Oxidative Stress and Inflammatory Markers in Relation to Circulating Levels of Adiponectin

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Objective: Previous epidemiological studies together with animal studies have suggested an association between adiponectin, and oxidative stress and inflammation, but community-based studies are lacking. Our objective was to investigate the relative importance of oxidative stress and inflammatory markers, representing different pathways in relation to adiponectin.

Design and Methods: In a cross-sectional sample of 929 70-year-old individuals (50% women) of the Prospective Investigation of the Vasculature in Uppsala Seniors study, relations between serum adiponectin and oxidative stress [conjugated dienes (CD), homocysteine, total antioxidant capacity, oxidized low-density lipoprotein (OxLDL), OxLDL antibodies, baseline CD of LDL, glutathione (GSH), total glutathione (TGSH), glutathione disulfide], circulation interleukins (IL-6, IL-8), other cytokines [tumor necrosis factor α, monocyte chemotactic protein-1 (MCP-1), epidermal growth factor (EGF), vascular endothelial growth factor], cell adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, P-selectin, L-selectin), and systemic inflammatory markers [C-reactive protein (CRP), leukocyte count] in separate models were investigated.

Results: In age- and sex-adjusted, as well as multivariable-adjusted models, adiponectin was significantly and positively associated with GSH, log TGSH, whereas an inverse association was observed for CD and log EGF. An inverse association between adiponectin and MCP-1, log E-selectin, and log CRP was significant in age- and sex-adjusted models, but not in multivariable-adjusted models.

Conclusions: Our results imply that higher levels of adiponectin are associated with a more beneficial oxidative stress profile, with higher levels of principal anti-oxidative GSH and total GSH together with lower levels of lipid peroxidation, possibly through shared pathways. Further studies are needed to investigate whether changes in the oxidative stress profile may be a mechanism linking adiponectin with type 2 diabetes and/or cardiovascular disease.

Introduction

Obesity and overweight are major contributors to the disease burden worldwide (1) and of great public health importance as major causes of morbidity and mortality (2). Obesity is accompanied by an activation of pro-inflammatory pathways (2-4) and also linked to increased oxidative stress (5,6). Inflammation is suggested to play a key role in the adverse effects of obesity, i.e. in type 2 diabetes and cardiovascular disease (2). Similarly, harmful oxidative stress plays a critical role in obesity-associated conditions such as diabetes, hypertension, and atherosclerosis (5).

Adipokines is a group of bioactive molecules secreted from adipose tissue, among which adiponectin is the most abundantly expressed (7), while being clearly downregulated in obesity (8). Adiponectin has attracted some recent attention for its potentially anti-inflammatory, anti-atherogenic, and anti-oxidative properties (9).

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Adiponectin, Oxidative Stress, and Inflammation

Some previous studies, mostly in smaller and/or selected study samples, have shown an association between adiponectin and pro- and anti-oxidative markers (5, 10-14). The association between adiponectin and glutathione (GSH) remains to be fully elucidated, but an association between adiponectin and the ratio of oxidized and reduced GSH has been suggested (10, 11). An inverse correlation between adiponectin and measures of lipid peroxidation has been reported in some studies (5, 12-14), but not all (15).

Based on previous studies, we hypothesized that higher adiponectin levels would be associated with anti-oxidative and anti-inflammatory properties reflected by circulating biomarkers. We aimed to investigate the importance of a broad set of well-recognized oxidative stress and inflammatory markers, representing different pathways, in relation to adiponectin in a large community-based sample of elderly.

