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Hypoadiponectinemia As an Independent Predictor for the Progression of Carotid Atherosclerosis: A 5-Year Prospective Study

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Abstract

Background: Hypoadiponectinemia predicts the development of diabetes and hypertension, both being potent atherosclerotic risk factors. Whether adiponectin predicts the progression of early atherosclerosis remains unclear. In this 5-year prospective study, we examined the relationship between serum adiponectin and carotid intima media thickness (CIMT), a marker of subclinical atherosclerosis.

Methods: A total of 265 subjects from the population-based Hong Kong Cardiovascular Risk Factor Prevalence Study, with no known cardiovascular disease, underwent CIMT measurement at baseline and at 5 years.

Results: In all, 129 men and 136 women, aged 54.6 ± 12.3 years, were studied. Median CIMT at baseline was 0.63 mm (interquartile range 0.52–0.73 mm) and increased to 0.67 mm (0.56–0.78 mm) after 5 years ($P < 0.001$). CIMT increment correlated with baseline adiponectin, age, and smoking (all $P < 0.05$) and baseline CIMT ($P < 0.001$), but not with sex, fasting glucose, lipid profiles, hypertension, or diabetes. In multiple linear regression analysis, baseline serum adiponectin level was an independent predictor of CIMT increment β (standardized beta) $= -0.17$, $P = 0.015$], after adjusting for age, smoking, baseline CIMT, hypertension, body mass index, fasting glucose, low-density lipoprotein cholesterol, and triglycerides.

Conclusion: Hypoadiponectinemia predicted CIMT progression, independent of known predictive factors such as age, smoking, hyperlipidemia, and hypertension.

Introduction

ADIPONECTIN, THE MOST ABUNDANT adipokine secreted from adipose tissues, exhibits insulin-sensitizing, anti-inflammatory, and antiatherogenic properties in animal models.[1,2] In humans, we and others have shown that hypoadiponectinemia predicts the development of cardiovascular risk factors, including hypertension[2,3] and type 2 diabetes mellitus,[4] in prospective studies. Carotid intima media thickness (CIMT), a marker of subclinical atherosclerosis, is increased in subjects with cardiovascular risk factors and is an independent predictor of stroke and myocardial infarction.[5] In cross-sectional studies, serum adiponectin levels have been shown to correlate inversely with CIMT in young obese adolescents,[6] healthy middle-aged adults,[7] and subjects with or without the metabolic syndrome.[8] Although data from these studies would suggest an etiologic role for hypoadiponectinemia in atherosclerosis, there has been limited data on the prospective relationship between circulating adiponectin levels and CIMT in subjects without known cardiovascular disease (CVD). It remains an open question whether adiponectin plays a causal role in the development of atherosclerosis. Therefore, in this 5-year prospective study, we investigated the relationship between serum adiponectin levels and CIMT in a community-based cohort of subjects with no known CVD.

Methods

Subjects

Subjects were recruited from the community-based Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS).[2,9] Briefly, 2875 unrelated subjects, aged 25–74

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years, were randomly recruited to participate in a population-based study to assess the prevalence of cardiovascular risk factors in our Chinese population between 1995 and 1996. All subjects who returned for CRISPS2 follow-up ($n = 1944$) were invited to undergo CIMT measurements at CRISPS2 and prospectively at CRISPS3. Subjects with known history of CVD were excluded from the present study. A total of 265 subjects with no known CVD consented to participate in the present study. These subjects had baseline and follow-up CIMT measurements at the second (CRISPS2) and third (CRISPS3) assessments. CRISPS2 was conducted in 2000–2004 and CRISPS3 in 2005–2008. CIMT measurements were performed by the same radiologist (S.C.W.C.) at the Department of Radiology, Queen Mary Hospital. Complete baseline demographic and biochemical data were available for all subjects. Detailed medical, drug, and family histories, including history of CVD, were obtained using a detailed questionnaire. Hypertension was defined as sitting blood pressure $\geq 140/90$ mmHg or on regular antihypertensive drugs. Subjects were classified as having diabetes mellitus according to the World Health Organization 1998 diagnostic criteria.[10]

