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ScienceDirect
Metabolism Clinical and Experimental 55 (2006) 1653–1657
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Association of hypoadiponectinemia in men with early onset of coronary heart disease and multiple coronary artery stenoses

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Received 11 October 2005; accepted 14 August 2006

Abstract

Adiponectin influences insulin sensitivity and lipid oxidation. Because low plasma adiponectin concentrations are suspected to promote atherosclerosis, we retrospectively assessed relationships of plasma adiponectin concentration to characteristics of coronary heart disease (CHD). Japanese men undergoing coronary angiography for CHD (n = 139) were grouped according to serum adiponectin concentration by enzyme-linked immunosorbent assay (low, <4.0; medium, 4.0-8; high, >8.0 μg/mL). Numbers of coronary arteries with at least 50% stenosis were determined. Serum adiponectin concentration correlated positively with age at onset of CHD (r = 0.285, P = .003). Age at CHD onset in the low-adinopectin group was younger than in the medium or high groups. Adiponectin was protective against CHD onset at ages younger than 58 years (relative risk, 0.778; P = .0047). Significantly more arteries were affected in low-adiponectin patients than in the medium or high group (each P < .01). Adiponectin concentration correlated positively with high-density lipoprotein cholesterol concentration and negatively with triglyceride concentration. Only in diabetic patients did serum adiponectin concentration correlate negatively with body mass index. Low plasma adiponectin concentrations were associated with early CHD onset and multiple atherosclerotic lesions in coronary arteries. Thus, adiponectin concentrations may influence risk of CHD and might serve as one of the screening tests facilitating early intervention.

1. Introduction

Low plasma concentrations of adiponectin (also called Acrp30 and adipoQ), a protein discovered through complementary DNA cloning techniques [1-4], have been implicated increasingly in the pathogenesis of atherosclerosis and insulin resistance [5-7]. Adiponectin, the product of the apM1 gene, is secreted by adipocytes. Hypoadiponectinemia has been reported to be associated with metabolic syndrome including obesity and insulin resistance, type 2 diabetes mellitus, coronary heart disease (CHD), and lipodystrophy [8-10]. Adiponectin gene mutations have been reported to result in the metabolic syndrome via impairment of secretion or multimerization [11,12]. Although an association of hypoadeponectinemia with CHD has been reported [13], only a few studies have examined correlations between clinical details of CHD and serum adiponectin concentrations. We therefore retrospectively analyzed associations between serum adiponectin concentrations and characteristics of CHD in patients evaluated for CHD by coronary angiography.

2. Subjects and methods

We randomly recruited 139 Japanese men admitted for CHD (myocardial infarction or unstable angina) who

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doi:10.1016/j.metabol.2006.08.005

Table 1
Characteristics of men with CHD according to adiponectin concentration

	Low	Medium	High
No. of subjects	35	75	29
Age (y)	60.26 ± 1.83	64.27 ± 1.05*	67.79 ± 1.97†
BMI (kg/m^2)	26.23 ± 0.62	24.96 ± 0.35	24.30 ± 0.65‡
Duration of CHD (y)	5.31 ± 1.04	4.95 ± 0.51	5.45 ± 0.90
DM, *n* (%)	24 (68.6)	44 (58.7)	14 (48.3)
Hypertension, *n* (%)	23 (65.7)	40 (53.3)	16 (55.3)
Hyperlipidemia, *n* (%)	20 (57.1)	46 (61.3)	7 (24.1)†

Age, BMI, and duration of CHD are presented as mean ± SE. Turkey-Kramer multiple comparisons were performed concerning age, BMI, and duration of CHD. A 2 × 2 χ^2 test was used to evaluate influences of diabetes mellitus (DM), hypertension, and hyperlipidemia.

* $P < .05$, low vs medium.

† $P < .01$, low vs high.

