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Plasma Adiponectin Levels in Relation to Carotid Intima Media Thickness and Markers of Insulin Resistance

Peter M. Nilsson, Gunnar Engström, Bo Hedblad, Jan Frystyk, Margaretha M. Persson, Göran Berglund, Allan Flyvbjerg

Background—Circulating adiponectin is a marker for insulin sensitivity, derived from fat cells. It is largely unknown if adiponectin is also an independent marker for early atherosclerosis.

Methods and Results—Plasma adiponectin levels were measured in 373 men and 514 women of middle-age by a time-resolved immunofluorometric assay. The subjects were sampled stratified for degree of insulin sensitivity (HOMA-IR). An ultrasound measurement of the right common carotid artery intima media thickness (IMT) was made. When the distribution of adiponectin was stratified into sex-specific quartiles (Q1 to Q4), men in Q4 differed from Q1 in higher mean age and high-density lipoprotein (HDL) cholesterol, but lower blood pressure, HbA_{1c}, HOMA-index, and body mass index. Women showed similar associations. Mean IMT for men was significantly lower ($P=0.03$) in adiponectin Q4 as compared with Q1 when adjusted for age, waist, smoking, HDL cholesterol, and diastolic blood pressure. When adding HbA_{1c} and HOMA to the model, the association was no longer significant ($P=0.15$). In women no difference in IMT was noticed across adiponectin quartiles.

Conclusion—Plasma adiponectin is a marker of glucose metabolism and obesity and shows an inverse age-adjusted association with carotid ultrasound IMT in men, but not in women. This association is attenuated after adjustments for other risk factors. (*Arterioscler Thromb Vasc Biol.* 2006;26:2758-2762.)

Key Words: adiponectin ■ atherosclerosis ■ glucose ■ IMT ■ insulin ■ obesity

Adiponectin is the most abundant adipokine secreted from adipose tissue cells and has been implicated to be a marker of insulin sensitivity and glucose metabolism, as well as involved in inflammatory processes.^{1,2} Previous studies have shown an inverse correlation between circulating adiponectin levels and measures of insulin resistance as well as C-reactive protein (CRP) levels. It is still an open question whether adiponectin plays a causal role for the development of arterial lesions caused by atherosclerosis. As atherosclerotic lesions are influenced by the interplay between metabolic abnormalities, hemodynamic factors, and local inflammation, it is assumed that adiponectin may play a role in this process because of cross-sectional associations with many of the risk factors.³ A few studies have investigated adiponectin levels in relation to intima-media thickness (IMT) in the carotid artery, being an early marker of atherosclerosis and the consequence of elevated cardiovascular risk factors. In 2 population-based screening studies from Austria it was reported that adiponectin levels were inversely correlated to carotid IMT, both in 140 obese juveniles compared with a group of matched control⁴ and in 1515 healthy middle-aged

subjects of both genders.⁵ Recently, common carotid IMT was shown associated with adiponectin levels in a US-based middle-aged female cohort.⁶ Furthermore, 2 Japanese case-control studies reported that adiponectin is associated with increased prevalence of coronary artery disease (CAD)⁷ and that adiponectin had a close relationship with CRP levels.⁸ It has been suggested that atherogenesis may be associated with a decrease of adiponectin through abnormal glyco-metabolism and lipid-metabolism induced by inflammation.⁸

It is still unclear to what extent the relationships between adiponectin and atherosclerosis could be accounted for by other risk factors related to insulin resistance and the metabolic syndrome. One of the aims of the Malmö Diet and Cancer–Cardiovascular (MDC-CV) cohort^{9,10} was to study the early atherosclerotic manifestations by means of ultrasound examinations of the carotid arteries. We have previously shown that insulin resistance, as measured by the HOMA index,¹¹ is associated with increased common carotid IMT in this cohort.¹⁰ With the purpose of exploring different aspects of insulin resistance, extended studies have been performed in subgroups of the same cohort.

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The aim of this study was to investigate the relationship between circulating plasma adiponectin levels and carotid IMT, before and after adjustment for metabolic variables, in middle-aged subjects of both genders.

Methods

Participants

The Malmö Diet and Cancer (MDC) study was a large (n=28 449) population-based study with recruitment from the city of Malmö, Sweden, between 1991 and 1996. The screening process has previously been described.^{9,10} Eligible participants were men in the age-range 46 to 73 years, and women in the age range 45 to 73 years, with Swedish reading and writing skills.