Anthropometric and biochemical measurements

All subjects were assessed after an overnight fast. The details of anthropometric measurements [including height, weight, body mass index (BMI), waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP)], and measurements of biochemical variables (fasting plasma insulin, glucose, and lipid profile) were reported previously.[2,9,11] The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: Fasting plasma glucose (mmol/L) × fasting insulin (microunits/mL)/22.5. Serum adiponectin levels, measured at baseline (CRISPS2), were determined with an enzyme-linked immunosorbent assay (ELISA) established in our laboratory.[11,12]

Measurement of CIMT and definition of carotid plaques

Intima media thickness of the common carotids was assessed on B-mode ultrasound (ATL HDI 3000 and 5000 ultrasound system; Advanced Technology Laboratories, Bothell, WA) using high-resolution 10- to 12-MHz linear transducers, as previously described.[9] Longitudinal views of both common carotid arteries were obtained through an anterolateral approach. The best image was selected to show the far wall intimal–lumen interface as a continuous straight line. Three determinations of CIMT were made at 2 cm proximal to the bulb and at the site of greatest thickness. The values at each site were averaged, and the highest value of the averaged CIMT used as the representative value for each individual.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 19 (SPSS, Chicago, IL). Change in CIMT (ΔCIMT) was defined as the difference between baseline and year-5 measures. Data that were not normally distributed, as determined using the Kolmogorov–Smirnov test, were natural logarithmically transformed to obtain near normality before analysis. Values are reported as means ± standard deviation (SD) or medians with interquartile range (IQR). One-way analysis of variance (ANOVA) for continuous variables or chi-squared test for categorical variables was used as appropriate for comparisons between groups. The relationship between the CIMT progression with adiponectin level and other metabolic variables at baseline were assessed by Pearson correlation analysis.

Multiple linear regression models were performed to assess the association between adiponectin level at baseline and δCIMT as a dependent variable. We performed regression modeling on those baseline parameters with significant correlations with the CIMT progression on univariate analyses. We then repeated the regression model with full adjustment for traditional CVD risk factors, including age, smoking status, BMI or WC, fasting glucose, hypertension, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or triglycerides (TGs), and CIMT at baseline. In all statistical tests, two-sided P values < 0.05 were considered significant.

Ethics statement

The study was approved by the ethics committee of the Faculty of Medicine, University of Hong Kong. All subjects gave written informed consent.

Results

A total of 265 subjects (129 men and 136 women) for whom baseline and follow-up CIMT measurements were available at the second (CRISPS2) and third (CRISPS3) assessments, were included in this study. The baseline clinical characteristics of the subjects are summarized in Table 1. Of these subjects, 76 (28.7%) were current or former smokers. The median adiponectin level at baseline was 5.29 μgrams/mL (interquartile range 3.6–7.69 μg/mL). Serum adiponectin levels were lower in men (4.01 μg/mL; 2.98–6.06 μg/mL) than in women (6.67 μg/mL; 4.18–9.43 μg/mL) ($P < 0.001$). Adiponectin was negatively correlated with baseline CIMT (age-adjusted $r = -0.184$, $P = 0.003$). Adiponectin was also negatively correlated with BMI, WC, blood pressure, fasting glucose, HOMA-IR, and TGs, and positively correlated with HDL-C (all $P < 0.05$; data not shown). CIMT at baseline was 0.63 mm (0.52–0.73 mm) and increased significantly to 0.67 mm (0.56–0.78 mm) over 5 years ($P < 0.001$). Men had significantly thicker CIMT at baseline and at follow-up, compared to women ($P < 0.001$). Both men and women had significant increments in CIMT at year 5 compared to baseline ($P < 0.001$). ΔCIMT values were not significantly different between the sexes ($P = 0.122$).

Low adiponectin levels at baseline predicted a greater IMT increment ($r = -0.13$, $P = 0.036$). ΔCIMT also correlated inversely with age and baseline CIMT ($r = -0.12$, $P = 0.048$, and $r = -0.32$, $P < 0.001$, respectively), but showed no significant correlation with BMI, WC, SBP, DBP, fasting glucose, insulin resistance as measured by HOMA-IR, serum creatinine, or lipid levels (Table 2). Subjects who were current or former smokers had a significantly greater increase in CIMT over 5 years than nonsmokers [0.07 (0.00–0.15) vs. 0.03(0.02−0.10), respectively; $P = 0.029$). The presence of diabetes or hypertension was not associated with ΔCIMT.

