Adiponectin may mediate the association between omentin, circulating lipids and insulin sensitivity: results from the KORA F4 study

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Abstract

Objective: Reduced circulating omentin levels have been reported in obesity and type 2 diabetes, but data were mostly derived from univariate analyses in small study samples. This study aimed to investigate the relationship between omentin, abnormal glucose tolerance and related metabolic factors in a large population-based cross-sectional study.

Design and methods: Serum omentin was measured by ELISA in 1092 participants of the German KORA F4 survey (2006–2008). Associations between omentin serum levels, glucose tolerance (assessed with an oral glucose tolerance test) and diabetes-related factors were estimated using logistic and linear regression models respectively.

Results: Serum levels of omentin were not related to categories of glucose tolerance. However, serum omentin was positively associated with whole-body insulin sensitivity index (ISI (composite)) and HDL cholesterol and showed inverse associations with 2-h post-load glucose, fasting insulin, homeostasis model assessment-estimated insulin resistance, BMI and triglycerides (all P ≤ 0.03 after adjustment for age, sex and lifestyle factors). Further adjustment for BMI and/or serum lipids attenuated the associations with parameters of glucose metabolism, whereas adjustment for serum adiponectin virtually abolished all aforementioned associations. In contrast, adjustment for omentin had no effect on the positive association between adiponectin levels and ISI (composite).

Conclusions: The data from this large population-based cohort show that circulating omentin levels are associated with insulin sensitivity. Our observations further suggest that omentin acts via upregulation of adiponectin, which in turn affects lipid metabolism and thereby also indirectly enhances insulin sensitivity, but mechanistic studies are required to corroborate this hypothesis.
Introduction

Adipose tissue is not only a source of pro-inflammatory immune mediators that contribute to the pathophysiology of type 2 diabetes, but also secretes proteins with a potential anti-inflammatory action that may protect against the development of the disease such as adiponectin, interleukin-1 receptor antagonist (IL1-RA) and omentin (also known as intejectin-1) (1). Of these factors, circulating levels of IL1-RA, the endogenous inhibitor of the potent pro-inflammatory cytokine IL1β, are upregulated before the onset of type 2 diabetes (2, 3, 4, 5). This can be considered as futile counter-regulation of metabolic and immunological stress in the prediabetic period (2, 3). In contrast, high circulating levels of adiponectin are consistently associated with decreased risk of type 2 diabetes (6), although it has to be noted that the causal association between adiponectin and insulin sensitivity in humans as well as the regulation of adiponectin in old age and in individuals with inflammatory conditions is still poorly understood and may partly also be attributable to noninflammatory mechanisms (1).

Adiponectin levels are correlated with circulating omentin levels (7, 8), a relatively novel adipokine predominantly released by visceral adipose tissue (9), although it is also expressed in other tissues of the body (10). Several cross-sectional studies further reported that omentin levels are inversely associated with insulin resistance (assessed as homeostasis model assessment-estimated insulin resistance (HOMA-IR)) (7, 8, 11, 12, 13, 14) and decreased in individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 diabetes (8, 11, 12, 14, 15, 16). Such an inverse association may be explained by the anti-inflammatory properties of omentin that have been observed in in vitro studies on endothelial cells and smooth muscle cells (17, 18, 19). However, data on omentin and type 2 diabetes as well as diabetes-related traits were collected in small cross-sectional studies. Therefore, it has not been investigated so far to what extent the observed link between omentin and type 2 diabetes is confounded or mediated by factors such as obesity, serum lipids, or adiponectin. To address this, we measured serum omentin levels in a large population-based cohort and assessed i) whether serum levels of omentin were inversely associated with IFG, IGT, or type 2 diabetes and with continuous metabolic factors related with type 2 diabetes (glucose, insulin, HOMA-IR, whole-body insulin sensitivity index (ISI (composite)), BMI, blood pressure and lipid levels), ii) whether associations between omentin, abnormal glucose tolerance and related risk factors are explained by BMI or independent of obesity and iii) to what extent these associations could be explained by circulating adiponectin levels.

