Serum adiponectin levels predict the risk of coronary heart disease in Japanese patients with type 2 diabetes

Yoshinari Obata[1]*, Yuya Yamada[1], Mitsuaki Kyo[1], Yasumitsu Takahi[1], Kenji Saisho[1], Sachiko Tamba[1], Koji Yamamoto[1], Kiyonori Katsuragi[2], Yuji Matsuzawa[1]

ABSTRACT

Aims/Introduction: An inverse association between adiponectin and coronary heart disease (CHD) has been found in Caucasians, but it is uncertain whether this association can be extrapolated to the East Asian population. The present study aimed to investigate whether serum adiponectin levels can predict CHD in Japanese patients with type 2 diabetes as observed in Caucasians.

Materials and Methods: This longitudinal study included 504 patients with type 2 diabetes (342 men and 162 women) who were admitted to Sumitomo Hospital between July 2005 and December 2006. We used Cox proportional hazard analysis to estimate the hazard ratio (HR) of CHD associated with serum adiponectin levels at baseline.

Results: During a median follow up of 5.7 years (2177 person-years), 40 participants had new CHD and 10 had recurrent CHD. After multivariate adjustment, the highest compared with the lowest quartile of serum adiponectin levels had a significantly reduced risk of CHD (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.13–0.94; $P = 0.017$). The multivariate adjusted HR for the risk of CHD according to a doubling of adiponectin at baseline was 0.61 (95% CI 0.39–0.97; $P = 0.037$).

Conclusions: High serum adiponectin levels are significantly associated with a lower risk of CHD in Japanese patients with type 2 diabetes. This association is independent of other well-known CHD risk factors. (J Diabetes Invest, doi: 10.1111/jdi.12078, 2013)

KEY WORDS: Adiponectin, Coronary disease, Type 2 diabetes mellitus

INTRODUCTION

Adiponectin is a collagen-like peptide, abundantly secreted by adipose tissue, and has several biological activities, such as enhancement of insulin sensitivity and stimulation of fatty-acid oxidation[1,2]. Hypoadiponectinemia is associated with an increased risk of type 2 diabetes[3], hypertension[4] and dyslipidemia[5], which are risk factors for atherosclerosis. In addition, adiponectin has anti-arteriosclerotic properties by various mechanisms. For example, adiponectin has anti-inflammatory properties by inhibiting the nuclear factor kappa beta pathway[6], it downregulates adhesion molecule expression[7], stimulates production of nitric oxide[8] and suppresses apoptosis[9] in endothelial cells. In apolipoprotein E-deficient mice, breeding with adiponectin transgenic mice inhibits the progression of atherosclerosis despite unaltered glucose and lipid metabolism[10]. These data suggest that high serum adiponectin levels might be related to a lower risk of coronary heart disease (CHD).

Several case–control and cohort studies have shown that high serum adiponectin levels are associated with a lower risk of CHD[11–16]. However, most previous studies were carried out in healthy Caucasians or patients with type 2 diabetes in Western countries. East Asian populations, including the Japanese, are less obese, less resistant to insulin and have a lower incidence of CHD than Caucasians[17,18], and CHD is not necessarily a leading cause of mortality[19]. In addition, compared with patients with type 2 diabetes in Western countries, those in East Asian countries have different features regarding cardiovascular complications, such as the relationship between predictors for macro- and microvascular complications[20], the effect of metabolic syndrome[21] or lipid profiles[22]. In Japanese patients with type 2 diabetes, serum triglyceride levels are a leading predictor of CHD, comparable with low-density lipoprotein (LDL), which is the best predictor of CHD in patients with type 2 diabetes in Western countries[22].

Based on the aforementioned findings, it is uncertain whether previous results in Caucasians can be extrapolated to the East Asian population, and ethnic specificity might need to be taken into account when the association between adiponectin and the risk of CHD is investigated.

[1]Department of Endocrinology and Metabolism, Sumitomo Hospital, Osaka, and [2]Otsuka Pharmaceutical Co. Ltd, Tokushima, Japan
*Corresponding author. Yoshinari Obata Tel.: +81-6-6433-1261 Fax: +81-6-6444-3975
E-mail address: obata-yosinari@sumitomo-hp.or.jp
Received 9 November 2012; revised 14 February 2013; accepted 19 February 2013

Therefore, the present study aimed to investigate whether serum adiponectin levels can predict CHD in Japanese patients with type 2 diabetes, as observed in Caucasians, after adjustment for well-known CHD risk factors and various parameters, which affect serum adiponectin levels.