In multiple linear regression analysis, baseline adiponectin levels (standardized β = −0.14, $P = 0.023$) was a significant independent predictor of ΔCIMT, after adjusting for parameters with significant correlations with ΔCIMT in

TABLE 1. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF STUDY SUBJECTS

	All subjects	Men	Women	P value (men vs. women)
N	265	129	136	—
Age (years)	54.6±12.3	54.3±12.3	54.9±12.3	0.688
BMI (kg/m^2)	24.9±3.73	25.1±3.50	24.7±3.94	0.443
Waist circumference (cm)	80.9±10.2	85.7±9.21	76.4±9.06	**<0.001**
Current/former smoker (%)	28.7	54.3	4.40	**<0.001**
Fasting glucose (mmol/L)	5.33±1.17	5.52±1.47	5.15±0.76	**0.009**
HOMA-IR	1.78 (1.29–2.71)	1.87 (1.32–2.94)	1.73 (1.27–2.58)	0.207
Diabetes (%)	12.5	15.6	9.6	0.136
Systolic blood pressure (mmHg)	125±19.4	127±19.2	123±19.3	0.053
Diastolic blood pressure (mmHg)	75±10.8	94±12.5	89.8±11.0	**<0.001**
Mean arterial pressure (mmHg)	92±12.0	94±12.5	90±11.0	**0.001**
Antihypertensive treatment (%)	18.1	20.9	15.4	0.234
Hypertension (%)	32.8	37.2	28.7	**0.018**
Total cholesterol (mmol/L)	5.37±0.92	5.39±0.88	5.34±0.95	0.652
HDL-C (mmol/L)	1.31±0.36	1.16±0.29	1.46±0.35	**<0.001**
LDL-C (mmol/L)	3.40±0.81	3.50±0.82	3.31±0.80	**0.048**
Triglycerides (mmol/L)	1.20 (0.80–1.90)	1.30 (0.90–2.10)	1.10 (0.70–1.50)	**<0.001**
Lipid-lowering treatment (%)	3.77	2.38	5.43	0.336
Serum creatinine (mmol/L)	72.0 (62.0–86.0)	86.0 (77.0–96.0)	62.0 (55.0–68.0)	**<0.001**
eGFR	83.9 (73.6–98.0)	80.2 (70.2–92.9)	85.9 (76.0–102.2)	**0.002**
Adiponectin (µg/mL)	5.29 (3.60–7.96)	4.01 (2.98–6.06)	6.67 (4.18–9.43)	**<0.001**
CIMT at baseline (mm)	0.63 (0.52–0.73)	0.62 (0.54–0.74)	0.58 (0.50–0.70)	**0.019**
CIMT at year 5 follow-up (mm)	0.67 (0.56–0.78)	0.71 (0.60–0.82)	0.63 (0.53–0.75)	**<0.001**
Change in CIMT (mm)	0.05 (–0.02 to 0.13)	0.05 (–0.02 to 0.13)	0.03 (–0.02 to 0.01)	0.122

Data are expressed as mean ± standard deviation (SD) or median (interquartile range).
Bold indicates significant P-values <0.05.
BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CIMT, carotid intima media thickness.

TABLE 2. PEARSON CORRELATION BETWEEN CHANGE IN CAROTID INTIMA MEDIA THICKNESS AND OTHER BASELINE PARAMETERS

Baseline variables	r	P value
Age	−0.12	**0.048**
Adiponectin[a]	−0.13	**0.036**
Baseline CIMT[a]	−0.32	**<0.001**
BMI	0.06	0.323
WC	0.06	0.375
SBP	−0.08	0.212
DBP	−0.04	0.550
Mean arterial pressure	−0.07	0.307
Fasting glucose	−0.05	0.447
HOMA-IR[a]	0.01	0.851
Cholesterol	0.02	0.700
HDL-C	0.04	0.577
LDL-C	0.05	0.400
Triglycerides[a]	−0.05	0.388
Creatinine[a]	−0.01	0.938
Estimated glomerular filtration rate[a]	0.11	0.087

[a]Log-transformed before analysis; change in carotid intima media was log-transformed before analysis.
Bold indicates significant P-values <0.05.
CIMT, carotid intima media thickness; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

univariate analyses (model 2, Table 3). Baseline adiponectin levels remained a significant predictor of ΔCIMT (β = −0.17, P = 0.015), even after adjusted for other traditional CVD risk factors, including BMI (or WC), fasting glucose, hypertension, LDL, and TGs (model 3, Table 3). With separate regression analysis on the basis of gender, the independent association of baseline adiponectin with ΔCIMT was significant in men (β = −0.23, P = 0.026), but not in women (P = 0.290) (Table 3).

