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Association of adipokines and inflammatory markers with lipid control in type 2 diabetes

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KEY WORDS

adiponectin, cholesterol, resistin, triglycerides, tumor necrosis factor α

ABSTRACT

INTRODUCTION Data regarding the effect of certain adipokines on lipid metabolism are equivocal.

OBJECTIVES The aim of this study was to evaluate the association of lipid control with adipokines and inflammatory markers in patients with type 2 diabetes.

PATIENTS AND METHODS The analysis included 195 patients with type 2 diabetes. The achievement of treatment targets in terms of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides was assessed in accordance with the current guidelines. Homeostatic Model Assessment–Insulin Resistance (HOMA-IR) index as well as concentrations of high-molecular-weight (HMW) adiponectin, leptin, resistin, high-sensitivity C-reactive protein, interleukin 6, and tumor necrosis factor α (TNF-α) were measured in all patients. Logistic regression analyses were performed to determine the risk factors for inadequate lipid control.

RESULTS Optimal control in terms of total cholesterol, LDL, HDL, and triglycerides was achieved in 61%, 43%, 53%, and 68% of the patients, respectively. In multivariate analyses, female sex, lower resistin concentrations, and the absence of statin treatment were predictors of total cholesterol levels above the treatment target; older age and lower statin dose—of LDL cholesterol levels above the treatment targets; female sex, higher HOMA-IR index, lower HMW adiponectin concentrations, and higher TNF-α concentration—of HDL levels below the treatment targets; and higher HOMA-IR, lower HMW adiponectin concentration, and the absence of statin treatment—of triglycerides above the treatment target.

CONCLUSIONS In type 2 diabetes, lower HMW adiponectin concentrations are associated with inadequate triglyceride and HDL control; higher TNF-α, with inadequate HDL control, and lower resistin concentrations, with inadequate total cholesterol control.

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INTRODUCTION Patients with type 2 diabetes are at a substantially increased risk of cardiovascular events and death, and the main goal of type 2 diabetes treatment is to reduce this risk. This cannot be achieved solely by amelioration of hyperglycemia but requires multiple strategies targeted at body weight reduction as well as achieving blood pressure and lipid control.[1-3]

Adipose tissue has long been considered purely an inert body compartment for energy storage. However, recent years have brought mounting evidence that adipose tissue is in fact an active endocrine and paracrine organ, secreting a broad spectrum of hormones, cytokines, and growth factors, collectively termed as adipokines. Some of them are synthesized exclusively or predominantly by adipocytes (eg, adiponectin, leptin), while others originate from other sources as well (eg, resistin, chemerin, proinflammatory cytokines).[4] Adipokines are involved in the regulation of a wide variety of physiological processes including insulin responsiveness, glucose and lipid metabolism,

endothelial function, inflammatory response, and cytokine signalling.[4] Thus, adipose tissue affects the function of numerous organs, and its endocrine dysregulation in obesity is associated with type 2 diabetes, dyslipidemia, arterial hypertension, atherosclerosis, heart failure, nonalcoholic steatohepatitis, and polycystic ovary syndrome.[4,5] As the actions of adipokines are immensely diverse, their role was also implied in pathological states that are not traditionally perceived as obesity-related, such as chronic hepatitis C, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, asthma, chronic obstructive pulmonary disease, lung cancer, or Alzheimer disease.[6-9]

Given the well-known association of obesity with dyslipidemia (and, in particular, with so called atherogenic dyslipidemia), it could have been presumed that the influence of adipokines on lipid metabolism would be axiomatic and unidirectional. However, the actions of various adipokines are not only heterogeneous but often also contrary to each other. Thus, the interplay between different adipokines is complex and its exploration—challenging. Although a considerable amount of evidence is available for some adipokines (such as adiponectin) with respect to their impact on lipid metabolism, data on others (such as resistin) are not consistent.[10-18]

The aim of this study was to investigate the association between selected adipokines and lipid control in type 2 diabetes patients. We focused on 6 key cytokines released from adipose tissue and, in order to simplify presentation of the results, decided to divide them into "classic" adipokines (adiponectin, leptin, and resistin) and inflammatory markers (C-reactive protein [CRP], interleukin 6 [IL-6] and tumor necrosis factor α [TNF-α]).

PATIENTS AND METHODS

Patient population The study group was recruited from the participants of the prospective randomized AVOCADO study (Aspirin Vs/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes). The objectives and methodology of the AVOCADO study, including patient inclusion and exclusion criteria, as well as detailed characteristics of the AVOCADO study population, were published previously.[19,20] Briefly, the AVOCADO study included 304 clinically stable patients aged between 30 and 80 years old, with type 2 diabetes diagnosed at least 6 months prior to study enrollment, burdened with additional cardiovascular risk factors, who had been taking aspirin at a dose of 75 mg/d for at least 3 months for primary or secondary prevention of acute coronary syndrome. As the goal of the AVOCADO study was to identify "aspirin-resistant" patients, main study exclusion criteria were: treatment with antiplatelet agents other than aspirin, treatment with anticoagulants, treatment with nonsteroidal anti-inflammatory drugs, coexisting contraindications to aspirin treatment, a history of bleeding diathesis, thrombocytopenia, thrombocytosis, significant anemia, malignancy, connective tissue disease, end-stage kidney disease, acute coronary syndrome, coronary angioplasty or coronary artery bypass grafting in the preceding 12 months, and major surgical procedures in the last 8 weeks prior to enrollment into the study. Patients with diet-controlled type 2 diabetes were also excluded. The recruitment phase of the AVOCADO study lasted from January 2008 to August 2010.