MATERIALS AND METHODS

Participants

The participants included 504 patients with type 2 diabetes (342 men and 162 women) who were admitted to Sumitomo Hospital, Osaka, Japan, between July 2005 and December 2006. They were admitted short-term for glycemic control and an examination of complications associated with diabetes. Type 2 diabetes was diagnosed according to the criteria published by the Japan Diabetes Society (JDS)[23]. Patients treated with pioglitazone were excluded, because this drug has been reported to be associated with high serum adiponectin levels[24]. Patients who had a history of CHD before admission were included in the present study.

Each participant's follow-up time began on the date of admission to the hospital and continued until the diagnosis of a cardiovascular end-point, death, discontinuation of follow up or June 2012, whichever came first.

Cardiovascular end-points consisted of fatal CHD, new-onset or recurrent non-fatal myocardial infarction and first or recurrent coronary angioplasty or coronary bypass surgery. The diagnosis of non-fatal myocardial infarction was confirmed by review of medical records using the criteria published by the World Health Organization[25]. Death from cardiovascular events or other causes was confirmed by review of medical records.

The present study was carried out according to the principles of the Declaration of Helsinki and was approved by the ethical committee of Sumitomo Hospital. Informed consent was obtained from all of the patients on admission to hospital.

Clinical and Laboratory Assessments

Participants provided information on their medication use, smoking status (current smokers, past smokers and never smokers), past history and family history of CHD on admission to hospital. Height and bodyweight were measured while people were wearing light underwear without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of the umbilicus according to the recommendation by the Japan Society for the Study of Obesity. Blood pressure (BP) was measured while the subject was sitting. After an overnight fast, blood was obtained to measure biochemical parameters and adiponectin. The value for hemoglobin A1c (HbA_{1c};%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS;%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)[26,27]. Plasma glucose and serum lipid levels were measured using routine automated laboratory methods. LDL was calculated using the Friedewald formula, except for when triglycerides (TG) exceeded 400 mg/dL, in which case LDL data were treated as "missing". This situation was applicable to 15 participants. Estimated glomerular filtration rate (eGFR) was calculated using the formula published by the Japanese Society of Nephrology[28]. Serum total adiponectin levels were measured by a latex particle-enhanced turbidimetric immunoassay (human adiponectin latex kit; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) as previously reported[29]. The within-run and total coefficient of variation of this assay were 0.8–1.9% and 1.1–2.0%, respectively, and the results were highly correlated with enzyme-linked immunosorbent assay-based methods ($r = 0.99$)[29].

Statistical Analysis

Participant characteristics are expressed as means ± SD, medians (25th–75th percentile) or percentage. Participants were divided into four categories based on serum adiponectin levels at baseline. Continuous variables were compared between each category using analysis of variance. *Post-hoc* multiple comparisons were made using Tukey's test. Extremely skewed variables, such as TG, duration of diabetes and adiponectin levels, were log-transformed before analysis. Categorical variables were compared using the χ^2-test. We used Cox proportional hazard analysis to estimate the multivariate adjusted hazard ratio (HR) and 95% confidence interval (CI) for each quartile of adiponectin compared with the lowest category, and tested for linear trends across categories using log-transformed serum adiponectin levels. We also estimated the multivariate adjusted HR associated with a doubling of serum adiponectin level. Serum adiponectin levels were log-transformed, and the HR was estimated for an increase by two units on the log scale, which corresponds to a doubling on the original scale. Multivariate models included the covariates of age, sex, waist circumference or BMI, HbA_{1c} (NGSP), duration of diabetes, high-density lipoprotein (HDL), log-transformed TG, LDL, eGFR, systolic BP (SBP), diastolic BP (DBP), aspirin use, insulin use, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use, statin use, fibrate use, smoking status (current, past, and never) and family history of CHD. Statistical analyses were carried out using SPSS software version 19.0 for Windows (SPSS, Chicago, IL, USA). Values of $P < 0.05$ were considered to be statistically significant.

