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Omentin associates with serum metabolite profiles indicating lower diabetes risk: KORA F4 Study

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ABSTRACT

Introduction Circulating omentin levels have been positively associated with insulin sensitivity. Although a role for adiponectin in this relationship has been suggested, underlying mechanisms remain elusive. In order to reveal the relationship between omentin and systemic metabolism, this study aimed to investigate associations of serum concentrations of omentin and metabolites.

Research design and methods This study is based on 1124 participants aged 61–82 years from the population-based KORA (Cooperative Health Research in the Region of Augsburg) F4 Study, for whom both serum omentin levels and metabolite concentration profiles were available. Associations were assessed with five multivariable regression models, which were stepwise adjusted for multiple potential confounders, including age, sex, body mass index, waist-to-hip ratio, lifestyle markers (physical activity, smoking behavior and alcohol consumption), serum adiponectin levels, high-density lipoprotein cholesterol, use of lipid-lowering or anti-inflammatory medication, history of myocardial infarction and stroke, homeostasis model assessment 2 of insulin resistance, diabetes status, and use of oral glucose-lowering medication and insulin.

Results Omentin levels significantly associated with multiple metabolites including amino acids, acylcarnitines, and lipids (eg, sphingomyelins and phosphatidylcholines (PCs)). Positive associations for several PCs, such as diacyl (PC aa C32:1) and alkyl-alkyl (PC ae C32:2), were significant in models 1–4, whereas those with hydroxytetradecenoylcarnitine (C14:1-OH) were significant in all five models. Omentin concentrations were negatively associated with several metabolite ratios, such as the valine-to-PC ae C32:2 and the serine-to-PC ae C32:2 ratios in most models.

Conclusions Our results suggest that omentin may influence insulin sensitivity and diabetes risk by changing systemic lipid metabolism, but further mechanistic studies investigating effects of omentin on metabolism of insulin-sensitive tissues are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Circulating levels of the adipokine omentin have been positively associated with insulin sensitivity, but the underlying mechanisms remain largely unknown.

WHAT THIS STUDY ADDS

⇒ Serum omentin levels associate with multiple metabolites, including acylcarnitines and lipids, as well as with metabolite ratios.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports a role for omentin in regulating systemic metabolism and warrants further studies on the role of omentin in modulating (lipid) metabolism in insulin-sensitive tissues.

INTRODUCTION

Omentin (also known as intelectin-1) is an adipokine produced by the stromal vascular fraction of visceral adipose tissue and was shown to increase insulin sensitivity of adipocytes.[1] In accordance with this observation, high concentrations of omentin have been associated with insulin sensitivity at the systemic level in multiple cross-sectional studies.[2 3] Several longitudinal studies, in contrast, have shown associations of higher omentin levels with a higher risk of type 2 diabetes.[4 5]

Effects of omentin on inflammatory processes may contribute to its association with metabolic diseases. Higher circulating omentin levels are negatively associated with interleukin-6 and tumor necrosis factor alpha,[2] and omentin was shown to induce changes in inflammatory pathways in adipocytes[6] and endothelial cells.[7] Moreover, circulating omentin levels associated positively with high-density lipoprotein (HDL)-cholesterol, which may be partially mediated by changes in adiponectin levels.[3 4] Although omentin-induced changes in glucose uptake at the cellular level and associations with HDL-cholesterol at the systemic level suggest a role

for omentin in regulating systemic metabolism, detailed mechanisms remain elusive.

In the population-based KORA (Cooperative Health Research in the Region of Augsburg) F4 Study, it has already been described that circulating omentin levels are on the one hand positively associated with insulin sensitivity[3] and on the other hand also positively associated with increases in glycemia and incidence of type 2 diabetes in a 5-year follow-up period.[5] In the same study population, targeted metabolomics analysis has revealed metabolites associated with pre-diabetes as well as newly diagnosed type 2 diabetes[8] and metabolic syndrome.[9] The mechanisms linking omentin with insulin sensitivity remain largely unknown and therefore, we characterized the relationship of serum omentin levels with metabolite concentrations in the KORA F4 Study. The aims of this study were therefore (1) to investigate whether serum omentin levels are associated with circulating concentrations of metabolites and (2) to explore which clinical variables, including anthropometric and clinical characteristics, may mediate these associations.