Subjects and methods

Study population

Data are based on the Cooperative Health Research in the Region of Augsburg (KORA) F4 study (2006–2008), the follow-up examination of the population-based KORA S4 study (1999–2001) (20). The study design and the enrolment of participants in the KORA S4 survey have been described in detail before (21). Briefly, 2656 men and women between 55 and 74 years of age were randomly selected from the region of Augsburg in the South of Germany to participate in the KORA S4 study. From the 2564 eligible subjects, 1653 (64%) completed the survey and a subsequent 1353 subjects without known diabetes successfully completed an oral glucose tolerance test (OGTT). Glucose tolerance categories were defined according to the 1999 World Health Organization diagnostic criteria (22).

The current study is based on data from the 7-year follow-up examination (F4 study) of the KORA S4 cohort, which took place in 2006–2008 and also included a standardised OGTT. Of the above-mentioned 1353 KORA S4 participants, a total of 1209 participated in the F4 follow-up examinations. We excluded individuals with unclear glucose tolerance status (n=36), type 1 diabetes (n=8), insufficient fasting time before the OGTT (n=1), or at least one missing variable for the statistical analyses (n=72), resulting in a final sample size of 1092 subjects. All participants gave written informed consent to the study, which was approved by the Ethics Committee of the Bavarian Medical Association.

Assessment of anthropometric and metabolic variables

Height, weight, waist circumference, and systolic and diastolic blood pressure were measured according to standardised protocols (21). Trained medical interviewers collected information on medical history, physical activity, smoking behaviour and alcohol consumption (20).

Cases of self-reported diabetes, as well as the date of diagnosis, were validated through contacting the participants’ general practitioners. All other participants
underwent an OGTT. After an overnight fasting period (≥ 8 h), a fasting blood sample was taken and participants ingested 75 g of anhydrous glucose orally (Dextro OGT, Boehringer Mannheim). A second blood sample was taken 2 h after the glucose challenge. The blood samples were collected without stasis. After withdrawal, the blood samples were centrifuged and kept cool at 4°C until analysis in the Central Laboratory of the Augsburg Central Hospital. Serum glucose levels were assessed by the hexokinase method (GLU Flex, Dade Behring, Marburg, Germany). Serum insulin was determined by ELISA (Invitrogen). HOMA-IR was calculated as (fasting glucose (mmol/l) × fasting insulin (μU/ml))/22.5. We also calculated the whole-body ISI (composite) as described by DeFronzo and Matsuda (23) using the formula ISI (composite) = 10 000/√((fasting glucose (mmol/l) × 2-h glucose (mmol/l) × fasting insulin (pmol/l) × 2-h insulin (pmol/l) × 36). HbA1c was determined by a reverse-phase cation-exchange HPLC method (Analyzer HA 8160, Menarini, Florence, Italy).

Serum LDL and HDL cholesterol were measured by an enzymatic method (CHOD-PAP, LDL Flex and AHDL Flex, Dade Behring). Serum triglycerides were quantified by the enzymatic GPO-PAP method (TGL Flex, Dade Behring).

Kidney function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24).

Measurement of serum concentrations of omentin and adiponectin

Serum concentrations of omentin were determined using the Human Omentin-1 ELISA from BioVendor (Brno, Czech Republic) according to the manufacturer’s instructions. Intra- and inter-assay coefficients of variation (CV) were 2.0 and 4.0% respectively. Serum concentrations of total adiponectin were measured using the Human Total Adiponectin/Acrp30 Quantikine ELISA from R&D Systems (Wiesbaden, Germany) as described (25). Intra- and inter-assay CV were 3.8 and 8.0% respectively.

Statistical analyses

Participants’ characteristics were stratified by quartiles of serum omentin and presented as mean±s.d. for normally distributed variables and as median (25th/75th percentiles) for variables without a normal distribution. A general linear model (F test) was used to test differences in the means of continuous variables. Logistic regression models or χ² tests were used to test for differences in percentages. Analyses were adjusted for age and sex except for categories of glucose tolerance and for smoking. Correlations between omentin and adiponectin (log-transformed) were additionally assessed by partial Pearson’s correlation coefficients and corresponding P values.

Multinomial logistic regression analyses were performed to estimate odds ratios (ORs) and 95% CI for the association between serum concentrations of omentin (standardised to an increase of 1 s.d. = 171.9 ng/ml) and categories of glucose tolerance with individuals with normal glucose tolerance (NGT) as reference group. Model 1 included age (continuous) and sex. Model 2 additionally included smoking (never/ex/current), alcohol consumption (low/high) and physical activity (low/high). Model 3 included all factors from model 2 and BMI (continuous). Model 4 included all factors from model 3 and HDL cholesterol (continuous), LDL cholesterol (continuous), triglycerides (continuous), hypertension (no/yes), history of myocardial infarction (MI) (no/yes) and eGFR (continuous).