RESULTS

Baseline characteristics by quartile of serum adiponectin levels are shown in Table 1. Serum adiponectin levels were positively associated with age, percentage of women, the proportion of insulin use, duration of diabetes and HDL, and negatively associated with the proportion of fibrate use, BMI, waist circumference, DBP, TG and eGFR. There were no significant differences in smoking status, previous CHD, family history,

Table 1 | Baseline characteristics by quartiles of adiponectin in 504 patients with type 2 diabetes

Variables	Quartile				*P*-trend
	1 (*n* = 118)	2 (*n* = 133)	3 (*n* = 126)	4 (*n* = 127)	
Adiponectin (μg/dL)	3.3 (1.9–4.1)	4.9 (4.2–5.8)	6.8 (5.9–8.6)	12.0 (8.7–35.6)	
Age (years)	56.6 ± 9.9	61.8 ± 8.5*	62.6 ± 8.7*	67.4 ± 9.3***,***	<0.001
Sex (men/women)	105/13	100/33	75/51	62/65	<0.001
Smoking status (%)					0.103
Current smoker	36.8	23.3	19.0	16.3	
Past smoker	26.5	32.3	30.2	27.6	
Never smoker	36.8	44.4	50.8	56.1	
Aspirin use (%)	16.9	18.0	10.3	23.6	0.048
Insulin use (%)	18.6	14.3	12.7	33.1	<0.001
ACEI/ARB use (%)	33.1	38.3	31.0	40.2	0.376
Statin use (%)	16.1	27.8	23.0	27.6	0.108
Fibrate use (%)	7.6	4.5	1.6	0.8	0.016
Previous CHD (%)	5.9	6.8	2.4	7.1	0.335
Family history (%)	1.7	3.9	2.4	8.5	0.057
BMI (kg/m^2)	25.6 ± 3.4	25.5 ± 4.3	25.3 ± 6.2	23.4 ± 4.2***,***	<0.001
Waist (cm)	90.8 ± 9.5	92.0 ± 10.4	90.5 ± 13.3	86.6 ± 12.3***,***	0.001
SBP (mmHg)	141.6 ± 19.5	143.6 ± 17.8	143.2 ± 18.4	146.4 ± 19.1	0.234
DBP (mmHg)	84.5 ± 12.4	81.9 ± 11.4	83.9 ± 10.9	80.4 ± 10.3*	0.014
FPG (mg/dL)	160.0 ± 50.6	160.5 ± 52.5	148.8 ± 38.2	152.4 ± 49.7	0.144
HbA_{1c} (NGSP; %)	9.2 ± 1.6	9.1 ± 1.6	8.8 ± 1.6	9.1 ± 1.8	0.374
Duration (years)	6.5 (2.0, 16.0)	8.0 (3.0, 18.0)	8.0 (3.0, 16.0)	17.0 (6.0, 25.0)*,***,***	<0.001
Tchol (mg/dL)	208.6 ± 35.9	208.0 ± 33.9	212.4 ± 36.4	206.1 ± 39.5	0.577
HDL (mg/dL)	49.7 ± 13.0	52.3 ± 13.7	55.7 ± 12.8*	61.0 ± 17.0***,***	<0.001
TG (mg/dL)	164 (117, 240)	149 (104, 213)	120 (82, 171)***	91 (61, 128)***,***	<0.001
LDL (mg/dL)	123.2 ± 31.5	120.9 ± 30.2	128.7 ± 31.4	123.0 ± 31.6	0.237
eGFR (mL/min/m^2)	89.3 ± 21.0	86.1 ± 21.3	86.7 ± 23.4	77.9 ± 21.7***,***	<0.001

Adiponectin is expressed as median (range). Other values are expressed as mean ± SD, median (25th–75th percentile) or percentage. *P < 0.05 vs Q1, **P < 0.05 vs Q2, ***P < 0.05 vs Q3 by analysis of variance. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; Previous CHD, previous coronary heart disease; DBP, diastolic blood pressure; Duration, duration of diabetes; eGFR, estimated glomerular filtration rate; FPG, fast plasma glucose; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; SBP, systolic blood pressure; Tchol, total cholesterol; TG, triglyceride; Waist, waist circumference.

the proportion of aspirin use, ACEI/ARB use, statin use, SBP, HbA_{1c} (NGSP) and LDL.

During a median follow up of 5.7 years (2177 person-years), 40 participants had new CHD, 10 had recurrent CHD and 12 died of any diseases other than CHD. A total of 167 (33.1%) participants were lost to follow up. Baseline characteristics of participants lost to follow up and those who completed follow up are shown in Table 2. Participants lost to follow up were younger, less likely to be taking aspirin and insulin, less likely to have a history of CHD, and had a shorter duration of diabetes. The HR for the risk of CHD across quartiles of serum adiponectin levels is shown in Table 3. After adjustment for age, sex, waist circumference, HbA_{1c} (NGSP) and duration of diabetes, participants in the highest compared with the lowest quartile of serum adiponectin levels had a significantly reduced risk of CHD (HR 0.40; 95% CI 0.16–0.96; P = 0.013). Further adjustment for HDL, LDL, log (TG), eGFR, SBP, DBP, aspirin use, insulin use, ACEI/ARB use, statin use, fibrate use, smoking status and family history of CHD at baseline did not significantly affect this relationship (HR 0.35; 95% CI 0.13–0.94; P = 0.017).

