Hypoadiponectinemia and Proinflammatory State: Two Sides of the Same Coin?

Results From the Cooperative Health Research in the Region of Augsburg Survey 4 (KORA S4)

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OBJECTIVE — Previous studies have yielded conflicting results on the association of adiponectin levels and inflammation. Low systemic concentrations of adiponectin, as well as elevated levels of immune mediators, represent risk factors for the development of type 2 diabetes and coronary artery disease. The major aim of this cross-sectional study was to investigate the interdependence of hypoadiponectinemia and low-grade systemic inflammation.

RESEARCH DESIGN AND METHODS — The study sample consisted of 606 participants aged 55–74 years (244 with normal glucose tolerance, 242 with impaired glucose tolerance, and 120 with newly diagnosed type 2 diabetes) of the population-based KORA S4 (Cooperative Health Research in the Region of Augsburg Survey 4; 1999–2001). Systemic concentrations of adiponectin and a wide range of anthropometric, metabolic, and inflammatory variables were available for analyses. The association of adiponectin with 15 immunological markers, including leukocyte count, acute-phase proteins, cytokines, cytokine receptors, and chemokines, was assessed using univariable and multivariable models.

RESULTS — No evidence for a significant correlation between adiponectin and all immunological parameters except eotaxin could be found after multivariable adjustments, whereas multiple strong correlations with obesity and metabolic factors were present.

CONCLUSIONS — From these data, we conclude that hypoadiponectinemia and a proinflammatory state are largely independent from each other.

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Abbreviations: CRP, C-reactive protein; IGT, impaired glucose tolerance; IL, interleukin; KORA S4, Cooperative Health Research in the Region of Augsburg Survey 4; NGT, normal glucose tolerance; TNF-α, tumor necrosis factor-α; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Hypoadiponectinemia is associated with insulin resistance, whereas an increase of circulating adiponectin concentrations improves glucose levels and increases fatty acid oxidation (1–4). Adiponectin may be considered a biomarker for insulin sensitivity, and in prospective studies, hypoadiponectinemia predicts the incidence of type 2 diabetes (5,6) and coronary artery disease (7). In addition to the insulin-sensitizing properties of adiponectin, the link between adiponectin and chronic subclinical inflammation, which is characteristic of obesity, type 2 diabetes, and cardiovascular disease, has also been investigated. In vitro, adiponectin inhibits adhesion molecule expression on endothelial cells (8), suppresses nuclear factor-κB–mediated signaling (9), impairs macrophage functions (10,11), and downregulates cytokine secretion from adipocytes (12).

However, in vivo data concerning the possible systemic anti-inflammatory effect of adiponectin are more ambiguous. Some clinical studies have reported significant inverse correlations between the systemic concentrations of adiponectin and circulating immune mediators (13–24), whereas others found no evidence for a significant correlation (14–18,21–24). Most of these reports are based on univariable analyses and do not take into account the potential modification of these relationships by variables that are related to metabolic syndrome.

Since obesity is associated with hypoadiponectinemia and with increased circulating levels of various immunological markers, which are both major risk factors for the development of type 2 diabetes and cardiovascular disease, it would be important to know whether hypoadiponectinemia and systemic low-grade inflammation are independent or whether inflammatory markers can be considered "as surrogate markers of hypoadiponectinemia," as recently proposed (17). The main aim of this study was therefore to assess the association of

Table 1—*Characteristics of the study sample and correlations between log adiponectin and inflammatory variables depending on glucose tolerance status (adjusted for age and sex)*