METHODS

Study population

Data are based on the KORA F4 Study (2006–2008), a follow-up of the population-based KORA S4 Study (1999–2001) conducted in the region of Augsburg, Germany. The baseline KORA S4 Study involved a random sample of participants aged 25–74 years, totaling 4261 individuals. Subsequently, 3080 of these participants took part in the follow-up examination, KORA F4.[10] Study design and enrollment of participants have been described before.[10]

With respect to glucose tolerance status, the age group of 55–74 years was intensively phenotyped with an oral glucose tolerance test (OGTT) in KORA S4.[10] These participants were aged 61–82 years in F4, eligible for additional examinations regarding diabetes-related complications such as polyneuropathy and more intensively characterized (including omentin measurements) than the younger study participants. Therefore, serum omentin levels were measured only in 1139 participants aged 61–82 years of the KORA F4 Study with available biosamples. This study included all participants of the KORA F4 Study, for whom both serum omentin measurements and metabolite data (N=121 metabolites, for inclusion criteria, see Shi *et al*[9]) were available (N=1124; figure 1). For each model, individuals without complete data for confounding variables were excluded, leading to a sample size of N=1124 for models 1–2, N=1118 for model 3, N=1115 for model 4 and N=1069 for model 5.

Assessment of anthropometric and metabolic variables

Height and weight as well as waist and hip circumference were measured with standardized protocols.[10] Information on medical history, physical activity, smoking behavior and alcohol consumption was obtained by trained medical interviewers.[11] Any self-reported diabetes diagnosis was validated by contacting the participants' general practitioners or by medical chart review. All other participants underwent an OGTT.[3] Serum HDL-cholesterol was measured by an enzymatic method (AHDL Flex, Dade Behring, Marburg, Germany).

Homeostasis model assessment 2 of insulin resistance (HOMA2-IR) was calculated based on fasting insulin (mU/L) and fasting glucose (mmol/L) levels. The HOMA2 model was chosen due to its more accurate estimations of insulin resistance for fasting plasma glucose values above 10 mmol/L.[12]

Measurement of serum adiponectin and omentin concentrations

Serum concentrations of total adiponectin were measured by ELISA (R&D Systems, Wiesbaden, Germany). Intra-assay and interassay coefficients of variation (CVs) were 3.8% and 8.0%, respectively.[3] Serum concentrations of omentin were measured by ELISA (BioVendor, Brno, Czech Republic). Intra-assay and interassay CVs were 2.0% and 4.0%, respectively.[3]

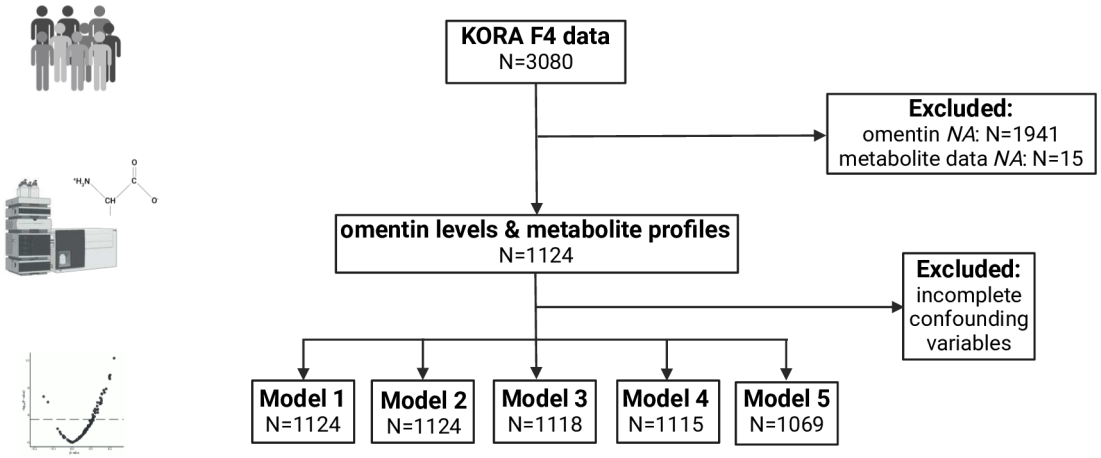

Figure 1 Description of the study design and population. Created with BioRender.com. KORA, Cooperative Health Research in the Region of Augsburg; NA, not available.