The HR for the risk of CHD according to a doubling of adiponectin at baseline is shown in Table 4. After adjustment for age, sex, waist circumference, HbA_{1c} (NGSP) and duration of diabetes, adiponectin was associated with a reduced risk of CHD (HR 0.64; 95% CI 0.43–0.96 P = 0.032). After further adjustment, adiponectin remained significantly associated with a reduced risk of CHD (HR 0.61; 95% CI 0.39–0.97; P = 0.037). Similar results were obtained when adjusting for BMI instead of waist circumference (Tables 3 and 4).

We repeated our analysis excluding participants who had a history of CHD before admission to hospital. After multivariate adjustment, participants in the highest compared with the lowest quartile of serum adiponectin levels had a reduced risk of CHD (HR 0.32; 95% CI 0.11–0.96; P = 0.036). The multivariate adjusted HR for CHD according to a doubling of adiponectin

Table 2 | Baseline characteristics of participants lost to follow up and those who completed follow up

Variables	Lost to follow up (n = 167)	Completed follow up (n = 337)	P
Adiponectin (μg/dL)	5.5 (4.1, 8.3)	5.9 (4.3, 8.7)	0.741
Age (years)	60.6 ± 11.4	63.0 ± 8.9	0.022
Sex (men/women)	115/52	227/110	0.734
Smoking status (%)			0.479
Current smoker	24.2	19.8	
Past smoker	31.5	31.7	
Never smoker	44.2	48.5	
Aspirin use (%)	11.4	20.2	0.014
Insulin use (%)	14.4	22.3	0.036
ACEI/ARB use (%)	30.5	38.9	0.067
Statin use (%)	21.0	27.9	0.231
Fibrate use (%)	5.4	2.7	0.122
Previous CHD (%)	0.6	8.0	0.001
Family history (%)	5.4	3.4	0.250
BMI (kg/m^2)	25.2 ± 4.9	24.8 ± 4.6	0.367
Waist (cm)	90.8 ± 12.2	89.6 ± 11.3	0.261
SBP (mmHg)	143.9 ± 19.8	143.7 ± 18.2	0.925
DBP (mmHg)	82.6 ± 11.6	82.6 ± 11.2	0.982
FPG (mg/dL)	157.6 ± 50.2	154.3 ± 47.2	0.464
HbA1c (NGSP) (%)	9.0 ± 1.7	9.1 ± 1.6	0.650
Duration (years)	6.0 (1.0, 12.0)	11.0 (4.0, 20.0)	<0.001
Tchol (mg/dL)	209.1 ± 38.5	208.6 ± 35.4	0.876
HDL (mg/dL)	55.9 ± 16.1	54.1 ± 14.1	0.216
TG (mg/dL)	121 (82, 192)	134 (88, 192)	0.557
LDL (mg/dL)	123.7 ± 31.3	124.1 ± 31.2	0.898
eGFR (mL/min/m^2)	86.2 ± 23.4	84.3 ± 21.6	0.380

Values are expressed as mean ± SD, median (25th–75th percentile) or percentage. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; Previous CHD, previous coronary heart disease; DBP, diastolic blood pressure; Duration, duration of diabetes; eGFR, estimated glomerular filtration rate; FPG, fast plasma glucose; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; SBP, systolic blood pressure; Tchol, total cholesterol; TG, triglyceride; Waist, waist circumference.

levels at baseline was 0.60 (95% CI 0.35–1.02), with borderline significance (P = 0.057).

DISCUSSION

The present prospective study showed that high serum adiponectin levels were significantly associated with a lower risk of CHD over a follow-up period of 5.7 years in Japanese patients with type 2 diabetes. This association was independent of well-known CHD risk factors.