Methods

Study sample

In the Prospective Investigation of the Vasculature of Uppsala Seniors (PIVUS), all 70-year-old men and women living in Uppsala County, Sweden between April 2001 and June 2004 were invited to participate. Out of 2,025 individuals invited, 1,016 (50% women) were investigated within 1 month of their 70th birthday in order to standardize for age. Cardiovascular disorders and medications was collected for 100 nonattendees which on average had a similar frequency of myocardial infarction, coronary revascularization, anti-hypertensive treatment, statin use, and insulin treatment, but higher a frequencies of diabetes, congestive heart failure, and stroke (16). To exclude individuals with acute infections, chronic inflammatory disorders or blood malignancies, participants with C-reactive protein (CRP) (16) were excluded in the present study. Further exclusions were made of participants without valid measures of adiponectin (n = 1) or of those missing any covariate used in the regression analyses (n = 21). Thus, 929 participants were eligible for the study. The study was approved by the Ethics Committee of Uppsala University, and all participants provided written informed consent.

Assessment and definitions of clinical covariates

After an overnight fast (lasting from midnight to the examination the following morning), with no medication or smoking allowed, anthropometrical measurements and blood samples were collected. All individuals answered a questionnaire regarding medical history, smoking habits, and medication. Body mass index (BMI) was calculated as the ratio between height and weight squared (kg/m²). The homoeostasis model assessment insulin resistance index (HOMA-IR) was defined as (fasting plasma glucose × serum insulin)/22.5 (17). Estimated glomerular filtration rate from cystatin C (eGFR) was calculated as eGFR (ml/min/1.73 m²) = 79.901 × (cystatin C in mg/l)^−1.4380 (18).

Lipid variables and blood glucose were measured by standard laboratory techniques from blood samples. Levels of total serum adiponectin were assessed with a double-antibody radioimmunoassay (Linco Res., St. Louis, MO). The total coefficients of variations for adiponectin were 15.2% at low (2-4 μg/ml) and 8.8% at high (26-54 μg/ml) levels.

Oxidative markers

Using a previously validated method (19), baseline conjugated dienes (CD) of low-density lipoprotein (BCD-LDL) were measured with a coefficient of variance for within-assay and between-assay precision of 4.4% and 4.5%, respectively. After precipitation of serum LDL with buffer heparin, BCD-LDL was measured spectrophotometrically. Levels of serum oxidized LDL were determined with enzyme-linked immunosorbent assay (ELISA) kits (Mercodia, AB); within-assay variation coefficient was 6.3% and between-assay CV was 4.7%. Autoantibodies to oxidized LDL (OxLDL) were measured with an ELISA kit (BioMedica), with intra-assay and inter-assay values 4.3% and 6.0%, respectively. All forms of GSH, CD, and total anti-oxidative capacity (TAOC) values were measured and calculated as described previously (20). In brief, total glutathione (TGSH) and GSSG were measured through enzymatic reactions, and GSH was further calculated as the difference between TGSH and GSSG. CD, formed after double-bound rearrangements in polyunsaturated fatty acid residues in a free radical reaction, were measured spectrophotometrically. TAOC was measured by assessing the ability of serum samples to inhibit linolenic acid peroxidation. Homocysteine was measured by using Axiom® Homocysteine Enzyme Immunoassay (Axis-Shield Diagnostics) with an intra-assay coefficient of 6.8%.

Inflammatory markers

High-sensitive CRP and intercellular adhesion molecule-1 (ICAM-1) were measured with commercially available ELISA (Medix Biotechnica, Kauniainen, Finland and R&D System Europe, Abingdon, Oxon, UK, respectively). Leukocyte count was measured by standard laboratory techniques at Uppsala University Hospital. Remaining inflammatory markers were analyzed with the Evidence® array biochip analyzer (Randox Laboratories, Crumlin, UK) (21). The functional sensitivity for the inflammatory markers was as follows: IL-6: 0.3 pg/ml; IL-8: 1.5 pg/ml; tumor necrosis factor (TNF): 1.8 pg/ml; monocyte chemotactic protein-1 (MCP-1): 19.4 pg/ml; vascular cell adhesion molecule-1 (VCAM-1): 31 ng/ml; E-selectin: 3.1 ng/ml; P-selectin: 11.2 ng/ml; L-selectin: 32.8 ng/ml; leukocyte count: 0.2 × 10^9 cells/l. IL-1α, IL-1β, IL-2, IL-4, IL-10, and interferon-γ were included in the Evidence® array biochip cytokine panel, but were not evaluated further due to insufficient sensitivity for measurements in the present sample.