The same stepwise modelling strategy was used to calculate regression coefficients (β, standardised to a 1 s.d. increase in omentin levels) and corresponding P values for the association between serum omentin levels and continuous metabolic variables from linear regression analyses. In this analysis, we added a fifth model that contained all factors from model 4 and serum levels of adiponectin (continuous).

P values of <0.05 were considered to be statistically significant. All analyses were performed with SAS Software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Study population

Table 1 gives the description on the study population stratified by quartiles of serum omentin levels. After adjustment for age and sex, individuals with higher omentin levels were older, more likely to be female and had a higher ISI (composite) as well as higher levels of HDL cholesterol and adiponectin. Moreover, individuals with higher omentin levels had lower BMI, 2-h glucose, fasting insulin, HOMA-IR and fasting triglyceride levels. The relationship between omentin and adiponectin was also assessed using partial Pearson’s correlation coefficients adjusted for age and sex (r = 0.277, P < 0.0001) as well as for age, sex and BMI (r = 0.259, P < 0.0001).
Table 1  Description of the KORA F4 study population stratified by quartiles of omentin serum concentrations a,b.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omentin (range) (ng/ml)</td>
<td>67.2–402.1</td>
<td>402.9–488.8</td>
<td>489.0–580.7</td>
<td>580.8–2501.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n</td>
<td>273</td>
<td>273</td>
<td>273</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.3 ± 5.3</td>
<td>69.7 ± 5.2</td>
<td>70.9 ± 5.3</td>
<td>71.3 ± 5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>60</td>
<td>54</td>
<td>49</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.8 ± 4.7</td>
<td>28.6 ± 4.2</td>
<td>28.6 ± 4.1</td>
<td>28.1 ± 4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.79 ± 1.00</td>
<td>5.83 ± 1.20</td>
<td>5.83 ± 1.33</td>
<td>5.79 ± 1.47</td>
<td>0.93</td>
</tr>
<tr>
<td>2-h glucose (mmol/l)</td>
<td>7.35 ± 2.16</td>
<td>7.10 ± 2.25</td>
<td>6.96 ± 2.10</td>
<td>6.99 ± 2.23</td>
<td>0.034</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>34.2 (22.2; 69.6)</td>
<td>32.4 (21.6; 58.2)</td>
<td>29.4 (19.8; 52.8)</td>
<td>27.0 (18.0; 46.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>2-h insulin (pmol/l)</td>
<td>328 (215; 608)</td>
<td>350 (189; 538)</td>
<td>316 (166; 503)</td>
<td>323 (161; 497)</td>
<td>0.006</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.52 (0.91; 3.02)</td>
<td>1.37 (0.88; 2.54)</td>
<td>1.19 (0.82; 2.23)</td>
<td>1.13 (0.70; 2.11)</td>
<td>0.003</td>
</tr>
<tr>
<td>ISI (composite)</td>
<td>15.4 (7.8; 23.9)</td>
<td>15.0 (9.7; 26.0)</td>
<td>17.5 (10.4; 30.6)</td>
<td>18.8 (11.0; 32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7 ± 0.5</td>
<td>5.8 ± 0.7</td>
<td>5.8 ± 0.7</td>
<td>5.8 ± 0.7</td>
<td>0.37</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>39 ± 5</td>
<td>40 ± 8</td>
<td>40 ± 8</td>
<td>40 ± 8</td>
<td>0.37</td>
</tr>
<tr>
<td>Glucose tolerance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>NGT (%)</td>
<td>51</td>
<td>53</td>
<td>55</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>IFG (%)</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>IGT (%)</td>
<td>17</td>
<td>18</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>IFG/IGT (%)</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed type 2 diabetes (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Known type 2 diabetes (%)</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>62</td>
<td>60</td>
<td>66</td>
<td>62</td>
<td>0.65</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128.6 ± 16.4</td>
<td>127.0 ± 20.4</td>
<td>131.5 ± 20.5</td>
<td>127.5 ± 21.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.5 ± 9.3</td>
<td>73.7 ± 10.3</td>
<td>74.2 ± 10.3</td>
<td>73.1 ± 10.3</td>
<td>0.42</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.59 ± 0.86</td>
<td>3.66 ± 0.93</td>
<td>3.65 ± 0.90</td>
<td>3.55 ± 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.33 ± 0.31</td>
<td>1.44 ± 0.36</td>
<td>1.44 ± 0.37</td>
<td>1.54 ± 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting triglycerides (mmol/l)</td>
<td>1.44 (0.97; 1.91)</td>
<td>1.28 (0.96; 1.75)</td>
<td>1.31 (0.95; 1.84)</td>
<td>1.20 (0.89; 1.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs (%)</td>
<td>26</td>
<td>26</td>
<td>23</td>
<td>23</td>
<td>0.61</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>79.9 (69.2; 89.8)</td>
<td>80.8 (68.4; 89.0)</td>
<td>77.0 (67.1; 87.7)</td>
<td>75.8 (63.8; 87.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking (active/ex/never) (%)</td>
<td>10/42/48</td>
<td>8/42/50</td>
<td>6/39/55</td>
<td>6/44/50</td>
<td>0.52</td>
</tr>
<tr>
<td>High alcohol consumption (%)d</td>
<td>14</td>
<td>16</td>
<td>20</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>44</td>
<td>58</td>
<td>49</td>
<td>48</td>
<td>0.01</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>7.8 (5.4; 11.1)</td>
<td>10.0 (6.4; 14.7)</td>
<td>10.6 (7.2; 15.1)</td>
<td>12.7 (9.1; 19.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; NGT, normal glucose tolerance.