The present study comprised several important features. First, this is the first prospective study in Japanese patients with type 2 diabetes. Several studies from other countries have shown that high serum adiponectin levels are associated with a lower risk of CHD. Zoccali *et al.*[11] first reported that serum adiponectin level was an inverse predictor of CHD among patients with end-stage renal disease in a prospective cohort study. In the Health Professionals Follow-up Study, high baseline serum adiponectin levels were associated with a significant reduction in the risk of myocardial infarction among healthy men after adjustment for several CHD risk factors in multivariate analyses[12]. This association was confirmed by an 8-year follow-up study reported by Frystyk *et al.*[13] and by the Framingham Offspring Study[14]. Pischon *et al.*[15] reported that high serum adiponectin levels were associated with a lower risk of CHD among healthy women in the Nurses' Health Study. Schulze *et al.*[16] reported a significant association between adiponectin and the risk of CHD among diabetic men in the Health Professionals Follow-up Study. All of these large-scale studies were carried out in Caucasians. In Japan, it was reported that serum adiponectin levels in patients with diabetes and CHD were lower than those in patients with diabetes without CHD[30]. Kumada *et al.*[31] reported that lower serum adiponectin levels were associated with an approximately doubled risk for CHD among 225 consecutive male patients who underwent coronary angiography and 225 voluntary blood donors. Another study found that serum adiponectin levels in 123 patients with CHD were significantly lower than those among 17 control subjects[32]. However, all of these studies regarding an association between adiponectin and the risk of CHD in Japan were cross-sectional or case–control studies. The present study is the first prospective study to show that serum adiponectin levels can predict CHD in Japanese patients with type 2 diabetes, similar to the relationship in Caucasians. Second, in our prospective study, serum adiponectin levels were measured at the start of the study, unlike previous prospective studies, in which they were measured several years after sampling, using frozen serum at baseline. Therefore, serum adiponectin levels in the present study are more reliable data in this regard. Third, unlike the previous study of Schulze *et al.*, which was designed for patients with type 2 diabetes, the present results were adjusted for diabetic and blood pressure control status, and the use of several drugs, which affect serum adiponectin levels.

Several other studies, including the British Regional Health Services follow-up study[33], the Strong Heart Study[34], as well as the British Women's Heart Health Study[35], have not supported an inverse association between serum adiponectin levels and a risk of CHD. Differences in the results between studies might reflect underlying differences in the sample size or incidence and risk of CHD. In addition, it is worth noting that, in these negative studies, renal dysfunction was not taken into consideration. Serum adiponectin levels are increased in patients with chronic kidney disease, although these patients show progression of arteriosclerosis[11]. Similarly, adiponectin is inversely associated with creatinine clearance[36], and is increased in the presence of macroalbuminuria[37]. High serum adiponectin levels with chronic kidney disease might not have numerous beneficial effects, because atherosclerosis is advanced with renal

Table 3 | Hazard ratios for new-onset or recurrent coronary heart disease by quartiles of adiponectin

	Quartile of adiponectin				*P*-trend
	1 (*n* = 118)	2 (*n* = 133)	3 (*n* = 126)	4 (*n* = 127)	
No. of cases	13	19	7	11	
Model 1	1.00	1.19 (0.57–2.48)	0.41 (0.15–1.07)	0.59 (0.24–1.44)	0.069
Model 2a	1.00	1.18 (0.56–2.48)	0.41 (0.16–1.10)	0.40 (0.16–0.96)	0.013
Model 3a	1.00	1.05 (0.48–2.31)	0.34 (0.12–0.95)	0.34 (0.13–0.86)	0.011
Model 4a	1.00	1.18 (0.53–2.63)	0.37 (0.13–1.06)	0.35 (0.13–0.94)	0.017
Model 2b	1.00	1.26 (0.60–2.64)	0.43 (0.16–1.14)	0.42 (0.17–1.01)	0.013
Model 3b	1.00	1.12 (0.51–2.42)	0.36 (0.13–0.99)	0.36 (0.14–0.91)	0.013
Model 4b	1.00	1.25 (0.57–2.76)	0.39 (0.14–1.12)	0.38 (0.14–1.00)	0.019

Data are hazard ratios (95% confidence interval). Model 1: age and sex; Model 2a: age, sex, waist circumference, hemoglobin A1c (National Glycohemoglobin Standardization Program) and duration of diabetes (<6 years, 6-17 years and >17 years); Model 3a: as in Model 2a, high-density lipoprotein cholesterol, log triglyceride, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure and diastolic blood pressure; Model 4a: as in Model 3a, insulin use and aspirin use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, statin use, fibrate use, smoking status (current, past, never) and family history of coronary heart disease; Model 2b: same as Model 2a, but with body mass index instead of waist circumference; Model 3b: same as Model 3a, but with body mass index instead of waist circumference; Model 4b: same as Model 4a, but with body mass index instead of waist circumference.