Statistical methods

To achieve a normal distribution of the residuals of the regression models, all oxidative and inflammatory markers except GSH, CD, TAOC, BCD-LDL OxLDL, MCP-1, P-selection, L-selection, and leukocyte count were transformed, as well as the covariates HOMA-IR and triglycerides. Natural log was used for all transformations, except TNFz for which a reciprocal root transformation was performed.

To account for the differences in mean adiponectin levels between sexes, adiponectin was z-score transformed in each sex separately before pooling; hence, an increase of β units of the dependent variable per 1-standard deviation increase in adiponectin is presented in the results. All regression models were sex-adjusted through the z-score-transformed adiponectin variable. Associations between adiponectin and measures of oxidative stress and inflammation were analyzed in age- and sex-adjusted, as well as multivariable-adjusted linear regression models with measures of oxidative stress [CD, homocysteine, TAOC, OxLDL, OxLDL antibody, BCD of LDL, CD, BCD-LDL OxLDL, MCP-1, P-selection, L-selection, and leukocyte count].
GSH, TGSH, glutathione disulfide], circulation interleukins (IL-6, IL-8), other cytokines [TNF-α, MCP-1, epidermal growth factor (EGF)], vascular endothelial growth factor (VEGF)], cell adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin, L-selectin), and systemic inflammatory markers (CRP, leukocyte count) as dependent variables in separate models. The multivariable regression models were adjusted for potential confounders including age, BMI, antihypertensive treatment, log HOMA-IR, anti-diabetic treatment, total cholesterol, high-density lipoprotein, log triglycerides, lipid-lowering medication, eGFR, and smoking (no, former, current).

In additional analyses, to investigate the effect of multiple testing, the regression P-values from the age- and sex-adjusted as well as multivariable-adjusted models were corrected with the Holm-Bonferroni method, using an uncorrected overall critical P-value of 0.05, and accounting for 22 tests (i.e. number of oxidative stress and inflammatory markers) (22).

To address potential effect modification by sex, previous CVD, and BMI, we added two-way interaction terms to the multivariable-adjusted models, in separate models for adiponectin × sex, adiponectin × previous CVD, and adiponectin × BMI. Also, we re-ran the multivariable-adjusted model stratified by sex, previous CVD, and overweight (BMI < 25 and BMI ≥ 25) in separate models. In an exploratory analysis, we also tested if the ratio of reduced and oxidized GSH, calculated as GSH/GSSG, was associated with adiponectin in age- and sex-adjusted as well as multivariable-adjusted models. The multivariable regression model was also performed after excluding all individuals with signs of chronic kidney disease (eGFR < 50 ml/min/1.73 m²) for all significant associations in the main multivariable-adjusted model.

Two-tailed significance values were given with P < 0.05 regarded as significant in all models not corrected for multiple testing. The statistical software package STATA 11.2 (Stata Corporation, College Station, TX) was used for all analyses.

Results

Table 1 presents the clinical characteristics along with markers of oxidative stress and inflammation. Mean adiponectin levels were significantly different between men and women (mean [men] = 5.60; mean [women] = 8.75; P-value < 0.0001) after adjustment for age and BMI. Individuals with BMI ≥ 25 had on average significantly lower adiponectin levels than those with BMI < 25 (mean [BMI < 25] = 8.17; mean [BMI ≥ 25] = 6.67; P-value < 0.0001) after adjustment for age and sex.

Primary analyses

In age- and sex-adjusted, as well as multivariable-adjusted models, adiponectin was positively associated with GSH and log TGSH, whereas a negative association with CD was observed. A positive association between adiponectin and TAOC was borderline significant in age- and sex-adjusted analysis. A positive association between adiponectin and homocysteine was borderline significant in both age- and sex-adjusted and multivariable-adjusted models (Table 2).