From the large MDC cohort, a subgroup (n=6103) was selected for further and more detailed studies on cardiovascular (CV) risk factors.¹⁰ From this MDC-CV cohort, a subgroup of 909 subjects without known diabetes was selected for an extended study of factors related to insulin resistance, as estimated by the HOMA-IR index.¹¹ The re-examination was performed in 1999 and 2000. A stratified sampling was performed according to the HOMA levels, so that 15% were sampled from each of the first 2 quartiles of HOMA, 30% from the third quartile, and 40% were sampled from the individuals with baseline HOMA in the fourth quartile. After exclusion of subject with diabetes (according to questionnaire) and subjects with missing information about adiponectin, waist, high-density lipoprotein (HDL), or HbA1c, 887 subjects remained (373 men and 514 women).

Measurements

Physical Examination and Laboratory Analyses

Body weight (kg) and height (m) were measured with subjects wearing light indoor clothing and without shoes. Body mass index (BMI) was calculated as kg/m². Waist (cm) was measured at the

umbilicus and hip (cm) at the widest part. A waist to hip ratio was calculated.

Supine blood pressure (BP) (mm Hg) was measured twice after 10 minutes rest by use of a sphygmomanometer with an appropriate cuff width and a mercury manometer, and a mean figure was recorded. Systolic blood pressure (SBP) was defined as the appearance of the first sound (Korotkoff phase 1) and diastolic blood pressure (DBP) when the sounds disappeared (Korotkoff phase V).

The methods of measuring total cholesterol, HDL cholesterol, triglyceride (TG) (all in mmol/L), HbA_{1c} (%), and the HOMA index have previously been described.¹⁰

Plasma adiponectin (mg/L) was determined as previously described by a novel in-house (Aarhus, Denmark) time-resolved immunofluorometric assay (TR-IFMA) based on 2 monoclonal antibodies and recombinant human adiponectin (R & D Systems, Abingdon, UK).¹² The adiponectin molecule is known to form a range of polymers, of which the predominant polymers include trimers, hexamers, and highly congregated multimers.¹³ Western Blotting experiments have demonstrated that both monoclonal antibodies used in the TR-IFMA assay, detect several adiponectin polymers in serum, including the major 3 molecular forms, ie, high-molecular-weight (HMW), medium-molecular-weight (MMW), and low-molecular-weight (LMW) adiponectin (data not shown). All standards and unknown samples were analyzed in duplicate, with the exception of nonspecific binding (NSB), which was analyzed in quadruplicate. The intra-assay coefficient of variation (CV) was <5% and the inter-assay CV was <10%.

B-Mode Ultrasound of Arteria Carotis

An Acuson Sequoia Ultrasound System (Acuson, Mountain View, Calif) with an 8-MHz transducer was used. The examination procedure and image analysis, which has been previously described in full detail^{10,14} was performed by 2 specially trained sonographers certified on completion of an extensive educational program. In brief, the right carotid bifurcation was scanned within a predefined window comprising 3 cm of the distal common carotid artery, the bifurcation

TABLE 1. Relationships Between Adiponectin and Cardiovascular Risk Factors in Men From the Malmö Diet and Cancer Study–Cardiovascular Cohort

