Omentin-1, Adiponectin, and the Risk of Developing Type 2 Diabetes

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Omentin-1 is a novel adipokine (1), and its potential role in diabetes pathogenesis is still under debate (2). We aimed to evaluate the longitudinal association of omentin-1 concentrations with the risk of type 2 diabetes.

This observational study was based on 2,500 randomly selected participants of the prospective European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort ($n = 27,548$) (3,4). Exclusion criteria were prevalent diabetes at baseline ($n = 112$), unclear diabetes status ($n = 19$), and incomplete follow-up information ($n = 50$). Missing biomarker information (HbA_{1c} 14%, all others below 10%) was handled by multiple imputation. The final sample comprised 2,319 participants, including 123 incident type 2 diabetes cases. Omentin-1 plasma concentrations were quantified by a commercial sandwich ELISA (BioVendor, Brno, Czech Republic). We previously demonstrated excellent reliability of single omentin-1 measurements (5). Applied statistical methods were multivariable-adjusted linear regression (cross-sectional associations) and Cox proportional hazards regression (longitudinal association of baseline omentin-1 with time-to-diabetes incidence) including multiplicative interaction analysis on a continuous scale between omentin-1 and diabetes-related biomarkers (adiponectin, HDL cholesterol, triglycerides, and CRP) on diabetes risk. Model 1 was adjusted for age, sex, and diet and lifestyle. Model 2 was additionally adjusted for waist circumference. Model 3 (longitudinal analyses only) was additionally adjusted for diabetes- and omentin-related biomarkers (for details see Table 1).

The median plasma omentin-1 concentration in the study population was 396 ng/mL (interquartile range 326, 486). In cross-sectional analyses, omentin-1 was associated with lower BMI and waist circumference and higher levels of adiponectin and HDL cholesterol, respectively; no significant associations of omentin-1 with triglycerides, CRP, or HbA_{1c} were observed in Model 2 (Table 1). In longitudinal analyses, omentin-1 showed no clearly directed association with diabetes risk in nonanthropometry-adjusted Model 1. Adjustment for waist circumference revealed a nonsignificant tendency toward higher diabetes risk with higher omentin-1 concentrations (Model 2), which was significant after adjustment for adiponectin and HDL cholesterol (Model 3, Table 1). Omentin-1 interacted significantly only with adiponectin on diabetes risk ($P = 0.03$). In stratified analyses, the diabetes risk for omentin-1 was significantly elevated in participants with adiponectin above the median (hazard ratio [HR] per SD 1.49 [95% CI 1.05–2.10]) but not in those with adiponectin below the median (HR per SD 1.09 [95% CI 0.84–1.42]) (Model 3, Table 1).

Here we reported for the first time, to our knowledge, data on the longitudinal association of omentin-1 with diabetes incidence. Despite inverse associations of omentin-1 with measures of body fat and direct associations with adiponectin and HDL cholesterol, we found no indication of a diabetes protective role of omentin-1 in prospective analyses.

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Table 1—Association of diabetes-related biomarkers with omentin-1 and of omentin-1 with the risk of type 2 diabetes

	1 SD	Model 1	Model 2	Model 3
Cross-sectional association of diabetes-related biomarkers with omentin-1†				
BMI (kg/m^2)	4.2	*–0.175 (−0.217 to −0.132)*‡		
Waist circumference (cm)	12.5	*–0.197 (−0.249 to −0.146)*		
Adiponectin (μg/mL)	4.2	*0.236 (0.191–0.280)*	*0.205 (0.159–0.251)*	
Triglycerides (mmol/L)	1.06	*–0.074 (−0.117 to −0.032)*	−0.033 (−0.077 to 0.011)	
HDL cholesterol (mmol/L)	0.39	*0.158 (0.115–0.201)*	*0.121 (0.076–0.166)*	
CRP (nmol/L)	3.65	*–0.052 (−0.095 to −0.009)*	−0.021 (−0.064 to 0.021)	
HbA_{1c} (% of total Hb)	0.65	−0.027 (−0.071 to 0.017)	−0.002 (−0.047 to 0.042)	
Longitudinal association of omentin-1 with type 2 diabetes risk¶				
All participants		1.06 (0.87–1.29)#	1.17 (0.97–1.41)	*1.24 (1.02–1.50)*
Stratified by adiponectin††				
Below median‡‡		0.98 (0.75–1.27)	1.06 (0.82–1.38)	1.09 (0.84–1.42)
Above median§§		1.34 (0.98–1.82)	*1.38 (1.00–1.91)*	*1.49 (1.05–2.10)*

Model 1: adjusted for age, sex, lifestyle (i.e., hours per week of activity [sports, biking]), smoking (four stages: never smoker, former smoker, current smoker <20 units/day, current heavy smoker ≥20 units/day), education (four stages: no vocational training or in training, vocational training, technical school, technical college or university), daily intake of energy (joules per day) and of alcohol and diabetes-related dietary items (intake of coffee, sugar-sweetened beverages, whole-grain bread, and red meat [grams per day]), and antihypertensive and antidyslipidemic medication use. Model 2: first model additionally adjusted for waist circumference. Model 3: longitudinal models were additionally adjusted for adiponectin and HDL cholesterol. †For cross-sectional analyses, multivariable-adjusted linear regression models were used. The outcome (omentin-1) was Box-Cox–transformed based on the applied model; consistent over all models, the selected λ was zero corresponding to a logarithmic transformation. Outcome and exposure were standardized to 1 SD (omentin-1: 1 SD = 145 ng/mL). ‡Standardized β (95% CI), all such values. Significant results are printed in italics. ¶In longitudinal analyses, diabetes HRs for omentin-1 were estimated applying Cox proportional hazards regression models; omentin-1 was log-transformed and standardized to 1 SD. #Diabetes HR (95% CI), all such values. ††Significant interaction between omentin-1 and adiponectin ($P = 0.03$); the population was split into halves according to the median adiponectin concentration (7.808 μg/mL). ‡‡Adiponectin <7.808 μg/mL, $n = 1{,}159$. §§Adiponectin ≥7.808 μg/mL, $n = 1{,}160$.

Unexpectedly, our data suggested an elevated omentin-1–related diabetes risk among participants with high adiponectin concentrations. The presented statistical evidence is consistent with an antagonistic interplay between omentin-1 and adiponectin on diabetes risk. Because of the observational nature of our study, the biological mechanisms underlying the reported interaction remain to be elucidated. Our findings warrant external validation in an independent cohort.

The reported results encourage mechanistic studies to explore a possible biological interplay between omentin-1 and adiponectin signaling in experimental setups. Such studies may become clinically relevant, as adiponectin signaling is considered a potential target to prevent or treat diabetes.

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