Adiponectin was inversely associated with log EGF in age- and sex-adjusted and multivariable-adjusted models. Adiponectin was negatively correlated with MCP-1, log E-selectin, and log CRP in age- and sex-adjusted analyses, but not in multivariable-adjusted models (Table 2).

Adiponectin remained associated with CD, log CRP, and GSH in the age- and sex-adjusted model, but no association remained significant in multivariable-adjusted models, when correcting for multiple testing using Holm-Bonferroni (corrected overall critical P-values were 0.00263 and 0.00227, respectively).

Additional analyses

No effect modification by sex was significant for any of the tested associations. The effect of adiponectin on OxLDL was clearly different between individuals with previous CVD (β, 12.49; 95% CI, 6.43, 18.55) and individuals without previous CVD (β, –3.38; 95% CI, –6.80, 0.04), which was supported by a highly significant interaction term of adiponectin and CVD status (P = 0.00047). A similar pattern was observed in analyses stratified by overweight status, where individuals with BMI < 25 had an inverse association with OxLDL (β, –1.01; 95% CI, –5.83, 3.81) individuals with BMI ≥ 25 was displayed a positive association (β, 1.43; 95% CI, –2.44, 5.29), with a significant interaction term (P = 0.006). Further, an effect modification by BMI on the association between adiponectin and ICAM-1 was significant (P = 0.016). Analyses stratified by sex, previous CVD, and overweight are presented in Supporting Information Tables 1-3, respectively.

All markers significant in the multivariable-adjusted model remained significant and with small changes in effect size after exclusion of individuals with eGFR < 50 ml/min/1.73 m². Adiponectin was not significantly associated with the ratio of reduced and oxidized GSH in age- and sex-adjusted or multivariable-adjusted models (P = 0.43 and P = 0.36, respectively).

In secondary analyses, we added total energy intake from a 7-day dietary registration to the multivariable model in which the results were similar to the main results (data not shown).

Discussion

Principal findings

We found that higher levels of adiponectin were associated with higher levels of GSH (GSH and total GSH), lower levels of lipid peroxidation products (CD), and lower levels of the growth factor EGF. These associations remained significant in age- and sex-adjusted models, as well as multivariable-adjusted models. We found no significant effect modification by sex for any association, but a significant difference of OxLDL levels between individuals with and without previous CVD, and the interaction between adiponectin and BMI was significant for OxLDL and ICAM-1.

Comparison with previous studies

A few previous smaller studies have investigated the association between adiponectin and the ratio of reduced and oxidized GSH. An inverse correlation between adiponectin and the ratio of GSSG/GSH was found in 12 obese psoriasis patients (10) and similarly adiponectin correlated positively with the GSG/GSSG ratio in 120...
TABLE 1 Clinical characteristics and markers of oxidative stress and inflammation, N = 929a

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.2 (0.2)</td>
<td>70.1 (0.2)</td>
<td>70.3 (0.1)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>49.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 (4.2)</td>
<td>27.0 (3.7)</td>
<td>27.0 (4.7)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Never: 49</td>
<td>Never: 43</td>
<td>Never: 55</td>
</tr>
<tr>
<td></td>
<td>Previous: 41</td>
<td>Previous: 48</td>
<td>Previous: 35</td>
</tr>
<tr>
<td></td>
<td>Current: 10</td>
<td>Current: 9</td>
<td>Current: 10</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.34 (3.15)</td>
<td>2.53 (3.73)</td>
<td>2.14 (2.41)</td>
</tr>
<tr>
<td>Anti-diabetic treatment (%)</td>
<td>6.1</td>
<td>7.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Anti-hypertensive treatment (%)</td>
<td>31</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Lipid-lowering treatment (%)</td>
<td>16</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.44 (1.01)</td>
<td>5.16 (0.96)</td>
<td>5.72 (0.98)</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.52 (0.42)</td>
<td>1.37 (0.37)</td>
<td>1.67 (0.41)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.28 (0.60)</td>
<td>1.29 (0.63)</td>
<td>1.26 (0.57)</td>
</tr>
<tr>
<td>eGFR from cystatin C</td>
<td>99 (25)</td>
<td>96 (24)</td>
<td>102 (26)</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>7.2 (4.3)</td>
<td>5.6 (3.2)</td>
<td>8.8 (4.7)</td>
</tr>
</tbody>
</table>