| | Plasma Adiponectin | | | | P (trend) |
|---------------------------------|--------------------|-------------|-------------|-------------|-----------|
| | Q1 | Q2 | Q3 | Q4 | |
| mg/L | <5.3 | 5.3–7.02 | 7.02–9.16 | >9.16 | |
| n | 94 | 93 | 93 | 93 | |
| Age, y | 63.8 (5.8) | 65.3 (6.0) | 64.3 (6.4) | 66.2 (5.4) | 0.025 |
| SBP, mm Hg | 146 (18) | 149 (20) | 145 (16) | 144 (17) | 0.14 |
| DBP, mm Hg | 91 (8.2) | 92 (10) | 91 (8.6) | 88 (10) | 0.042 |
| HbA _{1c} , % | 4.8 (0.91) | 4.5 (0.56) | 4.6 (1.2) | 4.4 (0.4) | 0.001* |
| HOMA | 4.00 (3.0) | 2.70 (1.8) | 2.48 (2.1) | 2.06 (2.0) | <0.001* |
| BMI, kg/m ² | 28.0 (3.4) | 27.3 (3.2) | 27.7 (3.7) | 25.6 (3.6) | <0.001 |
| WHR | 0.98 (0.04) | 0.98 (0.04) | 0.97 (0.05) | 0.96 (0.05) | 0.008 |
| Waist, cm | 100 (9) | 97 (9) | 98 (10) | 94 (11) | <0.001 |
| LDL, mmol/L | 3.4 (0.8) | 3.8 (0.8) | 3.5 (0.7) | 3.6 (0.8) | 0.30 |
| HDL, mmol/L | 1.2 (0.2) | 1.3 (0.3) | 1.3 (0.3) | 1.5 (0.3) | <0.001 |
| History of CVD, % | 5.3 | 4.3 | 4.3 | 5.4 | 0.99 |
| Current smokers, % | 23.4 | 14.0 | 15.1 | 20.7 | 0.59 |
| IMT CCA, mm | 0.92 (0.3) | 0.90 (0.17) | 0.89 (0.18) | 0.87 (0.16) | 0.067 |
| Lipid-lowering drug, % | 7.4 | 4.3 | 0 | 3.2 | 0.05 |
| Blood pressure-lowering drug, % | 25.5 | 28 | 21.5 | 12.9 | 0.02 |

Quartiles (Q1-Q4) of plasma adiponectin and means (SD).

*P values based on log-normalized values.

CCA indicates common carotid artery; CVD, cardiovascular disease; DBP, diastolic blood pressure; IMT, intima media thickness; SBP, systolic blood pressure.

TABLE 2. Relationships Between Adiponectin and Cardiovascular Risk Factors in Women From the Malmö Diet and Cancer Study—Cardiovascular Arm

| | Plasma Adiponectin | | | | <i>P</i> (trend) |
|---------------------------------|--------------------|-------------|-------------|-------------|------------------|
| | Q1 | Q2 | Q3 | Q4 | |
| mg/L | <7.72 | 7.72–10.53 | 10.53–14.2 | >14.2 | |
| n | 129 | 127 | 129 | 129 | |
| Age, y | 64.4 (5.8) | 64.0 (5.9) | 64.7 (6.0) | 64.4 (5.7) | 0.86 |
| SBP, mm Hg | 143 (19) | 143 (19) | 140 (18) | 140 (18) | 0.14 |
| DBP, mm Hg | 86 (9.5) | 86 (8.6) | 86 (8.9) | 85 (9.4) | 0.47 |
| HbA _{1c} , % | 4.6 (0.65) | 4.5 (0.45) | 4.4 (0.38) | 4.4 (0.44) | <0.001* |
| HOMA | 3.35 (2.6) | 2.52 (1.5) | 1.92 (1.1) | 1.59 (0.91) | <0.001* |
| BMI, kg/m ² | 28.3 (4.3) | 28.1 (4.4) | 27.4 (4.1) | 25.4 (3.5) | <0.001 |
| WHR | 0.87 (0.05) | 0.86 (0.05) | 0.85 (0.07) | 0.83 (0.05) | <0.001 |
| Waist, cm | 90 (11) | 88 (11) | 87 (10) | 81 (10) | <0.001 |
| LDL, mmol/L | 3.7 (0.9) | 3.8 (0.9) | 3.8 (0.8) | 3.6 (0.9) | 0.86 |
| HDL, mmol/L | 1.4 (0.3) | 1.6 (0.4) | 1.7 (0.3) | 1.9 (0.4) | <0.001 |
| History of CVD, % | 0.8 | 0 | 1.6 | 2.3 | 0.14 |
| Current smokers, % | 20.2 | 24.4 | 10.9 | 16.3 | 0.63 |
| IMT CCA, mm | 0.86 (0.14) | 0.83 (0.14) | 0.85 (0.14) | 0.82 (0.13) | 0.15 |
| Lipid-lowering drug, % | 5.4 | 1.6 | 1.6 | 2.3 | 0.14 |
| Blood pressure-lowering drug, % | 26.4 | 22.0 | 14.7 | 12.4 | 0.001 |

Quartiles (Q1-Q4) of plasma adiponectin and means (SD).