Table 4 | Hazard ratios for new-onset or recurrent coronary heart disease with a doubling of adiponectin

	Hazard ratio	95% Confidence interval	*P*
Model 1	0.75	0.49–1.14	0.174
Model 2a	0.64	0.43–0.96	0.032
Model 3a	0.62	0.40–0.94	0.026
Model 4a	0.61	0.39–0.97	0.037
Model 2b	0.65	0.43–0.97	0.034
Model 3b	0.63	0.41–0.96	0.030
Model 4b	0.62	0.39–0.99	0.043

Model 1: age and sex; Model 2a: age, sex, waist circumference, hemoglobin A1c (National Glycohemoglobin Standardization Program) and duration of diabetes (<6 years, 6-17 years and >17 years); Model 3a: as in Model 2a, high-density lipoprotein cholesterol, log triglyceride, low-density lipoprotein cholesterol, estimated glomerular filtration rate, systolic blood pressure and diastolic blood pressure; Model 4a: as in Model 3a, insulin use and aspirin use, angiotensin-converting enzyme inhibitor angiotensin receptor blocker use, statin use, fibrate use, smoking status (current, past, never) and family history of coronary heart disease; Model 2b: same as Model 2a, but with body mass index instead of waist circumference; Model 3b: same as Model 3a, but with body mass index instead of waist circumference; Model 4b: same as Model 4a, but with body mass index instead of waist circumference.

dysfunction. A recent study showed that adiponectin is inactivated by binding to cystatin C, which in turn contributes to elevated adiponectin levels in advanced kidney disease[38]. Therefore, these negative results might be influenced by an increase in inactive adiponectin in renal dysfunction.

Several other studies, including the Pravastatin or Atorvastatin Evaluation and Infection Therapy-thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study[39], have reported that high serum adiponectin levels in patients with acute coronary syndrome[39] or congestive heart failure[40] are associated with a higher risk of recurrent cardiovascular events. The reason for this result, which conflicts with the present result, is unclear. Serum adiponectin levels are positively associated with plasma brain natriuretic peptide levels[41], and natriuretic peptide enhances adiponectin production *in vitro* and in patients with congestive heart failure[42]. These data suggest that adiponectin might be elevated in a counter-regulatory fashion among patients with heart failure or excessive atherosclerosis. In the present study, the analysis could not be stratified by cardiac function or the degree of atherosclerosis, and therefore, we could not investigate this possibility.

Adiponectin, which is decreased by obesity, especially visceral fat accumulation, plays an important role in the development of obesity-related disorders, such as diabetes mellitus, hypertension and dyslipidemia, or so-called metabolic syndrome. Therefore, adiponectin is associated with a risk of CHD through these metabolic abnormalities[43]. The present study showed that the inverse association between serum adiponectin levels and the risk of CHD was independent of components of metabolic syndrome and other cardiovascular risk factors, such as age, renal function and smoking status. Some medications, for example, ACEI/ARB[44], statin[45] and fibrate[46], are reported to be associated with high adiponectin levels, but we adjusted for these variables. This result suggests that adiponectin has a direct role in the development of CHD, and is not just a mediator. Therefore, a strategy for intervention to increase serum adiponectin levels might be beneficial to prevent CHD.

We measured waist circumference at the level of the umbilicus. This method is different from the protocol used in the World Health Organization or the United States National Health and Nutrition Examination Survey. However, previous

studies in Japan have shown that waist circumference measured at the level of the umbilicus is strongly associated with visceral fat area measured by computed tomography, and this is inversely associated with serum adiponectin levels, and plays an important role in the clustering of cardiovascular risk factors[47,48]. In the present study, serum adiponectin levels were associated with a reduced risk of CHD, even when adjusting for BMI instead of waist circumference.

We measured total adiponectin levels, which included both low molecular weight isoforms (~30–60 kDa) and high molecular weight (HMW) isoforms (12–18 mers). HMW isoforms are reported to have more biological activity and are more strongly related to insulin sensitivity than other circulating isoforms, but most changes in the components of serum adiponectin consist of HMW isoforms[49]. Therefore, the change in HMW adiponectin levels might have been in parallel with total adiponectin levels, and measurement of total and HMW adiponectin levels might be equally useful. Previous studies have reported that total and HMW adiponectin are significantly inversely associated with the risk of CHD[15], the incidence of diabetes[50] and the development of metabolic syndrome[51] to a similar extent.