Metabolite quantification and normalization

The serum samples from the KORA F4 participants were measured with the AbsoluteIDQ p150 Kit (Biocrates Life Sciences, Innsbruck, Austria) and flow injection-electrospray ionization-tandem mass spectrometry.[13] The assay procedures of the AbsoluteIDQ p150 Kit as well as the metabolite nomenclature have been described in full detail.[14] In total, 3061 serum samples of the F4 Study were quantified for 163 metabolites in 38 randomly distributed kit plates (see online supplemental table 1 in Huang *et al*[15]). Each plate also contained three quality control (QC) samples (sex mixed human plasma samples provided by the manufacturer) and one zero sample (phosphate buffered saline). Identical QC procedures were used.[9] Each metabolite met three criteria: (1) missing values <10%; (2) median CV of three QC samples <25%; (3) 50% of measured sample values are equal to or above the limits of detection. In total, 121 metabolites passed the criteria and were used in the subsequent analysis (online supplemental table 1). To minimize the plate effect, metabolite concentrations were adjusted with TIGER.[16]

Statistical analysis

We used multiple linear regression models to assess the relationship between omentin and metabolites and adjusted for a number of variables. In each analysis, the metabolite concentration was used as the dependent variable and the omentin level as the independent variable, and step by step adjusted in five models. Model 1 did not consider any clinical variables. Age and sex were included in model 2. For example, $Y_{\text{metabolite concentration}} \sim X_{\text{omentin}} + \text{age}_{(\text{years})} + \text{sex}_{(\text{female=0, male=1})}$. Model 3 further included body mass index (BMI) and waist-to-hip ratio (WHR). Model 4 additionally adjusted for lifestyle variables (physical activity, alcohol intake, and smoking). Model 5a additionally included adiponectin levels. The full model (model 5) further included serum adiponectin levels, HDL-cholesterol, use of lipid-lowering medication, use of anti-inflammatory medication, history of myocardial infarction and stroke, HOMA2-IR, diabetes status, and use of oral glucose-lowering medication and insulin.

To ensure comparability between different metabolites, their concentrations were natural log-transformed and scaled to a mean value of 0 and SD of 1. The omentin level was also natural log-transformed and scaled to a mean value of 0 and SD of 1.

Each metabolite was analyzed separately. To account for multiple testing of the used 121 metabolites, a Bonferroni-corrected significance level was defined as p value of <0.05/121=4.13E-04.

In addition, we examined whether omentin levels were also associated with metabolite ratios. Based on literature reviews, we analyzed 11 metabolite ratios. Metabolite ratios were calculated (log[metabolite 1/metabolite 2]) and scaled to a mean value of 0 and SD of 1 and analyzed according to the method of single metabolite described above, and p<0.05/11 was considered as the Bonferroni-adjusted significance threshold.

Table 1 Characteristics of study participants (N=1124)*

Age (years)	70.0 (66.0–75.0)
Male sex (%)	574 (51.1)
BMI (kg/m^2)	28.2 (25.6–31.2)
Waiste-to-hip ratio	0.92 (0.85–0.97)
HOMA2-IR	1.15 (0.84–1.73)
Adiponectin levels (µg/mL)	10.2 (6.6–15.3)
HDL-cholesterol (mmol/L)	1.40 (1.16–1.65)
Omentin levels (ng/mL)	487.2 (401.8–581.1)
Smoking (%)	
Non-smoker	549 (49.0)
Former smoker	488 (43.5)
Current smoker	84 (7.5)
Alcohol intake (g/day)	5.7 (0.0–20.0)
Physically active (%)	563 (50.2)
Intake of lipid-lowering medication (%)	274 (24.4)
Intake of statins (%)	266 (23.7)
Glucose-lowering medication (%)	124 (11.1)
Regular use of NSAIDs (%)	275 (24.5)
History of myocardial infarction (%)	70 (6.2)
History of stroke (%)	48 (4.3)
Glucose tolerance status (%)†	
NGT	431 (38.3)
Pre-diabetes	434 (38.6)
Type 2 diabetes	233 (20.7)
Other	26 (2.3)

*Data are presented as median (25th–75th percentile) or number (percentage).
†Pre-diabetes: impaired fasting glucose or/and impaired glucose tolerance; other: type 1 diabetes, drug-induced diabetes and unclear, due to a lack of OGTT information.
BMI, body mass index; HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; NGT, normal glucose tolerance; NSAIDs, non-steroidal anti-inflammatory drugs; OGTT, oral glucose tolerance test.