Discussion

In this 5-year prospective study of a population-based cohort with no known CVD at baseline, serum adiponectin level was shown to predict the progression in carotid atherosclerosis, as reflected by the increment in CIMT, independent of conventional cardiovascular risk factors.

Previous cross-sectional studies demonstrated an inverse association between serum adiponectin and CIMT in Caucasian[7,8,13] and multiethnic populations.[14,15] However, it has been questioned whether the association of serum adiponectin with CIMT occurred secondary to the relationship of circulating adiponectin status with other cardiovascular risk factors. In populations without clinically manifest CVD, an association of adiponectin with CIMT was observed in cross-sectional studies, independent of other cardiovascular risks such as diabetes.[7,8,14] However, in subjects with a history of CVD, the relationship between CIMT and adiponectin was attenuated after full adjustment for risk factors including WC, DBP, HDL-C, and glycated haemoglobin (HbA1c).[16] This suggests that

TABLE 3.   LINEAR REGRESSION ANALYSIS SHOWING THE INDEPENDENT ASSOCIATION OF SERUM ADIPONECTIN
WITH CHANGE IN CAROTID INTIMA MEDIA THICKNESS

		Model 1	*Model 2*	*Model 3*
	N	*Standardized beta* (P *value*)	*Standardized beta* (P *value*)	*Standardized beta* (P *value*)
All	265	−0.13 (**0.032**)	−0.14 (**0.023**)	−0.17 (**0.015**)
Men	129	−0.20 (**0.026**)	−0.18 (**0.042**)	−0.23 (**0.026**)
Women	136	−0.03 (0.749)	−0.08 (0.334)	−0.09 (0.290)

Model 1, unadjusted; model 2, age, ever smoke, adiponectin, and CIMT at baseline; model 3, model 2 + additionally adjusted with HT, BMI, or WC, fasting glucose, LDL-C, and TGs or HDL-C.
Bold indicates significant *P*-values < 0.05.
CIMT, carotid intima media thickness; HT, hypertension; BMI, body mass index; WC, waist circumference; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol.

other risk factors related to insulin resistance and the metabolic syndrome may contribute to the inverse relationship between adiponectin and CIMT, depending on the selected population.[16]

In prospective studies, the relationship between adiponectin and CIMT was also not straightforward. In the Cardiovascular Risk in Young Finns Study, adiponectin levels at baseline were associated with baseline and 6-year CIMT in univariate analysis.[17] In a study of 85 Japanese hemodialysis patients with high cardiovascular risk and elevated serum adiponectin levels, no significant correlation was found between ΔCIMT and baseline adiponectin levels or the change in total or high-molecular-weight (HMW) adiponectin, but the change in the ratio of HMW to total adiponectin (ΔHMWR) was independently associated with CIMT progression at 1 year.[18] In 142 postmenopausal nondiabetic women studied by Stork et al. in Germany,[19] a significant linear relationship was not observed between age-adjusted ΔCIMT and baseline adiponectin levels. Whereas mean ΔCIMT was almost identical in the top three quartiles of baseline adiponectin levels, subjects in the lowest quartile showed a significantly higher ΔCIMT compared to the rest of the subjects, even after adjustment for confounding factors.[19] This threshold effect was not seen in other cross-sectional studies. In the current study, we observed instead a continuous inverse relationship between baseline serum adiponectin and ΔCIMT that persisted on multivariate analysis. This discrepancy may be attributed to differences in study subject characteristics and study design. It should be noted that the study by Stork et al. included high-risk postmenopausal women with baseline CIMT > 1 mm, recruited from a randomized control trial to study the effects of hormone replacement therapy that could impact on serum adiponectin level.[20]

Our current study, on the other hand, involved more subjects with a wider age range, included both sexes from a population-based study, and there was no known CVD at baseline. Whereas ΔCIMT was 0.023 mm after 1 year in the study by Stork et al., ΔCIMT in the current study was 0.05 mm after the much longer follow-up of 5 years. This, together with the median baseline CIMT of 0.63 mm (range 0.52–0.73 mm), would support our cohort being of much lower atherosclerotic risk compared to that of Stork et al.[19]