‡ $P < .05$, low vs high.

underwent coronary angiography. Characteristics of the patients are summarized in Table 1. We studied only men because adiponectin concentrations differ significantly between men and women. The mean age of women admitted for CHD was 64 years; adiponectin concentration, being regulated by estrogen, was reported to decrease in women after menopause. We felt that this menopausal decline would impede examination of associations between adiponectin concentrations and clinical features of CHD. No men studied were treated with thiazolidinedione derivatives, which increase serum adiponectin concentrations. The number of coronary arteries with stenoses of at least 50% was determined. Patients with no coronary arteries showing 50% stenosis and those with renal failure or nephrotic syndrome were excluded. Serum adiponectin concentrations were measured by an enzyme-linked immunosorbent assay that detected monomeric adiponectin (Otsuka, Tokyo, Japan) [6]. High-sensitivity C-reactive protein (hs-CRP) was measured by using an assay kit (Nittobo Medical Industry, Tokyo, Japan). We used a cutoff value of 4.0 μg/mL to define low adiponectin concentration, based on reports using the same assay method and finding concentrations in that range in patients with I164T mutation in adiponectin gene associated with higher CHD risk [14]. We assigned patients to one of 3 groups based on serum adiponectin concentration (low, <4.0; medium, 4.0 to 8.0; high, >8.0 μg/mL). Ten patients were excluded because they had no coronary stenoses exceeding 50% and were diagnosed accordingly with vasospastic angina. We retrospectively analyzed correlations between serum adiponectin concentrations and age at onset of cardiovascular events as well as findings in coronary angiograms. We also determined lipid profiles by routine methods using the same blood sample assayed for serum adiponectin. Serum samples were stored at −80°C until assays. Criteria for diabetes were those of the American Diabetes Association. This study was conducted according to the principles set forth in the Declaration of Helsinki.

2.1. Statistical analysis

Results are expressed as means ± SE. Statistical analysis was performed by using SPSS version 12J (Base Model + Regression Model, SPSS, Tokyo, Japan), Stat Light (Yukms, Tokyo, Japan), and StatView J 5.0 (SAS Institute, Tokyo, Japan). Group differences were determined by using Tukey-Kramer and χ^2 analyses. Single linear univariate correlations (Pearson correlation coefficients), forward and backward stepwise multivariate regression analyses, and simple and multivariate logistic regression analysis were performed to evaluate relationships between CHD onset age and serum CHD risk factor markers. *P* values less than .05 were considered to indicate statistical significance.