**P* values based on log-normalized values.

and 1 cm of the internal and external carotid arteries, respectively, for the presence of plaques, defined as focal IMT >1.2 mm. Thickness of the common carotid intima-media complex, eg, the mean distance between the leading edges of the lumen-intima and the media-adventitia interfaces of the far wall (mean IMT CCA), was measured off-line and along 1-cm section in the longitudinal projection using a specially designed computer-assisted image analyzing system based on automated detection of the echo structures, but with the option to make manual corrections by the operator.

Questionnaire

Data on drug medication, medical history, and lifestyle habits (smoking) were recorded from a self-administrated questionnaire, as previously described.^{10,15,16}

Statistical Analysis

Mantel-Haenzel's χ^2 test and analysis of variance was used to analyze the cardiovascular risk factors by quartile (Q1 to Q4) of adiponectin with means and standard deviation (SD). A general linear model was used to study the mean IMT CCA over the quartiles of adiponectin, with adjustments for confounding factors, and to calculate adjusted mean values. The analysis was performed with and without weighting for the stratified sampling procedure. Log-normalization was used for variables with positively skewed distribution (HOMA-IR, HbA_{1c}). The distribution of IMT showed a moderate positively skewed distribution (skewness: 2.3 for men and 0.9 for women). The relationships between adiponectin and IMT were therefore calculated both with and without log-normalization of IMT, with essentially the same results. *P*<0.05 was considered significant.

Results

Association Between Plasma Adiponectin and Risk Factors

Tables 1 and 2 present the baseline characteristics for men and women in relation to quartiles of adiponectin. Men in Q4

differed from Q1 in higher mean age and HDL cholesterol, but lower DBP, HbA_{1c}, HOMA-IR index, and body mass index (BMI) (Table 1). Women in adiponectin Q4 compared with Q1 had higher HDL cholesterol, but lower HbA_{1c}, HOMA-IR index, BMI, and waist-to-hip ratio (Table 2).

Plasma Adiponectin and Common Carotid IMT

Mean IMT for men was significantly lower in adiponectin Q4 as compared with Q1 when adjusted for age, waist circumference, smoking, HDL cholesterol, and DBP in a general linear model (Table 3). When adding HbA_{1c} to the model, the association was no longer significant (*P*=0.08). The associations were further attenuated after adjustment for HOMA and treatment for lipids and high blood pressure (*P*=0.15) (Table 3). Adjustments for fasting glucose instead of HbA_{1c} produced the same results (data not shown).

Because adiponectin levels <4 mg/L previously have been associated with CAD in men, we also explored the relationships with carotid IMT for men with concentration above (n=339) and below (n=34) that level. Even though IMT tended to be thicker in men with low adiponectin, the relationships still did not reach significance after full adjustments (*P*=0.07).

For women no difference in IMT was noticed across adiponectin quartiles. The results were essentially the same when log-transformed IMT values were used in the multivariate analysis.

The relationships between adiponectin and IMT were also calculated after weighting the data for the stratified sampling procedure. The results were essentially unchanged (data not shown).

TABLE 3. Relationship Between Sex-Specific Quartiles (Q1-Q4) of Plasma Adiponectin (mg/L) and Common IMT CCA, With Adjustments in 3 Models (1–3)

| | Plasma Adiponectin | | | | <i>P</i> (trend) | <i>P</i> (Q1 vs Q4) |
|--------------|--------------------|-------------|-------------|-------------|------------------|---------------------|
| | Q1 | Q2 | Q3 | Q4 | | |
| Men | | | | | | |
| mg/L | <5.3 | 5.3–7.02 | 7.02–9.16 | >9.16 | | |
| n | 94 | 93 | 93 | 93 | | |
| IMT CCA, | 0.92 (0.3) | 0.90 (0.17) | 0.89 (0.18) | 0.87 (0.16) | 0.067 | |
| Model 1 | 0.93 (0.02) | 0.89 (0.02) | 0.89 (0.02) | 0.86 (0.02) | 0.02 | 0.02 |
| Model 2 | 0.93 (0.02) | 0.89 (0.02) | 0.90 (0.02) | 0.86 (0.02) | 0.04 | 0.03 |
| Model 3 | 0.92 (0.02) | 0.89 (0.02) | 0.90 (0.02) | 0.87 (0.02) | 0.17 | 0.15 |
| Women | | | | | | |
| mg/L | <7.72 | 7.72–10.53 | 10.53–14.2 | >14.2 | | |
| n | 129 | 127 | 129 | 129 | | |
| IMT CCA | 0.86 (0.14) | 0.83 (0.14) | 0.85 (0.14) | 0.82 (0.13) | 0.15 | |
| Model 1 | 0.86 (0.01) | 0.84 (0.01) | 0.85 (0.01) | 0.82 (0.01) | 0.11 | 0.05 |
| Model 2 | 0.85 (0.01) | 0.83 (0.01) | 0.85 (0.01) | 0.83 (0.01) | 0.54 | 0.33 |
| Model 3 | 0.85 (0.01) | 0.83 (0.01) | 0.85 (0.01) | 0.83 (0.01) | 0.56 | 0.33 |