A limitation of the present study was the relatively small sample size, which might have led to unstable estimates. The attenuation of an association in stratified analysis by previous CHD might be attributed to a lack of power. In addition, the total follow-up rate was relatively low (66.9%; 337/504), which might have led to bias. However, most of the parameters, including adiponectin, were not significantly different between participants lost to follow up and those who completed follow up. We recruited admitted patients with diabetes who had poor glycemic control (average HbA_{1c} [NGSP], 9.1%) and a high risk of CHD. Therefore, the present results might not be able to generalize to all Japanese patients, but we adjusted for multivariate risk factors. Finally, we could not consider residual confounding, such as dietary habits, physical activities, cardiac function and several inflammatory cytokines. A larger investigation is expected to establish the association between adiponectin and the risk of CHD in the East Asian population.

In conclusion, a high serum adiponectin level is significantly associated with a lower risk of CHD over a follow-up period of 5.7 years in Japanese patients with type 2 diabetes, as similarly observed in Caucasians. This association is independent of various parameters, including well-known CHD risk factors. The regulation of serum adiponectin levels might be a good therapeutic strategy to prevent CHD.

ACKNOWLEDGEMENTS

This work was supported in part by Otsuka Pharmaceutical Corporation, which provided commercial kits for the measurement of serum adiponectin. Otsuka Pharmaceutical Corporation did not participate in the design and conduct of the study, research, analysis and interpretation of the data, or preparation, review or approval of the manuscript. The company also did not provide any grants and there are no financial or other relations that could lead to a conflict of interest.

REFERENCES

1. Maeda K, Okubo K, Shimoura I, *et al.* cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996; 221: 286–289.
2. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol* 2003; 148: 293–300.
3. Li S, Shin HJ, Ding EL, *et al.* Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009; 302: 179–188.
4. Adamczak M, Wiecek A, Funahashi T, *et al.* Decreased plasma adiponectin concentration in patients with essential hypertension. *Am J Hypertens* 2003; 16: 72–75.
5. Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. *J Clin Endocrinol Metab* 2002; 87: 2764–2769.
6. Ouchi N, Kihara S, Arita Y, *et al.* Adiponectin: an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 2000; 102: 1296–1301.
7. Ouchi N, Kihara S, Arita Y, *et al.* Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; 100: 2473–2476.
8. Chen H, Montagnani M, Funahashi T, *et al.* Adiponectin stimulated production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003; 278: 45021–45026.
9. Kobayashi H, Ouchi N, Kihara S, *et al.* Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ Res* 2004; 94: e27–e31.
10. Yamauchi T, Kamon J, Waki H, *et al.* Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 2003; 278: 2461–2468.
11. Zoccali C, Mallamaci F, Tripepi G, *et al.* Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002; 13: 134–141.
12. Pischon T, Girman CJ, Hotamisligil GS, *et al.* Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; 291: 1730–1737.
13. Frystyk J, Berne C, Berglund L, *et al.* Serum adiponectin is a predictor of coronary heart disease: a population-based 10-year follow-up study in elderly men. *J Clin Endocrinol Metab* 2007; 92: 571–576.
14. Ai M, Otokozawa S, Asztalos BF, *et al.* Adiponerctin: an independent risk factor for coronary heart disease in men in the Framingham Offspring Study. *Atherosclerosis* 2011; 217: 543–548.
15. Pischon T, Hu FB, Girman CJ, *et al.* Plasma total and high molecular weight adiponectin levels and risk of coronary heart disease in women. *Atherosclerosis* 2011; 219: 322–329.