Variable	NGT	IGT/type 2 diabetes	NGT: association with log adiponectin		IGT/type 2 diabetes: association with log adiponectin	
			β	*P*	β	*P*
WBC ($\times 10^{-3}/\mu$l)	5.7 (4.9–6.8)	6.2 (5.3–7.3)*	0.003	0.901	−0.043	0.064
CRP (mg/l)	1.3 (0.7–3.0)	2.4 (1.2–4.6)*	−0.013	0.600	−0.021	0.401
SAA (mg/l)	3.4 (2.1–5.6)	4.1 (2.6–7.0)*	−0.002	0.952	0.010	0.666
Fibrinogen (g/l)	2.8 (2.5–3.2)	3.0 (2.6–3.4)†	−0.027	0.266	−0.014	0.534
IL-6 (pg/ml)	1.7 (0.7–2.9)	2.5 (1.4–3.8)*	0.025	0.317	0.003	0.901
sIL-6R (ng/ml)	126 (91–167)	140 (103–183)‡	0.003	0.915	0.013	0.573
TNF-α (pg/ml)	0.2 (0.1–1.0)	0.5 (0.1–1.7)*	0.050	0.023	0.007	0.720
sTNFR60 (ng/ml)	2.3 (1.7–3.1)	2.1 (1.6–2.9)†	0.017	0.497	0.001	0.974
sTNFR80 (ng/ml)	8.2 (6.4–10.6)	8.2 (6.2–10.7)	0.011	0.665	0.028	0.215
MIF (ng/ml)	5.0 (2.4–8.5)	9.0 (5.9–13.8)*	0.025	0.316	−0.031	0.303
IL-8 (pg/ml)	13.5 (10.0–16.9)	14.3 (10.9–18.6)†	0.000	0.999	−0.004	0.844
RANTES (ng/ml)	19.9 (14.2–29.3)	26.1 (18.1–39.7)*	−0.046	0.063	−0.018	0.457
IP-10 (pg/ml)	281 (194–438)	310 (208–438)	0.000	0.996	0.005	0.842
Eotaxin (pg/ml)	74 (41–107)	76 (45–112)	0.035	0.153	0.043	0.059
MCP-1 (pg/ml)	311 (214–433)	306 (229–392)	−0.028	0.257	0.011	0.667

Data are median (25th–75th percentile) unless otherwise indicated. Data entered the linear regression models as discrete values based on quartiles of normoglycemic subjects, and datasets for all variables were complete or almost complete with no more than four or six values missing in the NGT and IGT/type 2 diabetic groups, respectively. *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$ compared with NGT. IP-10, interferon-inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MIF, macrophage-migration inhibitory factor; SAA, serum amyloid A; WBC, white blood cell.

serum adiponectin levels with 15 immunological variables compared with anthropometric and metabolic parameters in a population-based sample and to test in multivariable regression analyses for significant associations of immune mediators with adiponectin, which are independent of potentially confounding anthropometric and metabolic factors.

RESEARCH DESIGN AND METHODS

— The population-based Cooperative Health Research in the Region of Augsburg Survey 4 (KORA S4) study population has been described extensively (25–29). In the age range 55–74 years, 120 individuals with newly diagnosed type 2 diabetes (and thus without antidiabetic treatment, which could interfere with adiponectin and immune marker levels) and 242 subjects with impaired glucose tolerance (IGT) were available for analysis. Control subjects with normal glucose tolerance (NGT; $n = 244$) were randomly selected after frequency matching for age and sex.

The measurement of anthropometric parameters, metabolic and immunological variables (from fasting blood samples), blood pressure, and the assessment of alcohol intake, smoking, and physical activity has been described previously (25–29). Hypertension was defined as use of antihypertensive treatment or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. In the NGT group, 42 men and 31 women were on antihypertensive treatment. In the IGT/type 2 diabetic group, 89 men and 85 women received antihypertensive treatment. Serum adiponectin concentrations were determined using the human adiponectin radioimmunoassay from Linco Research (St. Charles, MO). Mean intra- and interassay variations in control sera were 5.5 and 9.2%, respectively.

Statistical analyses

Adiponectin concentrations were compared between men and women using Wilcoxon's test and between the different glucose tolerance status groups using the Kruskal-Wallis test (three groups), and in case of significance, Wilcoxon tests for each pairwise group comparison. The associations of anthropometric, metabolic, and immunological variables with adiponectin were estimated after adjustment for age and sex or after adjustment for age, sex, IGT, type 2 diabetes, BMI, hypertension, total cholesterol, HDL cholesterol, and uric acid using linear regression models with log values of adiponectin as dependent variables and the aforementioned variables and one of the immunological parameters as independent variables. Immune markers entered the linear regression models as dummy variables based on quartiles of normoglycemic subjects. $P < 0.05$ was considered statistically significant. Calculations were carried out using the SAS statistical package version 8.2 TS2M0.