All analyses were carried out using R, V.4.1.2.

RESULTS

The characteristics of the 1124 participants for whom complete omentin and metabolite data were available are shown in table 1. Overall, the KORA F4 participants were older individuals (median age 70 years) taking various medications (table 1). However, the participants had a relatively healthy lifestyle (about 7.5% were current smokers and 50.2% of participants were physically active). Therefore, we used five regression models with increasing complexity to analyze the relationship of circulating omentin levels with metabolite concentrations.

Of the 121 analyzed metabolites, in the unadjusted model 1, we found 33 metabolites significantly

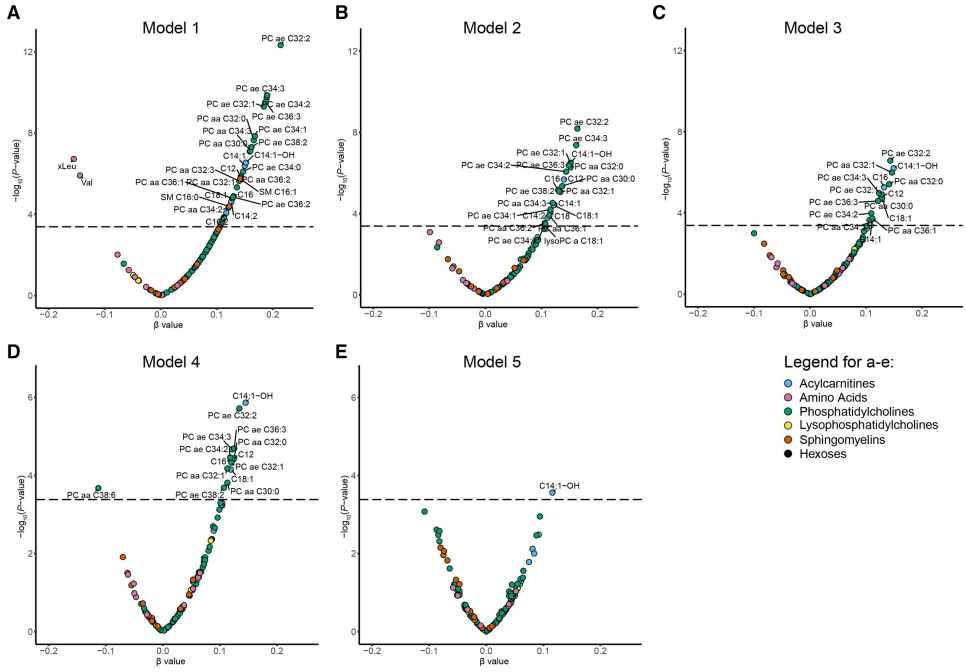

Figure 2 Associations of serum levels of omentin with serum metabolite levels. Volcano plots indicating beta values and corresponding p values (displayed as $-\log_{10}(P)$) of associations of serum omentin with serum metabolite levels in regression models 1–5. Each dot represents one metabolite. (A) Model 1: unadjusted; (B) model 2: adjusted for age and sex; (C) model 3: model 2 additionally adjusted for BMI and WHR; (D) model 4: model 3 further adjusted for physical activity, alcohol intake, smoking; (E) model 5 (full model): model 4 further adjusted for adiponectin levels, HDL-cholesterol, use of lipid-lowering and anti-inflammatory medication, history of MI, history of stroke, HOMA2-IR, diabetes status, and use of oral glucose-lowering medication and insulin. The horizontal line indicates the significance threshold adjusted for multiple comparisons (p=0.05/121). Metabolite nomenclature indicates Cx:y, with x: number of carbons in the fatty acid side chain and y: number of double bonds in the fatty acid side chain. BMI, body mass index; HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; MI, myocardial infarction; PC aa, phosphatidylcholine with ester bond; PC ae, phosphatidylcholine with ether bond; SM, sphingomyelin; WHR, waist-to-hip ratio.