*a*Data are given as mean ± s.d., median and 25th/75th percentiles or percentages. The P values indicates differences between groups.

*b*All analyses were adjusted for age and sex except for glucose regulation and smoking.

*c*Defined as ≥40 g/day for men and ≥20 g/day for women.

*d*Defined as ≥1 h sports/week in summer and in winter.

Association between serum omentin and glucose tolerance status

Supplementary Table 1, see section on supplementary data given at the end of this article, provides an overview of the study population stratified by categories of glucose tolerance. Several regression models were calculated to examine the relationship between omentin levels and glucose tolerance status. With NGT as reference category, no significant associations between omentin and IFG, IGT, combined IFG/IGT, newly diagnosed type 2 diabetes or known (previously diagnosed) type 2 diabetes were found in four models of increasing complexity (Table 2).

We also combined all groups with impaired glucose metabolism (e.g. IFG, IGT, IFG/IGT, newly diagnosed and known type 2 diabetes; n=513) and compared this group with the NGT reference category (n=579). ORs and 95% CIs for models 1–4 were 0.91 (0.81; 1.04), 0.92 (0.81; 1.04), 0.97 (0.84; 1.11) and 0.99 (0.86; 1.13), respectively, and therefore did not point towards a significant association between serum omentin and abnormal glucose tolerance.

Association between serum omentin and quantitative risk factors of type 2 diabetes

We further examined whether omentin was associated with quantitative traits and risk factors for type 2 diabetes (Table 3). In this analysis, individuals with known type 2 diabetes were excluded, which resulted in a sample size
Discussion

This large study of an elderly, population-based sample found that serum omentin does not associate with abnormal glucose tolerance, but shows positive associations with insulin sensitivity (ISI (composite)) and correlates inversely with 2-h glucose, fasting insulin, 2-h insulin and HOMA-IR. Omentin also associates positively with HDL cholesterol and inversely with triglycerides. These associations were independent of kidney function assessed by eGFR. Importantly, circulating adiponectin levels almost entirely explain the associations between omentin and insulin sensitivity as well as lipids. Collectively, these observations suggest that the associations between omentin on the one hand and insulin sensitivity as well as lipids on the other hand are mainly explained by adiponectin. Thus, our population-based study shows that most of the previously reported relations between omentin, obesity and type 2 diabetes may be ascribed to the regulatory effects on adiponectin (and to a lesser extent on lipid) levels as putative intermediaries.