RESULTS

— Clinical, anthropometric, metabolic, and immunological characteristics of the study sample are summarized in Tables 1 and 2. Serum adiponectin concentrations were highly dependent on sex and on glucose tolerance status. Adiponectin levels (median [25th–75th percentile]) were significantly higher in women than in men (10.6 [7.6–13.6] vs. 6.6 μg/ml [4.8–9.0]; $P < 0.0001$). Adiponectin concentrations in women with NGT, IGT, or type 2 diabetes were 12.2 (9.5–15.0), 9.7 (7.2–12.5), and 9.0 μg/ml (6.9–11.7), respectively. In men, adiponectin levels in subjects with NGT, IGT, or type 2 diabetes were 7.8 (5.4–9.7), 6.1 (4.6–8.5), and 5.9 μg/ml (4.3–7.8), respectively. In both women and men, adiponectin levels of normoglycemic subjects were significantly higher than in subjects with IGT or with type 2 diabetes, whereas adiponectin concentrations between subjects with IGT and type 2 diabetes did not differ statistically significantly.

First, the associations of adiponectin with leukocyte count, acute-phase proteins, cytokines, cytokine receptors, and

Table 2—*Characteristics of the study sample and correlations between log adiponectin and anthropometric and metabolic variables depending on glucose tolerance status (adjusted for age and sex)*

Variable	NGT	IGT/type 2 diabetes	NGT: association with log adiponectin		IGT/type 2 diabetes: association with log adiponectin	
			β	*P*	β	*P*
Sex (M/F)*	137/107	202/160	−0.488	<0.001	−0.392	<0.001
Age (years)*	65.3 ± 5.3	65.2 ± 5.3	0.017	0.001	0.011	0.026
BMI (kg/m^2)	27.4 ± 3.7	29.8 ± 4.0†	−0.011	0.147	−0.007	0.271
Waist circumference (cm)	94 ± 11	100 ± 11†	−0.003	0.282	−0.002	0.464
Hip circumference (cm)	104 ± 7	108 ± 8†	−0.003	0.481	0.000	0.989
WHR	0.90 ± 0.08	0.93 ± 0.07†	−0.625	0.247	−0.678	0.197
Body fat (kg)	27.3 ± 6.6	31.0 ± 7.0†	−0.004	0.376	−0.002	0.531
Body fat (%)	35.8 ± 5.5	38.0 ± 5.5†	−0.001	0.829	0.004	0.522
Fat-free mass (kg)	48.7 ± 8.7	50.3 ± 8.4‡	−0.010	0.057	−0.009	0.057
Fasting glucose (mg/dl)	96 ± 7	114 ± 25†	−0.003	0.440	−0.003	0.002
Fasting insulin (mU/l)§	8.4 (5.7–12.2)	12.5 (9.0–19.2)†	−0.143	0.001	−0.140	<0.001
HOMA-IR§	2.0 (1.4–3.0)	3.4 (2.3–5.6)†	−0.139	0.001	−0.146	<0.001
A1C (%)	5.5 ± 0.3	5.8 ± 0.7†	−0.197	0.019	−0.132	<0.001
Cholesterol (mmol/l)	6.3 ± 1.2	6.2 ± 1.1	0.011	0.669	0.004	0.870
LDL cholesterol (mmol/l)	4.0 ± 1.1	3.9 ± 1.0	−0.025	0.318	−0.033	0.189
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4†	0.384	<0.001	0.381	<0.001
Fasting triglycerides (mg/dl)§	106 (80–144)	131 (102–182)†	−0.253	<0.001	−0.203	<0.001
Uric acid (mg/dl)	5.5 ± 1.3	6.1 ± 1.5†	−0.032	0.218	−0.041	0.038
Serum albumin (g/l)§	37.8 (35.6–40.6)	38.4 (35.9–41.3)‡	−0.376	0.172	−0.581	0.016
Systolic blood pressure (mmHg)‖	122 ± 12	125 ± 11	0.001	0.810	0.002	0.732
Diastolic blood pressure (mmHg)‖	74 ± 7	76 ± 7	−0.007	0.217	0.009	0.185