(p<4.13E-04) associated with omentin levels (figure 2A and online supplemental table 1). Two branched chain amino acids (BCAAs), valine and (iso-)leucine (xLeu) were negatively associated with omentin levels. In contrast, 31 lipids (eg, phosphatidylcholines (PCs), acylcarnitines and sphingomyelins (SMs)) were positively associated with omentin. The strongest associations were observed for PC ae C32:2, PC ae C34:3, PC ae C34:2, PC ae C36:3 and PC ae C32:1. The acylcarnitines positively associated with omentin concentrations mainly had a medium or long chain length (C12, C14:1, C14:1-OH, C14:2, C16, C16:2, C18, C18:1) and SMs contained palmitic or palmitoleic acid (SM C16:0, SM C16:1).

In model 2 (adjusted for age and sex), the negative associations of omentin with BCAAs were attenuated, whereas 22 positive associations remained significant with PC ae C32:2 having the strongest association (figure 2B and online supplemental table 1). With additional adjustment for BMI and WHR (model 3), 15 lipids further remained significant and we observed a similar pattern of associations, with PC ae C32:2 most strongly associated with omentin (figure 2C and online supplemental table 1). In model 4, by adjusting additionally for the lifestyle factors physical activity, smoking behavior, and alcohol consumption, we observed 13 positive associations between omentin and lipids. These associations included four acylcarnitines and nine PCs including PC aa C32:1 (figure 2D and online supplemental table 1). Finally, in the fully adjusted model 5, only C14:1-OH remained significant (figure 2E and online supplemental table 1). Positive associations at nominal significance were observed with PCs and acylcarnitines, whereas negative associations were detected for PCs and SMs (SM C18:0, SM C18:1, SM C24:0, SM C24:1, SM (OH) C22:1). Collectively, C14:1-OH was significantly associated with omentin in all five models.

We previously showed that adiponectin may mediate the association between omentin and insulin sensitivity in the KORA F4 Study.[3] In order to characterize the role of adiponectin in the relationship between omentin and metabolites in more detail, we analyzed the effect of adiponectin, when added as the only covariable to model 4. In model 5a, beta coefficients were reduced on average by about 30% (online supplemental table 1), indicating that some of the associations between omentin and metabolites can be explained by adiponectin. In order to compare the associations of both adipokines with the measured metabolites, we assessed the correlation of the beta coefficients for both omentin and adiponectin in model 5. The correlation coefficient was r=−0.06