**Table 3** Association between serum omentin concentrations and continuous metabolic traits in the KORA F4 study. β coefficients with 95% CIs and P values standardised to 1s.0. Increases in omentin levels from linear regression analyses. Significant associations (P < 0.05) are highlighted by bold print.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th>P</th>
<th>Model 2</th>
<th></th>
<th>P</th>
<th>Model 3</th>
<th></th>
<th>P</th>
<th>Model 4</th>
<th></th>
<th>P</th>
<th>Model 5</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>-0.02 (-0.06; 0.02)</td>
<td>0.28</td>
<td></td>
<td>-0.02 (-0.06; 0.02)</td>
<td>0.27</td>
<td></td>
<td>-0.01 (-0.05; 0.03)</td>
<td>0.63</td>
<td></td>
<td>0.00 (-0.04; 0.04)</td>
<td>0.92</td>
<td></td>
<td>0.02 (-0.02; 0.06)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>2-h glucose (mmol/L)</td>
<td>-0.19 (-0.23; -0.05)</td>
<td>0.01</td>
<td></td>
<td>-0.18 (-0.22; -0.04)</td>
<td>0.01</td>
<td></td>
<td>-0.14 (-0.18; -0.01)</td>
<td>0.04</td>
<td></td>
<td>-0.00 (-0.02; 0.03)</td>
<td>0.69</td>
<td></td>
<td>-0.01 (-0.04; 0.04)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.00 (-0.03; 0.02)</td>
<td>0.77</td>
<td></td>
<td>-0.00 (-0.02; 0.02)</td>
<td>0.99</td>
<td></td>
<td>-0.05 (-0.09; 0.03)</td>
<td>0.27</td>
<td></td>
<td>-0.03 (-0.06; 0.01)</td>
<td>0.15</td>
<td></td>
<td>0.00 (-0.06; 0.05)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Ln (fasting insulin) (pmol/L)</td>
<td>-0.07 (-0.14; -0.01)</td>
<td>0.02</td>
<td></td>
<td>-0.07 (-0.13; -0.01)</td>
<td>0.02</td>
<td></td>
<td>-0.05 (-0.10; 0.01)</td>
<td>0.10</td>
<td></td>
<td>-0.05 (-0.10; 0.01)</td>
<td>0.10</td>
<td></td>
<td>0.01 (-0.05; 0.06)</td>
<td>0.82</td>
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<tr>
<td>Ln (2-h insulin) (pmol/L)</td>
<td>-0.08 (-0.14; -0.03)</td>
<td>0.005</td>
<td></td>
<td>-0.08 (-0.14; -0.02)</td>
<td>0.01</td>
<td></td>
<td>-0.06 (-0.11; -0.003)</td>
<td>0.04</td>
<td></td>
<td>-0.04 (-0.09; 0.01)</td>
<td>0.15</td>
<td></td>
<td>0.00 (-0.06; 0.05)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Ln (HOMA-IR)</td>
<td>0.10 (0.04; 0.16)</td>
<td>0.002</td>
<td></td>
<td>0.09 (0.03; 0.15)</td>
<td>0.03</td>
<td></td>
<td>0.07 (0.01; 0.12)</td>
<td>0.02</td>
<td></td>
<td>0.03 (-0.09; 0.10)</td>
<td>0.27</td>
<td></td>
<td>0.00 (-0.06; 0.06)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Ln IS (composite)</td>
<td>0.31 (-0.59; 0.03)</td>
<td>0.03</td>
<td></td>
<td>0.30 (-0.57; 0.02)</td>
<td>0.03</td>
<td></td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.05 (0.03; 0.08)</td>
<td>-0.001</td>
<td></td>
<td>0.05 (0.03; 0.07)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.04 (0.02; 0.06)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.04 (0.02; 0.06)</td>
<td>&lt;0.001</td>
<td></td>
<td>0.01 (-0.01; 0.03)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.05 (-1.31; 1.21)</td>
<td>0.94</td>
<td></td>
<td>0.10 (-1.36; 1.16)</td>
<td>0.88</td>
<td></td>
<td>0.06 (-1.33; 1.20)</td>
<td>0.92</td>
<td></td>
<td>0.05 (-1.29; 1.25)</td>
<td>0.98</td>
<td></td>
<td>0.41 (-0.89; 1.72)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.59 (-1.22; 0.04)</td>
<td>0.007</td>
<td></td>
<td>0.60 (-1.24; 0.03)</td>
<td>0.06</td>
<td></td>
<td>0.58 (-1.17; 0.10)</td>
<td>0.10</td>
<td></td>
<td>0.54 (-1.17; 0.10)</td>
<td>0.10</td>
<td></td>
<td>0.36 (-1.01; 0.29)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>-0.03 (-0.09; 0.02)</td>
<td>0.27</td>
<td></td>
<td>-0.03 (-0.09; 0.03)</td>
<td>0.24</td>
<td></td>
<td>0.03 (-0.09; 0.03)</td>
<td>0.35</td>
<td></td>
<td>0.03 (-0.08; 0.03)</td>
<td>0.37</td>
<td></td>
<td>0.01 (-0.07; 0.05)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.05 (0.03; 0.08)</td>
<td>0.003</td>
<td></td>
<td>0.05 (-0.08; -0.01)</td>
<td>0.004</td>
<td></td>
<td>0.04 (-0.07; -0.01)</td>
<td>0.02</td>
<td></td>
<td>0.04 (-0.07; -0.01)</td>
<td>0.01</td>
<td></td>
<td>0.01 (-0.04; 0.02)</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>