**Oxidative stress markers**

- **GSH (µg/ml)**: 834 (195) 840 (188) 828 (201)
- **GSSG (µg/ml)**: 76 (36) 78 (38) 74 (33)
- **Total GSH (µg/ml)**: 909 (203) 917 (196) 902 (210)
- **CD (µmol/l)**: 41 (11) 40 (11) 42 (11)
- **TAOC (%)**: 38 (4) 37 (4) 38 (4)
- **BCD LDL (µmol/l)**: 22 (7) 21 (7) 23 (7)
- **Homocysteine (µmol/l)**: 11 (4) 11 (4) 10 (4)
- **OxLDL (µl)**: 133 (48) 131 (47) 136 (48)
- **OxLDL antibodies (mU/l)**: 552 (589) 606 (637) 499 (534)

**Inflammatory markers**

- Circulation interleukins
  - **IL-6 (pg/ml)**: 27.8 (77.9) 28.7 (78.7) 26.9 (77.2)
  - **IL-8 (pg/ml)**: 8.8 (16.2) 8.5 (13.7) 9.1 (18.4)
- Other cytokines
  - **TNF (pg/ml)**: 5.7 (12.8) 5.7 (12.5) 5.8 (13.2)
  - **MCP-1 (pg/ml)**: 396 (134) 397 (134) 396 (134)
  - **EGF (pg/ml)**: 36 (33) 33 (31) 38 (34)
  - **VEGF (pg/ml)**: 233 (176) 210 (159) 255 (190)
- Cell adhesion molecules
  - **VCAM-1 (ng/ml)**: 536 (131) 552 (137) 519 (123)
  - **ICAM-1 (ng/ml)**: 233 (60) 230 (59) 236 (61)
  - **E-selectin (ng/ml)**: 15 (6) 16 (6) 15 (6)
  - **P-selectin (ng/ml)**: 102 (27) 103 (26) 101 (29)
  - **L-selectin (ng/ml)**: 720 (138) 693 (129) 747 (141)
- Systemic inflammatory markers
  - **CRP (mg/l)**: 1.69 (1.62) 1.62 (1.62) 1.76 (1.62)
  - **Leukocyte count (×10⁹ cells/l)**: 5.61 (1.34) 5.69 (1.31) 5.53 (1.37)

*aResults are expressed as means (standard deviations) or proportions. Abbreviations: BCD LDL, baseline conjugated dienes of low-density lipoprotein lipids; CD, conjugated dienes; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GSH, reduced glutathione; GSSG, oxidized glutathione; HDL, high-density lipoprotein; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; MCP-1, monocyte chemotactic protein-1; OxLDL, oxidized low density lipoprotein; TAOC, total antioxidant capacity; TGSH, total glutathione; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1.

|subjects with or without diabetes and with or without nonalcoholic fatty liver disease (11). Further, adiponectin was shown to restore the GSH/GSSG ratio after it was reduced when treating HepG2 cells with palmitate (11). We did not find a significant association with the GSH/GSSG ratio, but a strong association with the absolute levels of GSH and TGSH.||
TABLE 2 Adiponectin in relation to oxidative and inflammatory markers