In the AVOCADO study, patients found to be "aspirin-resistant" in laboratory tests performed at the first (baseline) study visit were subsequently randomized to treatment with aspirin at a double dose (ie, 150 mg/d) or to treatment with clopidogrel at a dose of 75 mg/d.

The current study included only clinical data and laboratory measurements obtained at baseline visits, that is, before randomization to study treatment.

The purpose of the current analysis was to reveal the effect of adipokines on lipid profile, irrespective of their effect on insulin sensitivity. Therefore, to evaluate insulin resistance using the Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) index, only patients with type 2 diabetes treated with oral antidiabetic agents were selected from the AVOCADO study population (patients on insulin in monotherapy or in combination were excluded).

The AVOCADO study was conducted in accordance with the current version of the Declaration of Helsinki. The local ethics committee approved the study protocol. All patients gave written informed consent to participate in the study.

Methods Venous blood samples were collected in the morning (between 8 AM and 9 AM) following an overnight fast. Regular laboratory testing, including lipid profile, fasting glycemia, hemoglobin A_{1c} (HbA_{1c}) and serum creatinine, was performed using standard methods. Serum (for the measurement of insulin, adipokines, and inflammatory markers) was obtained from venous blood by centrifugation at 1000 *g* for 15 minutes at 4°C, and aliquots were stored at –80°C until patients' enrollment was completed. Subsequently, the samples were defrosted and appropriate measurements were performed.

Evaluation of lipid control Lipid treatment targets were defined in accordance with the current (2014) American Diabetes Association guidelines and current European guidelines as achieving low-density lipoprotein (LDL) cholesterol concentrations below 100 mg/dl (2.5 mmol/l) in patients without overt coronary artery disease and below 70 mg/dl (1.8 mmol/l) in patients with coronary artery disease; total cholesterol concentrations below 175 mg/dl (4.5 mmol/l); high-density lipoprotein (HDL) cholesterol concentrations above 50 mg/dl (1.3 mmol/l) in women and above 40 mg/dl (1.0 mmol/l) in men; and triglyceride concentrations below 150 mg/dl (1.7 mmol/l).[1-3]

Evaluation of insulin resistance Serum insulin concentration was measured using Elecsys Insulin Assay® according to the manufacturer's instructions (Roche Diagnostics, Mannheim, Germany) with electrochemiluminescence, on Elecsys 2010 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). The HOMA-IR index was calculated based on the following formula: insulin concentration × fasting glycemia × 0.0555 / 22.5, with insulin concentrations expressed in μIU/ml and glycemia expressed in mg/dl.

Evaluation of adipokines and inflammatory markers Serum concentrations of high-molecular-weight (HMW) adiponectin, leptin, and resistin were measured using Human High Molecular Weight Adiponectin ELISA® (Millipore Corporation, Billerica, Massachusetts, United States), Human Leptin Quantikine ELISA Kit® (R&D Systems Inc., Minneapolis, Minnesota, United States), and Human Resistin Quantikine ELISA Kit® (R&D Systems Inc.), respectively. Serum concentrations of TNF-α and IL-6 were measured using Quantikine HS ELISA Human TNF-α Immunoassay® (R&D Systems Inc.) and Quantikine HS ELISA Human IL-6 Immunoassay® (R&D Systems Inc.), respectively. High-sensitivity CRP (hsCRP) concentration was assessed using Cobas Integra 800 (Roche, Basel, Switzerland).

Statistical analysis A statistical analysis was performed using the SAS® software, version 9.2 (SAS Institute, Cary, North Carolina, United States). Qualitative variables were presented as absolute and relative frequencies. Normally distributed quantitative variables were presented as a mean value ± standard deviation, and nonnormally distributed quantitative variables—as a median value and interquartile range (IQR). Normal distribution of quantitative variables was evaluated using the Shapiro–Wilk test. Correlations between quantitative variables were assessed using the Spearman correlation coefficient. Univariate and multivariate logistic regression analyses were performed to determine the risk factors of inadequate lipid control. Factors found to be significant in univariate analyses were then applied in multivariate logistic regression models. A value of P of 0.05 or less was considered significant for all tests.