Means (SD).

Model 1. Mean IMT CCA adjusted for age.

Model 2. Model 1+waist circumference, smoking, HDL cholesterol, diastolic BP.

Model 3. Model 2+HbA_{1c} (log-transformed) + HOMA (log-transformed) + lipid-lowering drugs+ blood pressure-lowering drugs.

Discussion

Previous studies have reported inverse relationships between adiponectin and carotid IMT.^{4–8} However, to what extent this could be explained by other risk factors associated with obesity and the metabolic syndrome has so far been unclear. The present population-based study showed inverse relationships between circulating adiponectin and carotid IMT in men, but not in women. Several other risk factors were also associated with adiponectin, including waist circumference, diastolic blood pressure, HDL cholesterol, and HbA_{1c}. The relationship between IMT and adiponectin was attenuated and nonsignificant (*P*=0.15) after full adjustments for these risk factors. The results thus suggest that traditional cardiovascular risk factors associated with obesity and the metabolic syndrome account for most of the inverse relationship found between adiponectin and carotid IMT.

Our results disagree with previous observations from a population-based study of healthy middle-aged subjects in Austria.⁵ The different results could in part be explained by the selection of covariates. In the Austrian study, the results were adjusted for low-density lipoprotein (LDL) cholesterol. In the present study, however, HDL cholesterol showed a substantial correlation with adiponectin, whereas LDL cholesterol had no effect on the relationship between adiponectin and IMT. In addition, the Austrian study in healthy subjects⁵ also showed a weaker but significant effect of adiponectin in female as compared with male subjects.

In contrast to previous studies, the present results were adjusted for HbA_{1c}, which attenuated the relationships and turned them nonsignificant. The close relationship between adiponectin and the glucose metabolism are also supported by other studies.¹⁷ Relationships with glucose and insulin sensi-

tivity seem to be an important explanation for the relationships between adiponectin and CVD.

Even though adiponectin was not independently associated with carotid IMT in this study, it is still possible that it could be a risk factor for myocardial infarction which has been previously reported in a nested case-control study of male health professionals in the US.¹⁸ This possibility has still to be evaluated in future follow-up studies of the MDC-CV cohort.

Limitations of the Study

There are some limitations of the study that should be pointed out. First, in a cross-sectional study, causality cannot be proven. Therefore, we cannot state that low adiponectin levels really precede the development of carotid IMT changes, but our findings are in line with previous observations in different populations.^{4–8} Second, our sample was recruited from the larger MDC-CV cohort based on measurement of insulin sensitivity (HOMA). This means that it was not a truly population-based sample, but skewed toward an increased prevalence of insulin resistance. This fact might have increased the development of early arterial lesions. However, because of this selection any associations between adiponectin levels and IMT should theoretically be more pronounced than in the normal healthy population.^{5,6} We have also adjusted for glycohemoglobin, previously not performed in similar studies. Third, even if we have adjusted for the use of antihypertensive and lipid lowering drugs that could potentially influence adiponectin levels we have no data on serum testosterone,¹⁹ a factor well-known to decrease adiponectin and thus able to explain gender differences in the association to IMT. At the time of the study only very few subjects used glitazone therapy in Sweden, another external

factor able to influence adiponectin levels. Finally, it is possible that larger sample would have produced significant findings even after adjustment. However, if there were strong independent relationships between carotid IMT and adiponectin, the present sample should be sufficiently large to detect this relationship.

In conclusion, we have shown that circulating adiponectin levels are inversely associated with IMT in males, but not in females from a sample of a middle-aged urban population with predominance of insulin resistance. This association is attenuated after full adjustment for metabolic risk factors. Potential gender difference should be confirmed in future studies.

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Disclosures

None.

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