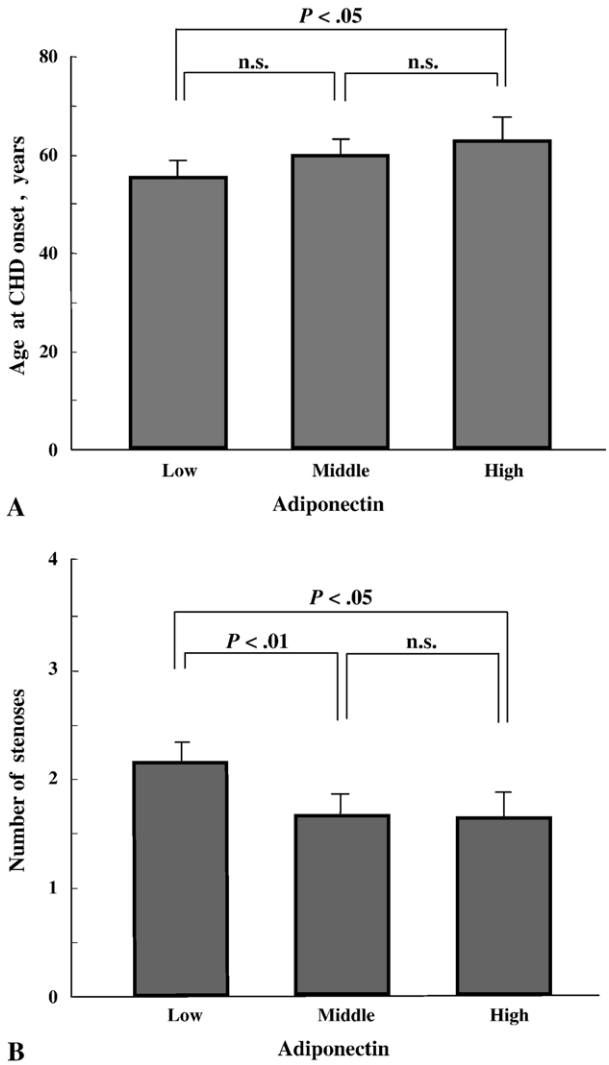

Fig. 1. A, Age at onset of coronary artery disease in a low-adiponectin group was 54.9 ± 2.2 years (n = 35), whereas younger than the medium (59.3 ± 1.1, $P < .05$; n = 75) or high (62.3 ± 1.8, $P < .001$; n = 29) groups. B: The number of affected coronary arteries was significantly higher in the low-adiponectin group (2.14 ± 0.12; n = 35) than the medium (1.64 ± 0.08, $P < .01$; n = 75) or high group (1.62 ± 0.13, $P < .01$; n = 29). Values are means ± SEM.

3. Results

3.1. Patient characteristics

The low-adiponectin group included 35 patients; the middle group, 75 patients; and the high group, 29 patients (Table 1). Body mass index (BMI) was significantly higher in the low group than in the high group ($P < .05$). The time interval between CHD onset and blood sampling for this study did not differ significantly between groups. The percentage of patients with hyperlipidemia was smaller in the high group than in the low group ($P < .05$), but prevalence of diabetes and hypertension did not differ significantly between groups (diabetes: low vs medium, $P = .32$; low vs high, $P = .10$; medium vs high, $P = .32$; hypertension: low vs medium, $P = .16$; low vs high, $P = .31$; medium vs high, $P = .39$). Angiotensin 2 receptor blockers, believed to increase serum adiponectin concentration, were used by 8.6% of the low group and 8.0% of the medium group (no significant difference); in the high group, no patients used angiotensin 2 receptor blockers. The percentage of patients taking angiotensin-converting enzyme inhibitor did not differ significantly (low, 25.7%; medium, 20%; high, 27.5%). Statin derivatives were given to 31 patients, but these patients were distributed essentially evenly between groups.

3.2. Serum adiponectin concentration and age at onset of CHD

Age at clinical onset correlated positively with serum adiponectin concentration ($r = 0.285$, $P = .003$), but not with levels of hs-CRP ($r = 0.107$, $P = .277$), glycosylated hemoglobin (HbA_{1c}) ($r = -0.026$, $P = .794$), total cholesterol ($r = -0.026$, $P = .412$), triglyceride (TG) ($r = -0.109$, $P = .271$), or high-density lipoprotein (HDL) cholesterol ($r = -0.037$, $P = .706$). Low serum adiponectin concentration was an independent risk factor for CHD onset as determined by stepwise multivariate regression analysis ($P = .0046$). BMI did not correlate with age of CHD onset ($r = -0.141$, $P = .1143$).

Age of CHD onset in the low-adiponectin group was 54.9 ± 2.2 years (n = 35), which was younger than in the high group (62.3 ± 1.8 years, $P < .05$, n = 29; Fig. 1A). No significant difference in onset age was found between the medium group (59.3 ± 1.0 years, n = 75) and either of the low or high group. No significant difference in hs-CRP was seen between the 3 groups (low, 170.9 ± 32.9; medium, 161.4 ± 20.8; and high, 168.3 ± 34.5 μg/dL).