Data are means ± SD, median (25th–75th percentile), or absolute numbers. Datasets for all variables except blood pressure were complete or almost complete with no more than 6 or 11 values missing for the NGT and IGT/type 2 diabetic groups, respectively. *Sex adjusted for age only, age adjusted for sex only. §Shown here as median and 25th–75th percentiles, but log values were used in regression models. ‖Subjects with blood pressure >140/90 mmHg or on antihypertensive treatment were excluded (remaining *n*: 115 NGT, 87 IGT/type 2 diabetes). ‡$P < 0.05$, †$P < 0.001$ compared with NGT. HOMA-IR, homeostasis model assessment for insulin resistance.

chemokines were evaluated in subjects with NGT or with disturbed glucose metabolism (IGT/type 2 diabetes) after adjustment for age and sex (Table 1). In the NGT group only, we found a positive correlation between adiponectin and tumor necrosis factor-α (TNF-α; $P = 0.023$). However, there was no evidence for a significant correlation between adiponectin and any of the other immunological markers in both NGT and IGT/type 2 diabetic groups.

In contrast, there were strong positive correlations between adiponectin and age or HDL cholesterol and strong negative correlations with fasting insulin, homeostasis model assessment of insulin resistance, HbA_{1c} (A1C), and triglycerides in both groups and additionally with fasting glucose, uric acid, and serum albumin in the IGT/type 2 diabetic group (Table 2). Adiponectin levels were also significantly associated with indexes of obesity and body fat distribution (e.g., inverse associations with BMI, waist circumference, and waist-to-hip ratio [WHR]) (data not shown), but these associations did not remain significant after adjustment for glucose tolerance status, sex, and age (Table 2).

Furthermore, we looked for associations between adiponectin and immunological variables in the total study sample using multivariable linear regression analyses (Table 3). After adjustment for sex, IGT, and type 2 diabetes as major modulators of adiponectin levels, only eotaxin was significantly associated with adiponectin ($P = 0.015$), unlike any of the other immunological markers ($P = 0.123$ for TNF-α). In a second model, adjusting for sex, IGT, and type 2 diabetes, as well as for other variables that were associated with either adiponectin or immune marker concentrations (age, BMI, hypertension, total cholesterol, HDL cholesterol, and uric acid), the positive correlation between adiponectin and eotaxin persisted ($P = 0.004$), whereas all other associations remained nonsignificant (Table 3).

CONCLUSIONS — In the present study, serum adiponectin levels in general were not associated with a wide panel of immunological markers that were chosen to represent different aspects of immunity. In particular, there was no statistically significant association between adiponectin and proinflammatory immune mediators such as C-reactive protein (CRP), interleukin (IL)-6, and IL-8 in both univariable and multivariable analyses, although an inverse association could be assumed if adiponectin were a potent anti-inflammatory protein. However, there was some evidence for positive correlations of TNF-α and eotaxin with adiponectin.

TNF-α was associated with adiponectin levels in the age- and sex-adjusted model in individuals with NGT but not in the IGT/type 2 diabetic group or in the multivariable models. Most studies on the relationship between both proteins showed mutually antagonistic effects: adiponectin suppresses TNF-α expression or TNF-α–induced gene expression (9), while TNF-α reduces the expression of adiponectin (30). In addition, adipose tissue mRNA levels and plasma concentrations of TNF-α and adiponectin have

Table 3—*Association between log adiponectin and inflammatory mediators: multivariable regression analysis for the total study population*