16. Schulze MB, Shai I, Rimm EB, *et al.* Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes* 2005; 54: 534–539.
17. Sone H, Ito H, Ohashi Y, *et al.* Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. *Lancet* 2003; 361: 85.
18. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
19. Hotta N, Nakamura J, Iwamoto Y, *et al.* Causes of death in Japanese diabetics: a questionnaire survey of 18,385 diabetics over a 10-year period. *J Diabetes Invest* 2010; 1: 66–76.
20. Sone H, Mizuno S, Yamada N. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005; 352: 1925–1927.
21. Sone H, Mizuno S, Fujii H, *et al.* Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study. *Diabetes Care* 2005; 28: 1463–1471.
22. Sone H, Tanaka S, Tanaka S, *et al.* Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). *J Clin Endocrinol Metab* 2011; 96: 3448–3456.
23. The Committee of Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J Jpn Diabetes Soc* 2010; 53: 450–467 (Japanese).
24. Maeda N, Takahashi M, Funahashi T, *et al.* PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 2001; 50: 2094–2099.
25. Rose GA, Blackburn H, Gillum RF, *et al.* Cardiovascular Survey Methods. World Health Organization, Geneva, 1982.
26. Seino Y, Nanjo K, Tajima N, *et al.* Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010; 1: 212–228.
27. Kashiwagi A, Kasuga M, Araki E, *et al.* International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 2012; 3: 39–40.
28. Japanese Society of Nephrology. Evidence-based practice guideline for the treatment of CKD. *Clin Exp Nephrol* 2009; 13: 537–566.
29. Nishimura A, Sawai T. Determination of adiponectin in serum using a latex particle-enhanced turbidimetric immunoassay with an automated analyzer. *Clin Chim Acta* 2006; 371: 163–168.
30. Hotta K, Funahashi T, Arita Y, *et al.* Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20: 1595–1599.
31. Kumada M, Kihara S, Sumitsuji S, *et al.* Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003; 23: 85–89.
32. Nakamura Y, Shimada K, Fukuda D, *et al.* Implications of plasma concentrations of adiponectin in patients with coronary artery disease. *Heart* 2004; 90: 528–533.
33. Sattar N, Wannamethee G, Sarwar N, *et al.* Adiponectin and coronary heart disease; a prospective study and meta-analysis. *Circulation* 2006; 114: 623–629.
34. Lindsay RS, Resnick HE, Zhu J, *et al.* Adiponectin and coronary heart disease: the strong heart study. *Arterioscler Thromb Vasc Biol* 2005; 25: e15–e16.
35. Lawlor DA, Davey Smith G, Ebrahim S, *et al.* Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. *J Clin Endocrinol Metab* 2005; 90: 5677–5683.
36. Mallamaci F, Zoccali C, Cuzzola F, *et al.* Adiponectin in essential hypertension. *J Nephrol* 2002; 15: 507–511.
37. Saraheimo M, Forsblom C, Faqeurudd J, *et al.* Serum adiponectin is increased in type 1 diabetic patients with nephropathy. *Diabetes Care* 2005; 28: 1410–1414.
38. Komura N, Kihara S, Sonoda M, *et al.* Increment and impairment of adiponectin in renal failure. *Cardiovasc Res* 2010; 86: 471–477.
39. Wilson SR, Sabatine MS, Wiviott SD, *et al.* Assessment of adiponectin the risk of recurrent cardiovascular events in patients presenting with an acute coronary syndrome: observations from the Pravastatin Or atorVastatin Evaluation and Infection Trial-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22). *Am Heart J* 2011; 161: 1147–1155. e1.
40. Kistorp C, Faber J, Galatius S, *et al.* Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005; 112: 1756–1762.
41. Tsutamoto T, Tanaka T, Sakai H, *et al.* Total and high molecular weight adiponectin, haemodynamics, and mortality in patients with chronic heart failure. *Eur Heart J* 2007; 28: 1723–1730.
42. Tsukamoto O, Fujita M, Kato M, *et al.* Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol* 2009; 53: 2070–2077.
43. Matsuzawa Y. The metabolic syndrome and adipocytokines. *FEBS Lett* 2006; 580: 2917–2921.
44. Furuhashi M, Ura N, Higashiura K, *et al.* Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension* 2003; 42: 76–81.
45. Nezu U, Tsunoda S, Yoshimura H, *et al.* Pravastatin potentiates increases in serum adiponectin concentration in dyslipidemic patients receiving thiazolidinedione: the DOLPHIN study. *J Atheroscler Thromb* 2010; 17: 1063–1069.

46. Hiuge A, Tenenbaum A, Maeda N, *et al.* Effects of peroxisome proliferator-activated receptor ligands, bezafibrate and fenofibrate, on adiponectin Level. *Arterioscler Thromb Vasc Biol* 2007; 27: 635–641.
47. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66: 987–992.
48. Hiuge-Shimizu A, Kishida K, Funahashi T, *et al.* Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). *Ann Med* 2012; 44: 82–92.
49. Komura N, Kihara S, Sonoda M, *et al.* Clinical significance of high-molecular weight form of adiponectin in male patients with coronary artery disease. *Circ J* 2008; 72: 23–28.
50. Zhu N, Pankow JS, Ballantyne CM, *et al.* High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study. *J Clin Endocrinol Metab* 2010; 95: 5097–5104.
51. Nakashima R, Yamane K, Kamei N, *et al.* Low serum levels of total and high-molecular-weight adiponectin predict the development of metabolic syndrome in Japanese-Americans. *J Endocrinol Invest* 2011; 34: 615–619.