When risk for CHD onset at an age younger than 58 years was analyzed by using logistic regression analysis, serum adiponectin concentration was a significant negative risk factor. Adiponectin was a protective factor against CHD onset at ages younger than 58 years (relative risk [RR], 0.778; $P = .0047$) when multivariate analysis was performed with all the factors listed (Table 2). Diabetic patients did not differ significantly from nondiabetic patients in age of CHD onset, although serum TG and HbA_{1c} concentrations were higher and HDL cholesterol concentrations were significantly lower in diabetic than in nondiabetic patients (Table 3). Adiponectin concentrations tended to be greater in nondiabetic (6.50 ± 0.42 μg/mL; n=44) than in diabetic patients (5.78 ± 0.29 μg/mL, n=76), but the difference fell short of significance ($P = .07$).

3.3. Number of affected coronary arteries and serum adiponectin concentration

The number of affected coronary arteries was significantly greater in the low-adiponectin group (2.14 ± 0.12; n=35) than in the medium (1.64 ± 0.08, $P < .01$; n = 75) or high group (1.62 ± 0.13, $P < .01$, n = 29; Fig. 1B). The

Table 3
Characteristics of men with CHD according to glycemic state

	Nondiabetic patients	Diabetic patients
No. of subjects	54	85
Age (y)	63.6 ± 1.50	64.2 ± 1.1
BMI (kg/m^2)	26.2 ± 2.50	25.2 ± 0.4
Duration of CHD (y)	6.0 ± 0.8	4.8 ± 0.5
Age at onset (y)	57.6 ± 1.6	59.4 ± 1.1
No. of stenoses	1.66 ± 0.16	1.80 ± 0.09
HbA_{1c} (%)	5.7 ± 0.1	7.3 ± 0.2**
TG (mg/dL)	129.0 ± 6.8	164.7 ± 10.1*
HDL cholesterol (mg/dL)	48.4 ± 1.7	47.2 ± 1.1*
hs-CRP (mg/dL)	154.8 ± 26.5	180.5 ± 20.0
Serum adiponectin (mg/mL)	6.50 ± 0.42	5.78 ± 0.29

Data are presented as mean ± SE.

* $P < .05$, diabetic vs nondiabetic patients, including all adiponectin-defined groups.

** $P < .001$, diabetic vs nondiabetic patients, including all adiponectin-defined groups.

Table 2
Logistic regression analysis of CHD onset at an age younger than 58 years

	Simple		Multiple[a]	
	RR (95% CI)	P	RR (95% CI)	P
HbA_{1c} (%)	0.982 (0.775-1.224)	.8797	1.055 (0.793-1.403)	.7144
Total cholesterol (mg/dL)	1.002 (0.989-1.016)	.7399	1.008 (0.990-1.026)	.3991
TG (mg/dL)	1.000 (0.996-1.005)	.8762	0.998 (0.992-1.005)	.6418
hs-CRP (μg/dL)	0.998 (0.996-1.000)	.0600	0.998 (0.996-1.001)	.1972
Serum adiponectin (μg/mL)	0.820 (0.715-0.941)	.0046	0.778 (0.654-0.926)	.0047

$R^2 = 0.075$ (n = 139). CI indicates confidence interval.

[a] Multivariate analysis was performed with all the factors listed.

number of affected coronary arteries did not differ significantly between hs-CRP–defined groups (hs-CRP <100 μg/dL, 1.70 ± 0.09, n = 71; hs-CRP 100-300 μg/dL, 1.71 ± 0.08, n=38; and hs-CRP >300 μg/dL, 1.91 ± 0.16, n = 22). Nondiabetic and diabetic patients also did not differ significantly in number of stenotic arteries (Table 3).

3.4. Correlations among serum HDL cholesterol, TG, and adiponectin concentration

Adiponectin concentrations showed a significant positive correlation with HDL cholesterol concentration ($r = 0.313$, $P < .001$) and a negative correlation with TG concentration ($r = -0.362$, $P < .001$), but had no correlation with total cholesterol ($r = 0.044$, $P = .623$) or hs-CRP ($r = -0.111$, $P = .208$) concentration. No significant change in body weight was noted between the time of symptom onset and the time of adiponectin determination ($P = .369$).