	Model 1		Model 2	
Variable	β	*P*	β	*P*
WBC	−0.021	0.219	−0.012	0.469
CRP	−0.016	0.371	−0.017	0.337
SAA	0.009	0.602	−0.003	0.845
Fibrinogen	−0.014	0.402	−0.002	0.923
IL-6	0.019	0.283	0.016	0.363
sIL-6R	0.022	0.204	0.013	0.449
TNF-α	0.023	0.123	0.017	0.233
sTNFR60	0.015	0.387	0.011	0.535
sTNFR80	0.027	0.103	0.027	0.090
MIF	0.001	0.942	0.010	0.605
IL-8	0.006	0.722	−0.006	0.736
RANTES	−0.032	0.065	−0.017	0.317
IP-10	0.008	0.632	−0.005	0.769
Eotaxin	0.041	0.015	0.046	0.004
MCP-1	−0.006	0.751	−0.012	0.474

All inflammatory mediators entered the linear regression models as discrete values based on quartiles of normoglycemic subjects. Model 1: adjusted for sex, IGT, and type 2 diabetes. Model 2: adjusted for sex, IGT, type 2 diabetes, age, BMI, hypertension, total cholesterol, HDL cholesterol, and uric acid. MCP-1, monocyte chemoattractant protein 1; MIF, macrophage-migration inhibitory factor; RANTES, regulated on activation, normal T-cell expressed and secreted; SAA, serum amyloid A; WBC, white blood cell.

been reported to be negatively correlated in nondiabetic subjects (14). Given the fact that some studies also found a somewhat surprising upregulation of TNF-α by adiponectin in their in vitro systems (31,32), the biological relevance of our finding remains to be elucidated.

Regarding the relation of eotaxin with adiponectin, there were positive but nonsignificant trends in the first analysis, which stratified the sample into subjects with NGT and IGT/type 2 diabetes. Both the sex- and glucose tolerance status–adjusted model and the fully adjusted model (also including age, BMI, hypertension, total cholesterol, HDL cholesterol, and uric acid) demonstrated a positive association between eotaxin and adiponection in the total study population. Eotaxin represents T helper 2 activity and is mostly expressed during allergic reactions (33). The authors are not aware of studies demonstrating a link between eotaxin and adiponectin expression. Eotaxin is also released from adipose tissue, but unlike adiponectin, stromal-vascular cells appear to be the major source of this chemokine (34). Since several recent studies did not find significant associations between eotaxin and type 2 diabetes (28) or cardiovascular disease (35), the meaning of our finding is difficult to assess.

To control the biological relevance of the adiponectin dataset, we performed additional analyses in the same study population and found, as expected, that adiponectin levels were significantly inversely correlated with variables that define the metabolic syndrome and strongly positively correlated with HDL cholesterol, another component of the metabolic syndrome. In the unadjusted analysis, we also found the previously described modulation of adiponectin levels by factors such as age, sex, glucose tolerance status, BMI, waist circumference, and WHR. The associations with indexes of obesity were considerably attenuated by adjusting for age and sex and by adjusting for glucose tolerance status. This finding may be attributable to our study sample, which exhibited a relatively small BMI or WHR range, since most of the elderly study participants were overweight or obese.

The overall lack of interdependence of adiponectin and inflammation was surprising since both hypoadiponectinemia and elevated leukocyte counts, as well as increased levels of CRP, serum amyloid A, fibrinogen, IL-6, sIL-6R, TNF-α (data for subgroup in 27), IL-8, RANTES (regulated on activation, normal T-cell expressed and secreted) (28), and macrophage-migration inhibitory factor (29) were associated with IGT and/or type 2 diabetes in the KORA S4 participants. Previous studies consistently demonstrated an inverse correlation between adiponectin and CRP (albeit weaker than the correlation between adiponectin and metabolic markers), which was not significant in our study population. However, there was some controversy about the association of adiponectin with IL-6, TNF-α, and fibrinogen (15–17,19–22,36), and other studies also reported no evidence for an association with sTNFR60, sTNFR80, serum amyloid A, and IL-8 (15,21–24). Some of these discrepancies may be explained by the widely different characteristics of the study populations regarding age, sex, glucose tolerance status, or degree of obesity; therefore, results from univariable analyses cannot be compared directly. Most analyses published thus far did not adjust for potential confounders, so data from multivariable regression, as performed in our study, are not currently available. There is some evidence that metabolic factors could have a major impact on the association of adiponectin with immune mediators since two studies reported that the inverse association between adiponectin and IL-6 (16) and CRP (18) disappeared after adjusting for obesity-related variables or for sex and BMI only, respectively.

