two-thirds for visceral fat area ($138\,cm^2$), HOMA-IR (1.61) and lower one-third for HOMA-β (40.1).

category = 0.03), although OR in the highest tertile of adiponectin was significantly decreased in both groups.

Incidence proportion of diabetes much differ according to baseline glucose level: 14.7% among those with an FPG $\geqslant 110$ $mg\,dl^{-1}$ ($6.1\,mmol\,l^{-1}$) and/or HbA1c $\geqslant 6.0\%$ ($42\,mmol\,mol^{-1}$), a status strongly predictive of definite progression to diabetes,[24] and 0.8% among those without prediabetes. Of patients who developed diabetes during the follow-up, 87% were in prediabetic state at baseline. Among subjects without prediabetes at baseline, OR (95% CI) of type 2 diabetes for the lowest through highest tertile of adiponectin levels was 1 (reference), 1.06 (0.41–2.78), 1.08 (0.41–2.89), respectively (*P*-value for trend >0.2).

DISCUSSION

In this large, prospective study among a Japanese population, we found that baseline serum adiponectin concentrations were statistically significantly, inversely associated with risk of type 2 diabetes during 3 years. This association persisted even after adjusting for known risk factors of type 2 diabetes (age, sex, family history of diabetes, smoking, alcohol drinking, physical activity, BMI) or precise measure of abdominal obesity (CT-assessed VFA) instead of BMI. After additional adjustment for both HOMA-IR and HbA1c, however, the association was attenuated and became statistically nonsignificant.

Numerous studies to date have consistently reported a lower risk of type 2 diabetes in individuals with higher circulating adiponectin levels. In a meta-analysis of prospective studies on this issue,[7] the inverse association was shown to be consistent across studies with diverse populations that varied in several methodologic aspects, including adiponectin measurement, diagnostic procedure of diabetes, length of follow-up and confounding variables considered, giving a strong creditability for a protective role of adiponectin against the development of type 2 diabetes. In the present study, nearly 90% of patients who developed diabetes during follow-up had in prediabetic condition

an FPG $\geqslant 110\,mg\,dl^{-1}$ ($6.1\,mmol\,l^{-1}$) and/or HbA1c $\geqslant 6.0$ (42 mmol/;mol^{-1}) at baseline. Thus, the present study provides data to support a protective role of adiponectin mainly in the progression from prediabetes to diabetes.

It is well known that circulating adiponectin concentrations decrease with increasing levels of obesity,[6] which may largely account for the association between this adipokine and diabetes risk. In the present study, the association between adiponectin levels and diabetes risk was materially unchanged after adjustment for BMI, a finding compatible with those in most previous reports.[7] Moreover, the adjustment for CT-assessed abdominal fat area, which is more closely associated with adiponectin levels than subcutaneous fat,[25] had little impact on the association between adiponectin and diabetes risk, a finding compatible with those in a few previous studies that measured abdominal fat levels using CT.[18,19] These results suggest that neither systemic nor regional fat deposition can fully explain the inverse association between adiponectin and type 2 diabetes risk.

The major, hypothesized role of adiponectin against impairment of glucose metabolism is its favorable effect on insulin sensitivity. Mechanistic studies show that adiponectin improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in the skeletal muscle and liver through improving AMP-activated protein kinase.[5] In the present study, the odds of diabetes in the highest quartile of adiponectin was modestly changed after adjustment for either baseline HOMA-IR (Model 4: OR = 0.53) or HbA1c (Model 5: OR = 0.56), but a more significant change was observed after additionally adjusting for both HOMA-IR and HbA1c (Model 6: OR = 0.69). Some studies have reported a sizable attenuation in association after adjusting for insulin resistance marker (HOMA-IR or fasting insulin)[17,18] or glycemic marker (glucose or HbA1c).[13–16,19] These findings are compatible with the hypothesized protective role of adiponectin against type 2 diabetes (i.e., lowering blood glucose through improving insulin sensitivity). Besides the etiologic importance of adiponectin, however, the measurement of this adipokine may not significantly improve predictive ability once data on traditional markers of glucose metabolism are available.

Hivert *et al.*[18] reported a decreased risk of type 2 diabetes associated with higher adiponectin in insulin-resistant but not in insulin-sensitive individuals in two cohorts, although the interaction was statistically significant in one of these cohorts. Similarly, in a 4-year follow-up study of older British men, Wannamethee *et al.*[17] found that risk of type 2 diabetes associated with higher adiponectin levels was decreased among obese participants but not among non-obese participants. In the present study, although the association was slightly stronger among obese than non-obese participants, diabetes risk in the highest tertile group was decreased in both those with higher and lower HOMA-IR and in both obese and non-obese participants. The inconsistency between the previous and present studies may be ascribed, at least in part, to lower capacity of people of East Asian origin than non-Hispanic whites to secrete insulin.[26] Even modest insulin resistance may confer diabetes risk in Japanese, who in turn might receive greater benefit from improving insulin sensitivity by maintaining higher level of adiponectin. Alternatively, the differential association may be due to chance. In fact, two other reports[11,20] did not find a significant difference in association by BMI level.

The strengths of the present study include a large number of participants, prospective design and the adjustment for known and potential confounders. As regards ascertainment of diabetes, most previous studies on this issue relied on fasting glucose and/or self-reported diabetes, whereas the present study additionally used HbA1c to exclude diabetes patients at baseline as well as to diagnose diabetes incidence at the follow-up. The present study also has some limitations. First, dietary information was not obtained. Some dietary factors including coffee[27] and fish oil[28] have been shown to be related to or influence circulating adiponectin levels, and thus the observed association in the present study might, at least in part, be ascribed to dietary factors. Second, follow-up period (3-year) of the present study was relatively short, and thus statistical power might not be sufficient to detect an association in a low-risk subgroup. Finally, the study participants were employees and their dependents of a large-scale company in Japan, and the majority were male (90%). Thus, caution should be exercised when generalizing the present finding.

In summary, higher levels of serum adiponectin were associated with decreased risk of type 2 diabetes in Japanese, and this association was independent of overall or abdominal fat deposition, supporting a significant protective role of adiponectin against the development of type 2 diabetes. Given that dietary and physical activity intervention, an established strategy of the prevention for type 2 diabetes, can increase circulating adiponectin levels,[29] the present data may help understand the biologic mechanism whereby lifestyle modification prevents diabetes. Additional studies are warranted to examine whether increasing circulating levels of adiponectin can decrease risk of type 2 diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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