RESULTS

Study group characteristics The current analysis included 195 patients. Median age in the whole group was 68 years (IQR, 61–74). Half of the study group (97 patients) were women. Median diabetes duration was 5 years (IQR, 3–10) and median HbA_{1c} was 6.5% (IQR, 6.1–7.1). Median body mass index (BMI) was 30.4 kg/m^2 (IQR, 27.1–32.9). Arterial hypertension was diagnosed in 178 patients (91%); chronic heart failure, in 69 patients (35%); and coronary artery disease, in 101 patients (52%) including 50 patients (26% of the study group) with previous myocardial infarction. Eleven patients (6%) had a history of previous stroke and/or transient ischemic attack, 35 patients (18%) had chronic kidney disease (CKD) stages 3–5 (including 34 patients with CKD stage 3 and 1 patient with CKD stage 4), with a median estimated glomerular filtration rate (eGFR) of 83.1 ml/min/1.73m^2 (IQR, 66.7–103.8) in the whole group. A history of smoking was reported in 108 patients (55%), including 18 patients (9%) who were still active smokers.

Dyslipidemia was diagnosed in 163 patients (84%). A total of 143 patients (73%) were treated with statins: mostly with simvastatin (82 patients) at a median daily dose of 20 mg and atorvastatin (58 patients) at a median daily dose of 20 mg. Three patients were treated with lovastatin. Twenty-three patients (12%) were treated with fibrate (fenofibrate) at a median daily dose of 200 mg.

Lipid control in the study group The median values of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were 166 mg/dl (IQR, 141–188), 86 mg/dl (IQR, 69–110), 47 mg/dl (IQR, 40–56), and 127 mg/dl (IQR, 97–171), respectively. Treatment targets in terms of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were achieved in 119 patients (61%), 84 patients (43%), 104 patients (53%), and 132 patients (68%), respectively. Comparative characteristics of patients achieving and those not achieving good lipid control are shown in TABLES 1 and 2.

Risk factors of inadequate lipid control Correlations of lipid parameters with concentrations of adipokines and inflammatory markers are presented in TABLE 3.

Univariate regression analyses included the following variables: age, sex, BMI, HOMA-IR index, HMW adiponectin, leptin, resistin, hsCRP, IL-6, and TNF-α concentrations, eGFR, presence or absence of statin treatment, statin dose (including all patients, that is, patients who were not treated with statins were assigned a dose of 0 mg/d; atorvastatin and lovastatin doses were converted to equivalent simvastatin doses), presence or absence of fibrate treatment and fibrate dose (including all patients, that is, patients who were not treated with fibrates were assigned a dose of 0 mg/d).

All variables found to be significant predictors of inadequate lipid control in univariate analyses (with the exception of fibrate treatment and fibrate dose in the case of triglyceride control) were included in multivariate regression analyses, as shown in TABLE 4. In comparison to patients who achieved triglyceride treatment targets, those who did not achieve triglyceride control were more often treated with fibrates (TABLE 2). In univariate analyses, fibrate treatment and higher fibrate dose were predictors of higher triglyceride concentrations (odds ratio [OR], 7.638; 95% confidence interval [CI], 2.837–20.561; P <0.0001 for fibrate treatment, and OR, 1.097; 95% CI, 1.048–1.149; P <0.0001 for every 10 mg of fenofibrate). Fibrates

TABLE 1 Comparative characteristics of patients achieving and those not achieving treatment targets in terms of total cholesterol and low-density lipoprotein cholesterol levels

Parameter	TC control		*P* value	LDL cholesterol control		*P* value
	achieved (n = 119)	not achieved (n = 76)		achieved (n = 84)	not achieved (n = 111)	
age, y	70 (61–75)	66 (61–73)	0.27	65 ±9	69 ±8	0.004
female sex	50 (42)	47 (62)	0.008	40 (48)	57 (51)	0.67
BMI, kg/m^2	30.4 (26.9–33.4)	30.6 (27.3–32.8)	0.41	29.5 (26.9–32.5)	30.5 (27.2–33.0)	0.30
HOMA-IR	3.6 (2.5–6.2)	4.0 (2.5–7.1)	0.79	3.4 (2.4–5.6)	4.2 (2.6–7.3)	0.16
HMW adiponectin, µg/ml	2.7 (1.9–4.2)	3.0 (1.8–4.5)	0.93	2.7 (1.9–4.5)	3.0 (1.8–4.3)	0.89
leptin, ng/ml	17.2 (8.1–29.7)	17.7 (9.7–28.0)	0.61	15.1 (6.7–26.3)	19.3 (9.9–29.7)	0.11
resistin, ng/ml	7.1 (5.7–9.7)	6.4 (5.2–7.7)	0.021	6.7 (5.4–8.9)	6.8 (5.6–8.6)	0.53
hsCRP, mg/dl	2.3 (1.3–5.2)	3.1 (1.6–4.5)	0.30	2.2 (1.2–3.5)	3.5 (1.6–5.7)	0.002
IL-6, pg/ml	2.4 (1.6–4.5)	2.0 (1.3–3.4)	0.047	1.8 (1.3–3.5)	2.4 (1.6–4.2)	0.028
TNF-α, pg/ml	1.7 (1.2–2.4)	1.6 (1.2–2.3)	0.57	1.4 (1.1–2.2)	1.9 (1.4–2.5)	0.003
statin treatment	96 (81)	47 (62)	0.002	68 (81)	75 (68)	0.069
statin dose,[a,b] mg	20 (20–40)	20 (20–40)	0.40	20 (20–40)	20 (20–40)	0.21
fibrate treatment	14 (12)	9 (12)	1.0	11 (13)	12 (11)	0.66
fibrate dose,[b] mg	208 (200–267)	200 (200–267)	0.42	200 (200–200)	241 (200–267)	0.16