Adiponectin acts on both the liver and peripheral tissues to enhance insulin sensitivity. Indeed, baseline serum adiponectin levels correlated inversely with baseline HOMA-IR ($r = -0.46$, $P < 0.001$) in the current study. However, although insulin resistance is a known risk factor of atherosclerotic diseases,[21] we did not find a significant correlation between HOMA-IR and CIMT progression in our study. It

should be noted that HOMA-IR, as a surrogate index of insulin resistance, primarily reflects on hepatic insulin resistance and correlates less well with CIMT in cross-sectional studies, when compared to insulin resistance indexes that reflect on peripheral or muscle insulin sensitivity.[22] Furthermore, the relatively low baseline atherosclerosis risk of our cohort may have also contributed to the lack of a correlation between HOMA-IR and CIMT progression, because this community-based cohort was relatively nonobese and the vast majority of the subjects were not diabetic. Their baseline TGs and HDL-C levels also did not suggest a high level of insulin resistance. It would appear that, in this cohort, the effect of adiponectin on CIMT progression was mainly mediated through its antiatherogenic, anti-inflammatory, and antioxidative actions,[1] rather than its insulin-sensitizing effect.

The findings of the current study provide support for adiponectin as a potentially modifiable risk factor for atherosclerosis before the clinical manifestation of CVD, even in a relatively low-risk population. In the Framingham Offspring Study, a higher adiponectin level predicted lower future coronary heart disease (CHD) events in men initially free of CHD.[23] Amongst Asians, in a Korean population without CVD, a low adiponectin level was again a significant risk factor for the development of cardiovascular events.[24] On the other hand, a compensatory increase in adiponectin in response to the presence of CVD[25] probably contributes to the association between elevated CVD risk and high adiponectin levels observed in subjects with known CVD. Indeed, in this and our earlier studies, serum adiponectin levels in men were significantly lower than those in women.[12] Sexual dimorphism in serum adiponectin concentrations may explain the gender-specific effect of adiponectin on carotid atherosclerosis, as we have previously demonstrated that the lower adiponectin levels in men were due to the suppressive effects of testosterone on adiponectin secretion.[12]

A genetic variant in the *ADIPOQ* gene, adipo4 (rs266729), was found to be nominally associated with CIMT and low circulating adiponectin levels in obese subjects from the Carotid Atherosclerosis Progression Study,[13] providing additional support for a causal role of hypoadiponectinemia in early atherosclerosis. In that study, the association with hypoadiponectinemia persisted after adjusting for HbA1c, suggesting a direct effect of hypoadiponectinemia to increase CVD risk, rather than through inducing glucose intolerance.[13] Our data also suggest that CIMT is more closely related to adiponectin levels than blood glucose, lipid profile, or blood pressure.

This study has several limitations. The findings from this Chinese cohort may not be directly extrapolated to other ethnic populations. However, recent data have shown that the relationship between adiponectin and CIMT did not differ significantly across racial/ethnic groups, even after controlling for vascular risk factors.[15] We have adjusted for the relevant confounding factors. However, other confounding factors, such as the effect of attrition, may lead to potential bias. There may also be selection bias because subjects who participated in the study may be more health conscious and more willing to consent, and therefore, not representative of the entire CRISPS cohort. Nonetheless, the relationships between adiponectin and other cardiometabolic risk factors were similar to findings in previous studies.[2,4] Therefore, we believe that this cohort with relatively low cardiovascular risk would be representative of other population-based cohorts. Moreover, the HMW form of adiponectin was not measured; hence, the effect of adiponectin oligomerization on subclinical atherosclerosis cannot be assessed. However, total adiponectin levels, as measured in this study, correlate strongly with the HMW form.[26] Although we have not accounted for intraobserver variability in the measurement of CIMT, standardized protocols as previously described[9] have been used at baseline and year-5 CIMT measurements.

In conclusion, this 5-year prospective study demonstrated that hypoadiponectinaemia was an independent risk factor for the progression of CIMT, a marker of early atherosclerosis, even after adjusting for other cardiovascular risk factors, in men without known CVD. This is in keeping with a vasoprotective effect of adiponectin in humans, as has been demonstrated in animal studies.

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Author Disclosure Statement

No competing financial interests exist.

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