In vitro approaches to characterize adiponectin functions suggested that adiponectin exerts anti-inflammatory properties in the interaction with leukocytes, endothelial cells, and adipocytes (8–12). These studies used a recombinant low–molecular weight form of adiponectin, which was derived from *Escherichia coli* and, thus, lacked posttranslational modifications and multimerization sites, whereas endogenous human adiponectin consists largely of middle– and high–molecular weight forms (37). This difference in adiponectin structure may explain the discrepancy of our in vivo data with previous in vitro studies. Given the frequent anatomical vicinity of adipocytes, lymph nodes, and blood vessels, it is conceivable that these in vitro data on the regulation of cytokines and chemokines by adiponectin represent paracrine effects that are not reflected by systemic levels in the circulation. Clinical studies to investigate the anti-inflammatory, antidiabetic, and antiatherogenic potency of the different molecular-weight forms of endogenous adiponectin would be highly desirable.

The cross-sectional design of the current study allows for the analysis of associations between systemic concentrations of adiponectin and immunological vari-

ables but not for causal investigation of the impact of adiponectin levels on disease risk or how an increase or decrease of adiponectin directly affects the markers of interest and vice versa. In addition, the selection of the study participants for this case-control study led to an overrepresentation of subjects with IGT and type 2 diabetes.

However, there are several strengths of the study that are relevant for the investigation of possible interdependence of adiponectin and immune markers. First, we used a well-characterized study population with extensive phenotype data covering many different aspects of systemic immunity and metabolism and allowing for multivariable analyses. Second, the oral glucose tolerance tests performed during the survey identified individuals with IGT and type 2 diabetes; therefore, the glucose tolerance status, as a potential confounder of relationships between adiponectin and immune markers, could be taken into account.

In conclusion, although adiponection levels exhibited strong negative correlations with several factors defining metabolic syndrome and a strong positive association with HDL cholesterol, there was no evidence for associations of adiponectin with a wide range of immunological parameters except eotaxin. We therefore conclude that hypoadiponectinemia and low-grade inflammation are independent and distinct factors and not just "two sides of the same coin."

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References

1. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
2. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T: The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 7:941–946, 2001
3. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE: The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7:947–953, 2001
4. Stefan N, Stumvoll M: Adiponectin: its role in metabolism and beyond. *Horm Metab Res* 34:469–474, 2002
5. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57–58, 2002
6. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF: Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228, 2003
7. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 291:1730–1737, 2004
8. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y: Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 100:2473–2476, 1999
9. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y: Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 102:1296–1301, 2000
10. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y: Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 96:1723–1732, 2000
11. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T, Matsuzawa Y: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 103:1057–1063, 2001
12. Dietze-Schroeder D, Sell H, Uhlig M, Koenen M, Eckel J: Autocrine action of adiponectin on human fat cells prevents the release of insulin resistance–inducing factors. *Diabetes* 54:2003–2011, 2005
13. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H, Matsuzawa Y: Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* 107:671–674, 2003
14. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G: Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-α expression. *Diabetes* 52:1779–1785, 2003
15. Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, Richelsen B: Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol Endocrinol Metab* 285:E527–E533, 2003
16. Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Mohlig M, Pfeiffer AF, Luft FC, Sharma AM: Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 52:942–947, 2003
17. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, Kobes S, Tataranni PA, Hanson RL, Knowler WC, Lindsay RS: Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. *Diabetes Care* 26:1745–1751, 2003
18. Shetty GK, Economides PA, Horton ES, Mantzoros CS, Veves A: Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. *Diabetes Care* 27:2450–2457, 2004
19. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB: Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. *Diabetes Care* 27:1680–1687, 2004
20. Kopp HP, Krzyzanowska K, Mohlig M, Spranger J, Pfeiffer AF, Schernthaner G:

Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. *Int J Obes Relat Metab Disord* 29:766–771, 2005
21. Rothenbacher D, Brenner H, Marz W, Koenig W: Adiponectin, risk of coronary heart disease and correlations with cardiovascular risk markers. *Eur Heart J* 26: 1640–1646, 2005
22. Salmenniemi U, Zacharova J, Ruotsalainen E, Vauhkonen I, Pihlajamaki J, Kainulainen S, Punnonen K, Laakso M: Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure, and cytokines in offspring of type 2 diabetic patients. *J Clin Endocrinol Metab* 90:4216–4223, 2005
23. Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R, Ricart W: Novel interactions of adiponectin with the endocrine system and inflammatory parameters. *J Clin Endocrinol Metab* 88:2714–2718, 2003
24. Vendrell J, Broch M, Vilarrasa N, Molina A, Gomez JM, Gutierrez C, Simon I, Soler J, Richart C: Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. *Obes Res* 12:962–971, 2004
25. Rathmann W, Haastert B, Icks A, Lowel H, Meisinger C, Holle R, Giani G: High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening: the KORA survey 2000. *Diabetologia* 46:182–189, 2003
26. Rathmann W, Martin S, Haastert B, Icks A, Holle R, Lowel H, Giani G, KORA Study Group: Performance of screening questionnaires and risk scores for undiagnosed diabetes: the KORA Survey 2000. *Arch Intern Med* 165:436–441, 2005
27. Muller S, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, Giani G, Illig T, Thorand B, Kolb H: Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. *Diabetologia* 45:805–812, 2002
28. Herder C, Haastert B, Müller-Scholze S, Koenig W, Thorand B, Holle R, Wichmann HE, Scherbaum WA, Martin S, Kolb H: Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). *Diabetes* 54 (Suppl. 2):S11–S17, 2005
29. Herder C, Kolb H, Koenig W, Haastert B, Muller-Scholze S, Rathmann W, Holle R, Thorand B, Wichmann HE: Association of systemic concentrations of macrophage migration inhibitory factor with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg, Survey S4 (KORA S4). *Diabetes Care* 26:194–199, 2006
30. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y: PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipocyte-derived protein. *Diabetes* 50:2094–2099, 2001
31. Lappas M, Permezel M, Rice GE: Leptin and adiponectin stimulate the release of proinflammatory cytokines and prostaglandins from human placenta and maternal adipose tissue via nuclear factor-kappaB, peroxisomal proliferator-activated receptor-gamma and extracellularly regulated kinase 1/2. *Endocrinology* 146:3334–3342, 2005
32. Tsatsanis C, Zacharioudaki V, Androulidaki A, Dermitzaki E, Charalampopoulos I, Minas V, Gravnis A, Margioris AN: Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other proinflammatory stimuli. *Biochem Biophys Res Commun* 335:1254–1263, 2005
33. Kaplan AP: Chemokines, chemokine receptors and allergy. *Int Arch Allergy Immunol* 124:423–431, 2001
34. Vasudevan AR, Wu H, Xydakis AM, Jones PH, Smith EO, Sweeney JF, Corry DB, Ballantyne CM: Eotaxin and obesity. *J Clin Endocrinol Metab* 91:256–261, 2006
35. Rothenbacher D, Muller-Scholze S, Herder C, Koenig W, Kolb H: Differential expression of chemokines, risk of stable coronary heart disease, and correlation with established cardiovascular risk markers. *Arterioscler Thromb Vasc Biol* 26:194–199, 2006
36. Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, Hoogeveen RC, Heiss G: Adiponectin and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes* 53:2473–2478, 2004
37. Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, Hara K, Hada Y, Vasseur F, Froguel P, Kimura S, Nagai R, Kadowaki T: Impaired multimerization of human adiponectin mutants associated with diabetes: molecular structure and multimer formation of adiponectin. *J Biol Chem* 278:40352–40363, 2003