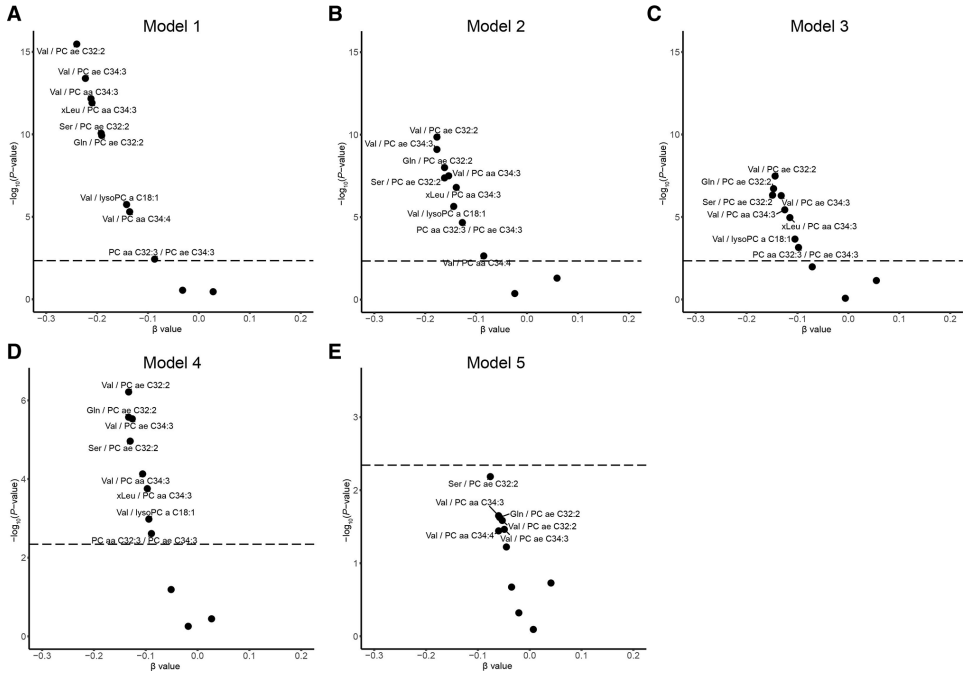

Figure 3 Associations of serum levels of omentin with ratios of serum metabolite levels. Volcano plots indicating beta values and corresponding p values (displayed as $-\log_{10}(P)$) of associations of serum omentin with ratios of serum metabolite levels in regression models 1–5. Each dot represents one metabolite ratio. (A) Model 1: unadjusted; (B) model 2: adjusted for age and sex; (C) model 3: model 2 additionally adjusted for BMI and WHR; (D) model 4: model 3 further adjusted for physical activity, alcohol intake, smoking; (E) model 5 (full model): model 4 further adjusted for adiponectin levels, HDL cholesterol, use of lipid-lowering and anti-inflammatory medication, history of MI, history of stroke, HOMA2-IR, diabetes status, and use of oral glucose-lowering medication and insulin. The horizontal line indicates the significance threshold adjusted for multiple comparisons (p=0.05/11). Metabolite nomenclature indicates Cx:y, with x: number of carbons in the fatty acid side chain and y: number of double bonds in the fatty acid side chain. BMI, body mass index; HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; MI, myocardial infarction; PC aa, phosphatidylcholine with ester bond; PC ae, phosphatidylcholine with ether bond; WHR, waist-to-hip ratio.

(p=0.49), indicating that the associations between both adipokines and these metabolites are not related.

PC ae C32:2 had a strong positive and significant association with omentin in models 1–4. Interestingly, the ratio of the amino acid valine to the PC ae C32:2 (Val/PC ae C32:2) has been described to associate with an increased risk of type 2 diabetes and measures of insulin secretion and resistance.[17] Metabolite ratios can be valuable biomarkers for diseases and may furthermore help to reveal relevant metabolic pathways involved in disease development or progression.[18] We therefore investigated whether circulating omentin concentrations are also associated with different metabolite ratios that have been associated with increased risk of type 2 diabetes.[17] Omentin concentrations were negatively associated with the Val/PC ae C32:2 ratio and with the serine-to-PC ae C32:2 ratio (Ser/PC ae C32:2) in models 1–4 as described above (figure 3 and online supplemental table 2). Similarly, omentin levels were also negatively associated with Val/PC ae C34:3, Val/lysoPC a C18:1, Gln/PC ae C32:2, xLeu/PC aa C34:3, Val/PC aa C34:3 and PC aa C32:3/PC ae C34:3 in models 1–4. In the final model 5, associations with metabolite ratios only reached nominal significance.

Since associations of omentin with metabolites may differ in males and females, we repeated our analysis and included sex as an interaction term. We did not find significant interaction terms for metabolites or metabolite ratios (data not shown), indicating that sex effects are likely not present.

DISCUSSION

This study shows multiple associations of serum omentin levels with circulating levels of lipids, which are independent of multiple clinical parameters. Especially, positive associations of omentin with C14:1-OH were significant in all five models. Moreover, omentin levels were negatively associated with the valine-to-PC ae C32:2 ratio, which was previously associated with an increased risk of type 2 diabetes, in several models. Therefore, our study suggests that omentin-induced changes in systemic metabolism may contribute to its role in type 2 diabetes.

Associations between omentin and PCs

We detected positive associations with multiple PCs in models 1–4, which were attenuated in the fully adjusted model 5. Since associations of omentin with PCs only reached nominal significance in model 5, it needs to be established, whether some of the selected covariables may actually act as mediators and not as confounders.

This will help to further clarify the relationship between omentin and PCs. Certain PC species, including PC ae C32:1 and PC ae C32:2 have lower levels in people with type 2 diabetes compared with normoglycemic individuals, and negatively associate with blood glucose levels in type 2 diabetes.[19] Thus, the numerous positive associations of omentin with PCs are in line with a protective role of omentin in type 2 diabetes.