<table>
<thead>
<tr>
<th>Associations with serum adiponectin</th>
<th>Age-adjusted</th>
<th>Multivariable-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Oxidative markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSH (µg/ml); n = 920</td>
<td>22.61 (10.05; 35.16)</td>
<td>0.00043</td>
</tr>
<tr>
<td>log GSSG (µg/ml); n = 922</td>
<td>0.02 (−0.01; 0.04)</td>
<td>0.22</td>
</tr>
<tr>
<td>log Total GSH (µg/ml); n = 921</td>
<td>0.02 (0.01; 0.03)</td>
<td>0.004</td>
</tr>
<tr>
<td>CD (µmol/l); n = 928</td>
<td>−1.62 (−2.33; −0.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TAOC (%); n = 920</td>
<td>0.24 (−0.00; 0.49)</td>
<td>0.053</td>
</tr>
<tr>
<td>BCD LDL (µmol/l); n = 925</td>
<td>−0.26 (−0.73; 0.20)</td>
<td>0.26</td>
</tr>
<tr>
<td>log Homocysteine (µmol/l); n = 928</td>
<td>0.02 (−0.00; 0.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>OxLDL (U/l); n = 928</td>
<td>−1.34 (−4.45; 1.77)</td>
<td>0.40</td>
</tr>
<tr>
<td>log OxLDL antibodies (mUI); n = 705</td>
<td>−0.05 (−0.13; 0.02)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Inflammatory markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log IL-6 (pg/ml); n = 912</td>
<td>−0.00 (−0.10; 0.10)</td>
<td>0.94</td>
</tr>
<tr>
<td>log IL-8 (pg/ml); n = 926</td>
<td>0.00 (−0.04; 0.05)</td>
<td>0.90</td>
</tr>
<tr>
<td>log VEGF (pg/ml); n = 926</td>
<td>−0.01 (−0.06; 0.04)</td>
<td>0.67</td>
</tr>
<tr>
<td>TNFα 1/2 (pg/ml); n = 926</td>
<td>−0.00 (−0.01; 0.01)</td>
<td>0.77</td>
</tr>
<tr>
<td>MCP-1 (pg/ml); n = 920</td>
<td>−9.87 (−18.53; −1.22)</td>
<td>0.025</td>
</tr>
<tr>
<td>log EGF (pg/ml); n = 928</td>
<td>−0.07 (−0.14; −0.01)</td>
<td>0.033</td>
</tr>
<tr>
<td>log VCAM-1 (ng/ml); n = 929</td>
<td>−0.01 (−0.02; 0.01)</td>
<td>0.25</td>
</tr>
<tr>
<td>log E-selectin (ng/ml); n = 929</td>
<td>−0.04 (−0.06; −0.01)</td>
<td>0.0039</td>
</tr>
<tr>
<td>P-selectin (ng/ml); n = 929</td>
<td>−1.53 (−3.30; 0.23)</td>
<td>0.089</td>
</tr>
<tr>
<td>log L-selectin (ng/ml); n = 929</td>
<td>2.74 (−6.14; 11.61)</td>
<td>0.55</td>
</tr>
<tr>
<td>log ICAM-1 (mg/ml); n = 927</td>
<td>−0.01 (−0.03; 0.01)</td>
<td>0.24</td>
</tr>
<tr>
<td>log CRP (mg/l); n = 929</td>
<td>−0.11 (−0.17; −0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocyte count (×10⁹ cells/l); n = 929</td>
<td>−0.06 (−0.15; 0.03)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Values are β coefficients (95% confidence intervals) from age- and sex-adjusted or multivariable-adjusted models with adiponectin and covariates as independent variables, and markers of oxidative stress and inflammation as dependent variables. β coefficients represent change in the oxidative or inflammatory marker per 1-SD increase in adiponectin. Abbreviations: CI, confidence interval; see Table 1.

Consistent with our results, several studies have reported that lower adiponectin associates with increased levels of lipid peroxidation byproducts (5,12-14); however, this is not supported by all previous studies (15). A negative correlation between adiponectin and 8-epi-PGF2α was found in 105 Japanese men and women without diabetes, CVD, or renal disease (13). 8-epi-PGF2α was inversely correlated with adiponectin in 259 Japanese men and women with normal glucose tolerance, impaired glucose tolerance or diabetes; however, not significantly when adjusting for the full set of confounders (14). No association with urinary 8-epi-PGF2α was found in 76 non-diabetic, hypercholesterolemic patients (15). Further, an inverse association between adiponectin and thiobarbituric acid-reacting substance (TBARS) as well as urinary 8-epi-PGF2α was found in 140 Japanese individuals (5) and an inverse association with TBARS in 1,178 Japanese men (12). No association between a 1-year change in adiponectin and a 1-year change in TBARS was found significant (12).