Data are presented as median (interquartile range), mean (standard deviation), or number (percentage). *P* values are given for differences between the groups.

a as an equivalent of simvastatin dose: atorvastatin and lovastatin doses were converted to equivalent simvastatin doses (simvastatin, 20 mg; equivalent to atorvastatin, 10 mg; and lovastatin, 40 mg)
b in patients receiving these drugs

Conversion factor for hsCRP to SI units is 8.45.

Abbreviations: BMI, body mass index; HMW, high-molecular-weight; HOMA-IR, Homeostatic Model Assessment–Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; TC, total cholesterol; TNF-α, tumor necrosis factor α

are the most effective agents decreasing triglyceride concentration; thus, it might have been anticipated that the direction of the relationship between fibrate treatment and triglyceride level should be opposite to the one we observed. However, as hypolipidemic therapy had been chosen at the discretion of the patients' treating physicians and initiated prior to the enrollment in the study, the presence of fibrate treatment was in fact a "marker" of high triglyceride concentration (ie, patients with higher triglyceride concentrations had been more frequently prescribed fibrates by their attending physicians). Therefore, to avoid a methodological bias, we decided not to include fibrate treatment or fibrate dose in the multivariate analysis of predictors of triglyceride control.[21]

Multivariate predictive models of poor lipid control in terms of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are shown in **TABLE 4**.

Association of adipokines with indices of obesity, insulin resistance, and inflammatory markers In order to better understand the interplay between lipid parameters, adipokines, inflammatory markers, and insulin resistance, we performed an additional analysis on the associations between BMI, HOMA-IR index, adipokines, and inflammatory markers in the studied group. As expected, BMI correlated positively with the HOMA-IR index ($r = 0.365$, $P < 0.0001$). Correlations of adipokines and inflammatory markers with BMI and HOMA-IR index and of adipokines with inflammatory markers are shown in **TABLE 5**.

DISCUSSION The results of our study demonstrate that adipokines exert diverse effects on the lipid profile. Multivariate logistic regression analyses revealed resistin, HMW adiponectin, and TNF-α as independent predictors of lipid control in type 2 diabetes patients.

Resistin is secreted from adipose tissue as well as from macrophages and mononuclear leukocytes. In rodent models, resistin was shown to be involved in glucose metabolism and to trigger insulin resistance.[22] Initially, such a role was also proposed for human resistin. Indeed, increased resistin concentrations were reported in obesity, metabolic syndrome, and type 2 diabetes in some, although not all, publications.[4,10-12,14,23] However, recent human studies have revealed resistin mainly as an inflammatory mediator.[4] Resistin induces the expression of endothelial adhesion molecules, such as vascular cell-adhesion molecule 1 involved in leukocyte recruitment to sites of infection, and increases the secretion of other proinflammatory cytokines including interleukin 1, IL-6, interleukin 12, and TNF-α.[4,11,12,14] Consistent with these observations, in our study, resistin levels correlated significantly with concentrations of all 3 measured inflammatory markers (hsCRP, IL-6, and TNF-α), but not with BMI

TABLE 2 Comparative characteristics of patients achieving and those not achieving treatment targets in terms of high-density lipoprotein cholesterol and triglyceride levels

Parameter	HDL cholesterol control		*P* value	TG control		*P* value
	achieved (n = 104)	not achieved (n = 91)		achieved (n = 132)	not achieved (n = 63)	
age, y	69 (61–74)	68 (61–75)	0.72	70 (63–75)	65 (58–72)	0.004
female sex	41 (39)	56 (62)	0.003	67 (51)	30 (48)	0.76
BMI, kg/m^2	29.8 (26.9–33.0)	30.7 (27.2–32.8)	0.59	29.8 (26.8–32.4)	31.2 (28.4–34.5)	0.013
HOMA-IR	3.5 (2.2–5.1)	4.7 (3.0–8.4)	0.002	3.3 (2.1–5.3)	5.4 (3.5–10.5)	<0.0001
HMW adiponectin, µg/ml	3.1 (2.0–4.9)	2.5 (1.7–3.9)	0.052	3.1 (2.2–5.0)	2.0 (1.5–3.2)	<0.0001
leptin, ng/ml	15.3 (6.8–25.7)	19.2 (10.9–32.4)	0.043	17.7 (8.0–28.0)	16.3 (10.0–33.7)	0.38
resistin, ng/ml	6.5 (5.1–8.6)	7.2 (5.7–9.0)	0.071	6.8 (5.5–8.8)	6.7 (5.5–8.3)	0.77
hsCRP, mg/dl	2.6 (1.4–4.4)	3.1 (1.5–5.6)	0.38	2.3 (1.3–4.3)	3.4 (1.0–5.6)	0.028
IL-6, pg/ml	1.8 (1.3–3.3)	2.7 (1.7–4.2)	0.004	2.2 (1.4–3.7)	2.4 (1.6–4.4)	0.20
TNF-α, pg/ml	1.5 (1.2–2.2)	2.0 (1.4–2.7)	0.005	1.5 (1.2–2.3)	2.1 (1.4–2.5)	0.032
statin treatment	78 (75)	65 (71)	0.51	102 (77)	41 (65)	0.055
statin dose,[a,b] mg	20 (20–40)	20 (20–40)	0.95	20 (20–40)	20 (20–40)	0.27
fibrate treatment	10 (10)	13 (14)	0.38	6 (5)	17 (27)	<0.0001
fibrate dose,[b] mg	200 (200–267)	215 (200–267)	0.46	200 (200–200)	215 (200–267)	0.44