*Hypertension was replaced by use of antihypertensive drugs in models 4 and 5.

**HDL cholesterol, LDL cholesterol and triglycerides were replaced by use of lipid-lowering drugs in models 4 and 5.**
analyses. However, it is striking that most studies failed
to detect an association between omentin and fasting
glucose. Moreover, most studies have analysed associ-
ations with HOMA-IR, but only three (7, 12, 14) adjusted
for covariables. Among these studies, one did not
observe a significant association in an Amish population
(7), whereas the two others found inverse associations
in Chinese samples (12, 14), but their multivariate
models did not consider lipid levels or adiponectin as
potential mediators. In this context, three small inter-
vension studies are of interest, which examined the
association between changes in omentin and HOMA-IR
in overweight/obese individuals resulting from weight
loss following a hypocaloric diet for 4 months (29),
aerobic exercise for 3 months (13) or bariatric surgery
(30). Both the hypocaloric diet study and the exercise
study reported significant increases in omentin, which
associated with an improvement of HOMA-IR, but these
interventions also decreased LDL cholesterol and trigly-
eride levels (13, 29). Bariatric surgery induced a
substantial weight loss and a decrease in HOMA-IR
within 3 months (means at baseline and after 3 months
3.6 and 1.4), but no notable change in plasma omentin
levels (30). Interestingly, the levels of total, LDL and
HDL cholesterol as well as triglyceride levels remained
also unchanged during these 3 months. However,
omentin levels were increased at the 3-year follow-up
concomitantly with a significant increase in HDL
cholesterol (+36%) and a 33%, albeit non-significant,
decrease in triglycerides. Therefore, there is increasing
evidence that previous reports of omentin as a novel
biomarker for insulin resistance may have been based on
indirect effects owing to alterations in lipid meta-
bolism in their underlying analyses, indicating that the
relationship between omentin and lipid metabolism
needs further attention as discussed in more detail below.
Unfortunately, adiponectin levels were not reported in
these three studies.

Omentin and BMI

One finding that triggered the interest in omentin several
years ago was the observation that its circulating con-
centrations correlated with adiponectin levels (7) and
were – similarly to adiponectin, but in contrast to
other adipokines – downregulated in obesity (7, 8, 10,
12, 14, 15). We confirmed the inverse association between
serum omentin and BMI, but extended previous studies
by the observation that this association was largely due to
lipid levels and adiponectin. The aforementioned study
on bariatric surgery corroborates the notion that omentin
and BMI may not be causally related because a 17% 
reduction in BMI corresponding to a weight loss of 22.8 kg
was not associated with any change in omentin during
the first 3 months of follow-up (30).

Omentin, lipid levels and adiponectin

We found a positive association between omentin levels
and HDL cholesterol, an inverse association with trigly-
eride levels as well as no association with LDL cholesterol.
These associations were independent of age, sex, BMI,
lifestyle factors, hypertension, history of MI and the use
of lipid-lowering drugs. Our findings go beyond previous
reports that were based on smaller samples and on
univariate analyses. Most studies observed a positive
association between omentin and HDL cholesterol (7, 11, 15, 26, 28, 31), whereas the inverse association
with triglycerides was found only in some (26, 28), but not
all (7, 11, 15, 16) samples.

A central observation of our study is that the
associations between omentin and lipids as well as
insulin sensitivity, which are notably similar to those
between adiponectin and these two parameters, were
virtually abolished when adiponectin entered the multi-
variate model. This finding is in line with the
hypothesis that omentin upregulates adiponectin release
which in turn favourably affects lipid levels and thereby
improves insulin sensitivity. The fact that adjustment
for omentin did not attenuate the association between
adiponectin and insulin sensitivity argues against the
alternative hypothesis that adiponectin upregulates
omentin which then acts as mediator and influences
lipid and glucose metabolism. However, it should be
emphasised here that our study is cross-sectional and
does not allow drawing firm conclusions. Nevertheless,
it does help to generate hypotheses that can be tested in
further experiments.