In the present study, a significant positive correlation between PC aa C32:1 and omentin was consistently observed across models 1–4, and additionally in model 5a. Prior research has linked PC aa C32:1 to various stages of type 2 diabetes, including pre-diabetes, newly diagnosed and incident cases.[8 20] Specifically, the cross-sectional KORA F4 Study revealed positive associations of PC aa C32:1 with both pre-diabetes and newly diagnosed type 2 diabetes. However, these associations diminished upon adjustment for HbA1c, fasting glucose, and fasting insulin levels, highlighting a potential connection of this lipid with these clinical parameters.[8] Further associations were identified in the EPIC-Potsdam Study, where PC aa C32:1 was associated with an increased risk of developing type 2 diabetes.[20] Conversely, in the Tübingen Family Study, a negative association was reported between PC aa C32:1 and insulin sensitivity.[20] This lipid was also implicated as a potential early biomarker for type 2 diabetes in a Finnish cohort, where it strongly differentiated between progressors and non-progressors in a discovery study, although this finding was not replicated in the validation study.[21] Additional insights come from analyses in the KORA F4 and the Health Study of Pomerania-TREND-0 Studies, where PC aa C32:1 exhibited significant associations with metabolic syndrome components—positively with hypertriglyceridemia and inversely with decreased HDL-cholesterol, meaning positively with HDL-cholesterol.[9] Considering the known risks of hypertriglyceridemia for atherosclerosis and its cardiac complications, and the link between low HDL-cholesterol and an increased risk of heart failure and type 2 diabetes, these findings are particularly relevant. Collectively, the observed positive correlation of PC aa C32:1 with omentin levels, but not in the fully adjusted model 5, suggests a nuanced relationship between omentin and HDL-cholesterol. This relationship may play a protective role against the risk of type 2 diabetes, warranting further investigation to elucidate the underlying biological mechanisms.

Overall, associations of omentin with PCs may therefore contribute to elucidate the partially contradictory results of cross-sectional and prospective studies on the role of omentin in type 2 diabetes. As already suggested in the context of cardiovascular disease,[22] higher omentin levels in diabetes might also reflect a counter-regulatory mechanism, with increased concentrations of omentin being a potential surrogate parameter of disease or early derangements in glucose metabolism. In order to further unravel the mechanisms linking omentin and diabetes, studies investigating the effect of omentin on lipid composition of insulin-sensitive tissues may therefore be important.

Associations between omentin and SMs

We observed positive associations of circulating omentin levels with SM C16:1 and SM C16:0 in model 1, but significance was attenuated after correction for clinical parameters in models 2–5. Although serum concentrations of SM C16:1 have been associated with a decreased risk of type 2 diabetes,[20] other studies did not find this association in different cohorts[23] or reported lower levels of SM C16:1 in people with recent-onset type 2 diabetes compared with normoglycemic individuals.[19] Nevertheless, it may be interesting to study the role of omentin in diabetic cardiac autonomic neuropathy, where reduced heart rate variability was associated with SM C16:0 and SM C16:1 in people with type 2 diabetes.[24]

Associations between omentin and acylcarnitines

After full adjustment for all confounding variables, the positive association of omentin with hydroxytetradecenoylcarnitine C14:1-OH remained significant. Additionally, associations with several other medium-chain and long-chain acylcarnitines such as C12, C16, and C18:1 were significant in models 1–4. Acylcarnitines play an important role in metabolism by regulating the mitochondrial acyl-coA/coA ratio and the transport of long-chain fatty acids into mitochondria for subsequent beta-oxidation. Whereas short-chain acylcarnitines have been associated with higher risk of type 2 diabetes in meta-analysis, evidence for medium-chain acylcarnitines is less robust.[25] In the KORA Study, levels of the acylcarnitine C2 have previously been associated with impaired glucose tolerance.[8] Moreover, levels of the short-chain acylcarnitines C3 and C4 were higher in serum of people with type 2 diabetes compared with normoglycemic individuals[19] and a greater 10-year increase in C4-OH and C5 acylcarnitines was associated with a higher type 2 diabetes risk.[26] Other studies showed associations of elevated levels of medium-chain, but not long-chain acylcarnitines with early stages of type 2 diabetes[27] and associations of medium-chain and long-chain acylcarnitines with lower beta cell function.[28] Interestingly, a recent population-based study in Chinese individuals detected positive associations of multiple medium-chain and long-chain acylcarnitines, including C14:1-OH, with future risk of type 2 diabetes.[29] As a possible mechanism, medium-chain acylcarnitines impaired glucose-stimulated insulin secretion in islets that was linked to defects in mitochondrial respiratory capacity.[27] Nevertheless, in a recent meta-analysis, higher levels of short-chain and long-chain acylcarnitines were associated with higher type 2 diabetes risk, whereas no association was found for medium-chain acylcarnitines.[25] Whether the strong positive association of C14:1-OH with omentin supports any role for type 2 diabetes remains unclear and requires further studies on the functional studies of C14:1-OH.