Data are presented as median (interquartile range) or number (percentage). *P* values are given for differences between the groups.

a as an equivalent of simvastatin dose: atorvastatin and lovastatin doses were converted to equivalent simvastatin doses (simvastatin, 20 mg; equivalent to atorvastatin, 10 mg; and lovastatin, 40 mg)
b in patients receiving these drugs

For conversion factors, see **TABLE 1**

Abbreviations: HDL, high-density lipoprotein; TG, triglicerydes; others, see **TABLE 1**

and HOMA-IR index. Furthermore, resistin has been also implied as a biomarker of atherosclerosis and cardiovascular disease.[4,10,24]

In our analysis, lower resistin levels proved to be an independent predictor of higher total cholesterol concentrations. Additionally, we observed weak but statistically significant inverse correlations of resitin concentrations with LDL cholesterol and HDL cholesterol levels. Previous studies have provided conflicting results regarding the effect of resistin on total cholesterol and its fractions, with some studies demonstrating no such relationship and most (including studies conducted in type 2 diabetes patients) showing positive correlations of resistin levels with LDL and total cholesterol levels (contrary to the results of our study) and a negative correlation of resistin levels with HDL cholesterol levels.[10-12,23,24] It was suggested that resistin downregulates hepatic LDL-receptor expression leading to diminished LDL hepatic clearance and elevated serum LDL levels.[25] However, 2 large cross-sectional studies (a recently published study by Cabrera et al.[13] including 6637 adults, and a subsample of the Finnish Health 2000 Survey including 1508 subjects) demonstrated an inverse association of resistin concentrations with total cholesterol, LDL cholesterol, and HDL cholesterol levels in general population, even after adjustment for confounding factors—a finding largely consistent with the results of our study.[13,14] Another study, conducted in 65 diabetic patients and 134 obese normoglycemic subjects, yielded similar results showing inverse correlations of resistin levels with LDL cholesterol (in both subgroups) and with total cholesterol levels (in the normoglycemic subgroup).[26] Those observations were confirmed by the results of an experimental study in a rodent model: transgenic overexpression of resistin led to lower total cholesterol and HDL cholesterol concentrations compared with the control group.[27] While the association of higher resistin levels with lower HDL cholesterol concentrations can be explained by its ability to induce insulin resistance and is concordant with its positive correlation with triglyceride levels, as demonstrated in previous studies, it seems more difficult to elucidate the mechanism responsible for the association of resistin with lower total and LDL cholesterol concentrations.[12,13] It was hypothesized that the inverse association between resistin and serum cholesterol levels could be attributed to the resistin-dependent sequestration of serum cholesterol in macrophages.[13,28,29] Increased cholesterol uptake by macrophages would also promote their transformation into foam cells.[28,29] This would explain the association of higher resistin concentration with atherosclerosis, despite its negative correlation with total and LDL cholesterol.

Another possible explanation of the inverse relationship between resistin and cholesterol concentrations could be that cholesterol regulates resistin expression in adipose tissue. Jove et al.[30] demonstrated that a reduction in total and LDL cholesterol on fenofibrate treatment induced resistin synthesis, and reported a negative correlation between cholesterol and resistin mRNA levels in adipose tissue samples.