4. Discussion

In Japanese patients undergoing coronary angiography, we retrospectively found that adiponectin concentrations less than 4.0 μg/mL were associated with early onset of CHD and multiple atherosclerotic lesions in coronary arteries. Plasma adiponectin concentrations have been reported to be related to insulin sensitivity and HDL concentrations [15]. Recently, the multimer form of adiponectin was reported to be important in insulin sensitivity [16,17]. Although we assayed the adiponectin monomer in this study, we ascertained that correlation was strong between concentrations of monomer and multimer forms (Fujirebio, Tokyo, Japan; $r = 0.923$, $P < .0001$). Therefore, we think that our data concerning the monomer reflect the antiatherogenic and insulin sensitivity effects of the multimers. A recent report concluded that plasma adiponectin concentrations were related to severity of coronary atherosclerosis, although the difference fell short of significance; adiponectin concentrations decreased as the number of significantly narrowed coronary arteries increased [18]. The study population described in the previous report was different from ours and included smaller patient numbers, and correlation between age at onset and serum adiponectin concentration was not analyzed. Also at variance with our findings, Lim et al [19] reported that adiponectin concentrations did not correlate with coronary atheroma or coronary stenosis scores. In that study, data from women and men were analyzed together, which may have obscured correlations; furthermore, patient ethnicity differed from that of our subjects. In a large-scale prospective study in the United States, Pischon et al [20] found high plasma adiponectin concentrations to be associated with lower risk of CHD. Although some characteristics of CHD in those subjects were not clear, our present smaller study in Japanese men might provide more detail in some aspects. When Schulze et al [21] analyzed the relationship between serum adiponectin and subsequent coronary events in type 2 diabetes mellitus, increased adiponectin was found to be associated with decreased CHD risk. That study focused on risk of onset, whereas our study considered CHD severity and age at onset.

Adiponectin might lower coronary atherosclerosis by activating peroxisome proliferator–activated receptor α [5], inhibiting nuclear factor κB signaling, or modulating either adhesion molecule or scavenger receptor expression [22]. Clinically, low adiponectin concentrations are associated with development of insulin resistance, atherosclerosis [22], and hypertriglyceridemia [23]. Low adiponectin concentrations may decrease HDL and elevate TGs through decreased activation of peroxisome proliferator–activated receptor α in the liver, as well as accelerating very low-density lipoprotein synthesis [5]. Insulin resistance induced by hypoadiponectinemia, hypertriglyceridemia, or obesity decreases activity of lipoprotein lipase, in turn decreasing the HDL concentration. A recent report concerning correlation between serum adiponectin and carotid arterial wall thickness suggested that hypoadiponectinemia was correlated closely with CHD [24]. In adiponectin knockout mice, intimal thickening was accelerated, whereas adiponectin supplementation abolished enhanced neointimal formation, suggesting a direct effect of adiponectin [25].

To better understand the importance of adiponectin in severity of CHD, a prospective study would be desirable but difficult, given the need to repeatedly sample and test blood in a large number of subjects long before CHD onset. Our retrospective study was not a definitive determination of how adiponectin concentrations directly affected the coronary arteries because the adiponectin concentration immediately before onset of CHD was not known. Even if adiponectin were measured precisely at onset of CHD, long-term effects of hypoadiponectinemia would not be detectable.

hs-CRP level, considered an important indicator in CHD [26], did not correlate with number of affected coronary arteries in our retrospective analyses. In 31 patients, statins were given, which may have decreased LDL cholesterol and hs-CRP levels, but had little apparent effect on adiponectin concentrations. These drugs had not been used before onset of CHD. Thiazolidinedione derivatives were not used. In any event, clinical CHD was more closely related to adiponectin concentrations than to hs-CRP level.

In conclusion, in patients with CHD, low plasma adiponectin concentrations were associated with early onset and multiple atherosclerotic lesions. Adiponectin determinations, therefore, might be of use in early screening to identify candidates for interventions to prevent CHD.

Acknowledgment

We thank Dr T Ishizuka for helpful discussions.

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