Associations between omentin and metabolite ratios

In addition to the analysis of single metabolites, the analysis of metabolite ratios has been shown to deliver valuable information on the relationship of metabolomics data with clinical parameters.[18 19] Molnos *et al* found that the ratio of valine to PC ae C32:2 was positively associated with measures of insulin secretion and resistance, including second phase glucose-stimulated insulin secretion and HOMA-IR, as well as prevalent and incident type 2 diabetes.[17] Similarly, the serine-to-PC ae C32:2 ratio was associated with insulin secretion, as well as prevalent and incident diabetes. We detected a strong negative association of omentin with the serine-to-PC and valine-to-PC ae C32:2 ratios, which was only attenuated in the fully adjusted model 5, suggesting a role for omentin in supporting insulin sensitivity. In order to verify this relationship, the covariables used in model 5 should be investigated for potential mediator effects and results should be confirmed in an independent cohort.

Valine is a BCAA that has been associated with a higher risk of type 2 diabetes in meta-analyses.[25 30] Serine, however, was not significantly associated with type 2 diabetes risk.[30] The PC ae C32:2 was associated with prevalent[19] and incident[20] type 2 diabetes. Although BCAAs have been causally linked with type 2 diabetes risk,[31] it remains elusive whether a causal relationship exists between changes in the valine-to-PC ae C32:2 ratio, measures of insulin resistance and the development of type 2 diabetes. Moreover, it is unknown, whether omentin directly influences levels of serine, valine and PC ae C32:2 or whether the relationship is rather indirect.

Strengths and limitations

Our study represents the first description of data linking omentin levels with various metabolites including amino acids, lipids and acylcarnitines and thereby covers a wide range of metabolic pathways that may relate to the function of omentin. Other strengths of our study include the population-based design, the fact that the study participants were well phenotyped and that our analysis was adjusted for multiple covariables including clinical variables and lifestyle factors.

Limitations of our study include the cross-sectional study design, which does not allow us to draw conclusions on mechanistic effects. In addition, the receptor for omentin is unknown, which limits the possibility of mechanistic studies analyzing how omentin could affect metabolite levels. The study population of individuals from a region in Germany aged 61–82 years limits generalization of our results to younger people and those with a non-European descent. Moreover, observational studies such as ours might be affected by residual confounding due to unknown or unmeasured factors, which we cannot exclude and which could have had an impact on effect sizes. With the kit used for metabolomics analysis, it is not possible to determine detailed analysis of the exact lipid composition, for example, the metabolite PC ae C32:2 can for instance be composed of the fatty acids C16:1/C16:1, C18:1/C14:1 or C18:2/C14:0. Finally, model 5 was strictly adjusted for numerous covariables, which we treated as confounders, but which may also act as mediators that might link omentin and metabolite concentrations. Therefore, we cannot exclude that we lost important associations in model 5 due to overly strong adjustment.

CONCLUSION

Our study identifies multiple associations of circulating omentin levels with serum metabolites and thereby supports a role for omentin in regulating systemic metabolism. Overall, the associations point towards a protective role of omentin in type 2 diabetes and warrant further investigations to unravel a role for omentin in modulating (lipid) metabolism in insulin-sensitive tissues.

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Competing interests None declared.

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Ethics approval This study involves human participants. All investigations were performed in accordance with the Declaration of Helsinki, including obtaining written informed consent from all participants. The study was approved by the Ethics Committee of the Bavarian Chamber of Physicians (number 06068; Munich, Germany).

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Data availability statement Data from this KORA Study are not publicly available because the data are subject to national data protection laws, and restrictions were imposed by the Ethics Committee of the Bavarian Chamber of Physicians to ensure data privacy of the study participants. However, data are available on request to researchers through a project agreement from KORA (http://epi.helmholtz-muenchen.de/kora-gen/). Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA board.

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