TABLE 3 Correlations of lipid parameters with indices of obesity and insulin resistance as well as with concentrations of adipokines and inflammatory markers

	TC	LDL	HDL	TG
BMI	$r = 0.071$ $P = 0.36$	$r = 0.106$ $P = 0.14$	$r = -0.119$ $P = 0.097$	$r = 0.184$ $P = 0.010$
HOMA-IR	$r = -0.003$ $P = 0.97$	$r = 0.005$ $P = 0.94$	$r = -0.211$ $P = 0.003$	$r = 0.247$ $P = 0.0005$
adipokines				
HMW adiponectin	$r = 0.038$ $P = 0.60$	$r = -0.006$ $P = 0.93$	$r = 0.368$ $P < 0.0001$	$r = -0.295$ $P < 0.0001$
leptin	$r = 0.084$ $P = 0.25$	$r = 0.020$ $P = 0.78$	$r = 0.095$ $P = 0.19$	$r = 0.127$ $P = 0.078$
resistin	$r = -0.212$ $P = 0.003$	$r = -0.171$ $P = 0.018$	$r = -0.151$ $P = 0.035$	$r = 0.002$ $P = 0.98$
inflammatory markers				
hsCRP	$r = 0.007$ $P = 0.92$	$r = 0.056$ $P = 0.44$	$r = -0.070$ $P = 0.33$	$r = 0.018$ $P = 0.80$
IL-6	$r = -0.148$ $P = 0.039$	$r = -0.091$ $P = 0.21$	$r = -0.156$ $P = 0.029$	$r = -0.002$ $P = 0.98$
TNF-α	$r = -0.046$ $P = 0.52$	$r = 0.019$ $P = 0.80$	$r = -0.166$ $P = 0.020$	$r = 0.046$ $P = 0.53$

Abbreviations: see TABLES 1 and 2

TABLE 4 Multivariate analyses of predictors of inadequate lipid control

Dependent variable	Explanatory variables	OR	95% CI	*P* value
TC ≥175 mg/dl	female sex	2.357	1.261–4.404	0.007
	resistin, per 1 ng/ml	0.887	0.796–0.989	0.032
	statin treatment	0.336	0.168–0.673	0.002
LDL cholesterol ≥100 mg/dl in patients without CAD; ≥70 mg/dl in patients with CAD	age, per 5 years	1.058	1.021–1.095	0.002
	statin dose, per 20 mg simvastatin[a]	0.980	0.965–0.995	0.009
HDL cholesterol ≤50 mg/dl in women; ≤40 mg/dl in men	female sex	4.198	2.111–8.349	<0.0001
	HOMA-IR, per 1	1.073	1.010–1.140	0.023
	HMW adiponectin, per 1 µg/ml	0.793	0.667–0.943	0.009
	TNF-α, per 1 pg/ml	1.769	1.279–2.446	0.0006
TG ≥150 mg/dl	age, per 5 years	0.968	0.930–1.007	0.103
	BMI, per 5 kg/m^2	1.026	0.959–1.098	0.454
	HOMA-IR, per 1	1.086	1.017–1.159	0.014
	HMW adiponectin, per 1 µg/ml	0.772	0.630–0.944	0.012
	statin treatment	0.467	0.222–0.979	0.044

a atorvastatin and lovastatin doses were converted to equivalent simvastatin doses (simvastatin, 20 mg; equivalent to atorvastatin, 10 mg; and lovastatin, 40 mg)

Conversion factors to SI units are as follows: for total, LDL, and HDL cholesterol, 0.0259; for triglycerides, 0.0113.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; OR, odds ratio; others, see TABLES 1 and 2

Adiponectin is a hormone most profusely released from adipose tissue in physiological conditions. It circulates in the blood as 3 oligomeric complexes including low-, medium-, and high-molecular-weight adiponectin, with the latter constituting approximately half of plasma adiponectin and its most biologically active form.[15] Its properties are opposite to those exerted by resistin, as adiponectin is an insulin-sensitizing, anti-inflammatory, and antiatherogenic adipokine.[15] There is evidence suggesting that adiponectin might contribute to longevity.[16] Serum adiponectin concentration is inversely associated with BMI, the amount of visceral adipose tissue and insulin resistance, and hypoadiponectinemia was shown to predict type 2 diabetes, coronary artery disease, and acute coronary syndromes.[4,15-18] As expected, in the studied group of type 2 diabetes patients, HMW adiponectin concentrations correlated negatively with BMI and HOMA-IR index. We also observed a trend towards an inverse correlation of HMW adiponectin levels with hsCRP concentrations.

In our study, lower HMW adiponectin concentrations were an independent risk factor of higher triglyceride and lower HDL cholesterol concentrations. A negative correlation of adiponectin concentrations with triglyceride levels and its positive correlation with HDL cholesterol concentrations have been reported previously.[16-18,31,32] However, so far few studies have demonstrated that HMW adiponectin is a predictor of HDL cholesterol and triglyceride concentrations irrespective of sensitivity towards insulin.[33] Insulin resistance is known to be associated with so called atherogenic dyslipidemia characterized by hypertriglyceridemia, low HDL cholesterol concentration, and the presence of small, dense LDL particles. It might be assumed that the association of adiponectin with lower triglyceride and higher HDL cholesterol concentrations is secondary to its insulin-sensitizing properties.[15,18] Nevertheless, in our study, higher HMW adiponectin concentrations remained an independent predictive factor of triglyceride and HDL cholesterol control even after adjustment for HOMA-IR. Thus, the observed effect of adiponectin on the lipid profile must have arisen from its other characteristics. A similar conclusion can be derived from the fact that an inverse relationship between adiponectin and triglyceride concentrations was also observed in studies conducted in type 1 diabetic patients.[34] Data from single studies suggest that insulin resistance and adiponectin affect different aspects of triglyceride metabolism: a lower HOMA-IR index is predominantly associated with lower hepatic very-low-density lipoprotein (VLDL) synthesis, while adiponectin itself increases skeletal muscle lipoprotein lipase activity and skeletal muscle VLDL-receptor expression and, consequently, accelerates triglyceride catabolism.[35,36] Thus, adiponectin may influence triglyceride metabolism both in a direct and indirect (ie, associated with its insulin-sensitizing properties) way. Recently, it has also been suggested that abdominal obesity, hypoadiponectinemia, and hypertriglyceridemia share the same genetic background, as all of these factors were associated with a single nucleotide polymorphism of the RNA-specific adenosine deaminase gene, previously reported to be related to human longevity.[37]