We found an inverse association between adiponectin and EGF. A previous study has found an inverse association between mRNA expression of adiponectin and heparin-binding epidermal growth factor (HB-EGF), which is structurally similar to EGF. Further, the EGF receptor (EGFR) activation and transverse aortic constriction-induced cardiac hypertrophy was higher in adiponectin knockout mice compared with wild-type, and treatment with adiponectin reduced the EGFR activity (23).

Our results indicated an inverse association between adiponectin and OxLDL in individuals without prior CVD, whereas somewhat unexpectedly a positive association was observed in individuals with prior CVD. A similar pattern was seen for normal-weight versus overweight individuals. Previous large studies have indicated an inverse association between adiponectin and OxLDL, including one bi-racial sample of 2,985 individuals (24) and 1,309 postmenopausal women without coronary artery disease and diabetes (25). However, a significant positive association was found in 106 pregnant women, but not in matched nonpregnant women (26).

Some prior studies have indicated an inverse association between adiponectin and ICAM-1; however, this association did not remain significant after adjustment for a full set of confounders in these studies (27,28). In one of these previous studies, an interaction term for obesity was close to significant for the association between adiponectin and ICAM-1 (27). Further, previous studies have reported that adiponectin
is inversely associated with CRP (27-29), E-selectin (27,29), and MCP-1 (30); markers that did not remain significantly associated with adiponectin in the multivariable-adjusted model in this study.

Potential mechanisms

Adiponectin can both affect and be affected by the oxidative environment. Previous studies have suggested that the oxidative environment could influence adiponectin secretion and assembly. One study in rats suggested that adiponectin secretion might be decreased in response to an oxidative environment (31) and an in vitro study indicated that adiponectin oligomerization is dependent on the redox environment (32). Strong correlations were found between the mRNA expression levels of the adiponectin receptors (ADIPOR1 and ADIPOR2) and GSH peroxidase-1 in 60 morbidly obese patients with nonalcoholic fatty liver disease (33), suggesting shared/linkedin factors regulating gene expression. Further, adiponectin has been shown to protect against elevated oxidative stress levels. A study showed that addition of adiponectin maintained normal oxidative stress levels and GSH levels in cells exposed to OxLDL (34). An in vitro experiment revealed that hypoxia-induced lipid peroxidation in cells was completely attenuated after treatment with adiponectin and that treatment with adiponectin partly attenuated hypoxia-induced loss of intracellular GSH. Further, in an in vivo experiment, adiponectin-overexpressing transgenic mice had significantly lower levels of lipid peroxidation products (hypoxia-induced) compared with wild-type mice. The levels of GSH were also higher in the lungs of the transgenic mice compared with wild-type (35).

Some studies have found that adiponectin is associated with worse cardiovascular outcomes and have suggested that this might be part of a compensatory mechanism in response to poor CVD health (36). The observed positive association between adiponectin and OxLDL, among those with prior CVD, could potentially be explained by a similar phenomenon.

Strengths and limitations

The large community-based sample of individuals from the general population with careful characterization of the participants and the large set of oxidative stress and inflammatory markers representing several relevant pathways are the main strengths of the study. Some limitations of oxidative stress is associated with visceral fat accumulation and the metabolic syndrome. Further studies are needed to investigate whether anti-oxidative effects may be a mechanism linking adiponectin with type 2 diabetes and/or cardiovascular disease.

Conclusions

In our sample of elderly individuals from the general population, adiponectin levels were positively associated with GSH (GSH and TGS) and negatively associated with CD. It is accepted that GSH is a primary anti-oxidant and CD are products of lipid peroxidation. Together these associations suggest that adiponectin is associated with a more beneficial oxidative stress profile, potentially through shared pathways. Further studies are needed to investigate whether anti-oxidative effects may be a mechanism linking adiponectin with type 2 diabetes and/or cardiovascular disease.

References