Indeed, the precise mechanisms that link adiponec-
tin, omentin and lipid or glucose metabolism remain
obscure. Although in vitro studies show that omentin
exerts direct anti-inflammatory and insulin-sensitising
effects on multiple cell types (9, 15, 17, 18, 19), there is
only limited knowledge of the signalling cascade utilised
by this soluble lectin. Although it is known that
omentin binds to the iron-binding protein lactoferrin
(32), which has been linked with insulin resistance and
altered glucose tolerance (33), a more detailed under-
standing of the molecular mechanism of omentin action
will undoubtedly help to gain further insights into the
triangular relationship between adiponectin, omentin and lipid metabolism. Importantly, we are not aware of any study that analysed whether omentin upregulates adiponectin expression or release, which should be tested in order to corroborate our hypothesis.

Adiponectin has recently been described as downstream effector of fibroblast growth factor-21 (FGF21) (34). This finding raises the questions whether omentin and FGF21 may be correlated and whether they interact in the regulation of adiponectin. However, data on such an interaction are neither available in our study nor in the published literature.

Strengths and limitations

Our study has several strengths and limitations that need to be mentioned. Of note, our study represents the so far largest and only population-based sample in which the association between omentin, glucose metabolism and diabetes-related factors was analysed. The study sample was well-phenotyped, including an OGTT. We adjusted our observations for multiple covariates. In addition, data for adiponectin were available allowing us to interpret our findings regarding potential mediators of the effects of omentin.

Limitations of our study include the cross-sectional design, which allows us to generate testable hypotheses with respect to potential metabolic effects and putative intermediaries (adiponectin and lipids), but not to draw firm conclusions with respect to mechanistic effects. We used the HOMA-IR and ISI (composite) as surrogate measures of insulin resistance rather than the gold standard measure, the hyperinsulinaemic–euglycaemic clamp. Further limitations are the age range and the homogeneous ethnicity of our study population, so that our data are not generalisable to younger and to non-Caucasian populations. We also refrained from correction for multiple testing because the anthropometric and metabolic outcome variables are not independent so that correction using, for example, the method of Bonferroni would be overly conservative.

Conclusions

In our population-based study sample, we observed that insulin sensitivity assessed using ISI (composite) and HDL cholesterol levels was positively associated and 2-h glucose, fasting and 2-h insulin, HOMA-IR and triglycerides were inversely associated with omentin levels. These associations were partially explained by BMI and/or lipid levels, but adjustment for adiponectin had the most attenuating effect on these associations. In contrast, adjustment for omentin did not affect the association between adiponectin and insulin sensitivity. Collectively, our data are in line with the hypothesis that circulating levels of omentin regulate adiponectin levels, which in turn improve lipid metabolism and may affect glucose metabolism indirectly by adiponectin and lipid-mediated processes. The identification of a membrane-bound omentin receptor and subsequent signalling cascades as well as studies on the interaction between omentin and adiponectin will help to better understand the physiological role of omentin and its impact on metabolic regulation.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-14-0879.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

C Herder designed the study, obtained funding, drafted statistical analysis plans and wrote the manuscript. D M Ouwens and M Carstensen obtained funding, contributed to study design, contributed to discussion, reviewed and edited the manuscript. B Kowall conducted data analysis and reviewed the manuscript. C Huth, C Meisinger and W Rathmann contributed to study organisation, provided data and reviewed the manuscript. M Roden and B Thorand contributed to study organisation, provided data, contributed to discussion and reviewed and edited the manuscript.

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References


23 DeFronzo RA & Matsuda M. Reduced time points to calculate the composite index. Diabetes Care 2010 33 e93. (doi:10.2337/dc10-0464)


30 Stiejka A, Jankiewicz-Wika J, Kolomecki K, Cywiński J, Pietrzeniwicz K, Swietelskiowski J, Stepien H & Kelmowski J. Long-term improvement of vertical banded gastroplasty (VBG) on plasma concentration of leptin, soluble leptin receptor, ghrelin, omentin-1, obestatin, and retinol


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