TABLE 5 Correlations of adipokines with body mass index, insulin resistance index, and inflammatory markers

	HMW adiponectin	Leptin	Resistin	HsCRP	IL-6	TNF-α
BMI	$r = -0.248$ $P = 0.0005$	$r = 0.440$ $P < 0.0001$	$r = 0.066$ $P = 0.36$	$r = 0.289$ $P < 0.0001$	$r = 0.088$ $P = 0.22$	$r = 0.014$ $P = 0.84$
HOMA-IR	$r = -0.349$ $P < 0.0001$	$r = 0.398$ $P < 0.0001$	$r = 0.030$ $P = 0.68$	$r = 0.207$ $P = 0.004$	$r = 0.252$ $P = 0.0004$	$r = 0.009$ $P = 0.90$
hsCRP	$r = -0.133$ $P = 0.065$	$r = 0.149$ $P = 0.038$	$r = 0.182$ $P = 0.011$	NA	NA	NA
IL-6	$r = -0.030$ $P = 0.68$	$r = 0.170$ $P = 0.017$	$r = 0.347$ $P < 0.0001$	NA	NA	NA
TNF-α	$r = 0.034$ $P = 0.64$	$r = 0.021$ $P = 0.77$	$r = 0.258$ $P = 0.0003$	NA	NA	NA

Abbreviations: NA, not available; others, see **TABLE 1**

Apart from secreting "classic" adipokines, adipose tissue is also known to release proinflammatory cytokines, including TNF-α and IL-6. In our study, higher TNF-α concentrations were an independent risk factor for inadequate HDL cholesterol control. Although in the logistic regression analysis, IL-6 did not prove to be a predictor of any of the lipid parameters, its concentration correlated inversely with both total cholesterol and HDL cholesterol levels. There could be several explanations of the observed relationships. Firstly, inflammation is known to play an important role in the development of insulin resistance, type 2 diabetes, metabolic syndrome, and atherogenic dyslipidemia.[1,38] However, this does not justify the inverse correlation between IL-6 and total cholesterol level. Secondly, hypocholesterolemia (including low concentrations of HDL cholesterol) is commonly observed in inflammatory diseases and might be related to a dose-dependent reduction in secretion of both apolipoprotein (apo)B and apoA1 under TNF-α and IL-6 treatment, which was demonstrated in experimental studies.[38,39] Furthermore, both TNF-α and IL-6 were shown to adversely influence reverse cholesterol transport—the main mechanism responsible for antiatherogenic HDL properties—by decreasing lecithin-cholesterol acyltransferase activity.[39] Additionally, TNF-α was suggested to affect HDL cholesterol metabolism on other levels, including its formation and catabolism: in experimental studies, TNF-α attenuated intestinal cholesterol efflux to apoA1 as well as substantially enhanced macrophage degradation of HDL.[40,41] On the other hand, the inverse association of HDL and TNF-α could arise from the anti-inflammatory properties of HDL, including the ability of HDL to inhibit TNF-α production.[42] Regardless of the underlying mechanism, clinical studies confirmed the inverse correlation of HDL with TNF-α level.[32,43] However, prospective interventional trials exploring the effects of anti-TNF-α therapy on serum lipid profile yielded conflicting results with some studies demonstrating an increase and others—a reduction in HDL concentration following anti-TNF-α treatment.[44-46]

Interestingly, in the study group, female sex proved to be a risk factor for inadequate total cholesterol and HDL cholesterol control. This could be partly due to higher HDL cholesterol treatment targets in women, which may become difficult to achieve in overweight postmenopausal women.[47] Secondly, our observation probably reflects less intensive statin treatment in women, who are generally considered to be at lower cardiovascular risk than men.[48] Some evidence suggests that women might indeed benefit less from statin treatment in primary prevention.[49] Furthermore, women seem to be at a considerably higher risk of type 2 diabetes while on statin therapy than men.[50] However, this should not discourage statin treatment nor the attempts to achieve target lipid profile in women already diagnosed with type 2 diabetes who, by definition, are burdened with high or very high global cardiovascular risk.[2]

The least frequently implemented criterion of lipid control in the study population was a reduction of LDL cholesterol levels, although according to the European Society of Cardiology, it is the primary target of lipid-lowering therapy in type 2 diabetes patients.[1,2] Almost three-quarters of the group were treated with statins but the target values of LDL cholesterol were only achieved in 43% of the patients, which indicates the choice of too weak statin preparations (with simvastatin prescribed to most patients and with no patients treated with rosuvastatin) and the use of too low doses of these drugs (with median daily doses of both simvastatin and atorvastatin of 20 mg). Indeed, a lower statin dose proved to be one of the two independent predictors of poor LDL control. The second risk factor was older age, suggesting a more cautious implementation of statin treatment in older patients, which might be attributed to an expected higher risk of adverse effects.[48]

Limitations of the study This study was a cross-sectional analysis conducted in a group of patients whose hypolipidemic treatment had been initiated before study enrollment and chosen at the discretion of the treating physicians. It might have been beneficial for the analysis to

include treatment-naive patients and assess both adipokine concentrations and lipid parameters before and after the initiation of hypolipidemic treatment. Secondly, a larger number of patients would have increased the statistical power of our analysis.

Conclusions Adipokines might affect serum lipid profile in a diverse manner, irrespective of insulin resistance. In the studied group of type 2 diabetes patients, lower HMW adiponectin concentrations proved to be a predictor of inadequate triglyceride and HDL cholesterol control; higher TNF-α, of inadequate HDL control; and lower resistin, of inadequate total cholesterol control. Women and older patients should be given more attention regarding the achievement of lipid treatment targets.

Contribution statement AK-C designed the analysis, conducted data research and interpretation, and wrote the manuscript. MPo, MR, AS, and ET conducted data research. MPe performed statistical analysis. AK performed laboratory tests. MPo, GO, and KJF designed the AVOCADO study. All authors reviewed the manuscript and approved its final version.

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ARTYKUŁ ORYGINALNY

Związek adipokin i wykładników stanu zapalnego z wyrównaniem gospodarki lipidowej w cukrzycy typu 2

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SŁOWA KLUCZOWE

adiponektyna, cholesterol, czynnik martwicy nowotworu α, rezystyna, triglicerydy

STRESZCZENIE

WPROWADZENIE Dostępne dane dotyczące wpływu adipokin na gospodarkę lipidową są niejednoznaczne.
CELE Celem badania była ocena zależności między wyrównaniem gospodarki lipidowej a stężeniami adipokin i wykładników stanu zapalnego u chorych na cukrzycę typu 2.
PACJENCI I METODY Analizą objęto 195 pacjentów z cukrzycą typu 2. Ocenę uzyskania docelowych stężeń cholesterolu całkowitego, cholesterolu frakcji lipoprotein o niskiej gęstości (*low-density lipoprotein* – LDL) oraz o wysokiej gęstości (*high-density lipoprotein* – HDL) i triglicerydów przeprowadzono w oparciu o obecnie obowiązujące wytyczne. U wszystkich pacjentów dokonano oceny wskaźnika insulinooporności (Homeostatic Model Assessment–Insulin Resistance – HOMA-IR) oraz pomiaru stężeń adiponektyny wielkocząsteczkowej (*high-molecular-weight* – HMW), leptyny, rezystyny, białka C-reaktywnego, interleukiny 6 i czynnika martwicy nowotworu α (*tumor necrosis factor* α – TNF-α). W celu identyfikacji czynników ryzyka braku wyrównania gospodarki lipidowej przeprowadzono analizę regresji logistycznej.
WYNIKI Wyrównanie gospodarki lipidowej w zakresie cholesterolu całkowitego, cholesterolu LDL, cholesterolu HDL i triglicerydów uzyskano odpowiednio u 61%, 43%, 53% i 68% pacjentów. W analizach wieloczynnikowych płeć żeńska, niższe stężenie rezystyny i brak leczenia statyną były predyktorami stężeń cholesterolu całkowitego powyżej celu terapeutycznego; starszy wiek i niższa dawka statyny – predyktorami stężeń cholesterolu LDL powyżej celów terapeutycznych; płeć żeńska, wyższy wskaźnik HOMA-IR, niższe stężenie adiponektyny HMW i wyższe stężenie TNF-α – predyktorami stężeń cholesterolu HDL poniżej celów terapeutycznych, a wyższy wskaźnik HOMA-IR, niższe stężenie adiponektyny HMW i brak leczenia statyną – predyktorami stężeń triglicerydów powyżej celu terapeutycznego.
WNIOSKI U pacjentów z cukrzycą typu 2 niższe stężenie adiponektyny HMW wiąże się z nieoptymalną kontrolą stężeń triglicerydów i cholesterolu HDL, wyższe stężenie TNF-α – z nieoptymalną kontrolą stężeń cholesterolu HDL, a niższe stężenia rezystyny – z nieoptymalną kontrolą stężeń cholesterolu całkowitego.

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