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Elevation of plasma retinol-binding protein 4 and reduction of plasma adiponectin in subjects with cerebral infarction

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Abstract

The present study was undertaken to determine plasma retinol-binding protein 4 (RBP4) and adiponectin levels in subjects with cerebral infarction. Fifty-eight subjects with cerebral infarction and 53 age- and sex-matched control subjects were enrolled. Plasma RBP4, adiponectin, and high–molecular-weight adiponectin were measured by the method of enzyme-linked immunosorbent assay. Plasma RBP4 was 16.4 ± 2.8 μg/mL in the subjects with cerebral infarction, a value significantly greater than that of 10.1 ± 1.2 μg/mL in the controls (P = .044). Inversely, plasma adiponectin was significantly less in the subjects with cerebral infarction than the control subjects (8.1 ± 0.8 vs 10.8 ± 0.7 μg/mL, P = .015). However, there was no difference in plasma high–molecular-weight adiponectin between the 2 groups of subjects. In the control subjects, there were negative correlations between plasma RBP4 and adiponectin and between plasma RBP4 and high–molecular-weight adiponectin levels; and they totally disappeared in the subjects with cerebral infarction. The multiple regression analysis showed that adiponectin and hypertension were independent factors contributing to cerebral infarction (P < .001). These findings indicate that hypoadiponectinemia is concomitantly involved in the pathogenesis of atherosclerosis, and that an elevation of plasma RBP4 may be a useful marker for the development of atherosclerosis, in subjects with cerebral infarction.

1. Introduction

Retinol-binding protein 4 (RBP4) is synthesized by adipose tissues and hepatocytes [1]. Circulating RBP4 binds to retinol and delivers it to the tissues [2]. It is reported that plasma RBP4 is increased in subjects with obesity, impaired glucose tolerance, and diabetes mellitus [3-7]. Retinol-binding protein 4 increases insulin resistance by inhibiting insulin signaling in muscles and increasing hepatic glucose output. It binds to the large transthyretin homotetramer, and alterations in RBP4-transthyretin binding contribute to elevated plasma RBP4 levels in insulin-resistant states [8]. However, there are controversial reports regarding insulin resistance because other studies did not support the relation of RBP4 with insulin resistance [9-14]. Furthermore, adiponectin is synthesized in adipose tissues [15]. Plasma adiponectin levels vary in several pathologic states; that is, plasma adiponectin decreases in pathologic conditions of obesity, hypertension, diabetes mellitus, and dyslipidemia. In addition, hypoadiponectinemia is related to insulin resistance [16] and further to atherosclerotic disorders including myocardial infarction, cerebral infarction, and arteriosclerosis obliterans [17-22]. Therefore, adiponectin plays a role in a cluster of these common disorders linked to metabolic syndrome.

Cerebral infarction is a major disorder of atherosclerosis in Japan [23,24]. Metabolic syndrome has a common risk factor for cerebral infarction. We previously showed hypoadiponectinemia in subjects with cerebral infarction [17]. However, it is not known whether plasma RBP4 levels change in pathologic states of atherosclerotic disorders, although RBP4 could be related with insulin resistance.

In the present study, we determined plasma RBP4, adiponectin, and high–molecular-weight adiponectin in subjects with cerebral infarction. Furthermore, we analyzed

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any correlation of plasma RBP4 and adiponectin with varying factors in the subjects with cerebral infarction.

2. Subjects and methods

2.1. Subjects

Fifty-eight consecutive subjects with cerebral infarction and 53 age- and sex-matched control subjects were enrolled between April 2004 and March 2007 in Jichi Medical University Saitama Medical Center and Chichibu Municipal Hospital. The subjects with cerebral infarction were 35 men and 23 women, with a mean age of 65.5 ± 10.0 years (range, 35-82 years). Forty-two subjects had been admitted to the hospital because of acute onset of stroke, and 16 subjects had subacute (more than 48 hours from onset) cerebral infarction. Sixteen subjects had lacunar infarction; 42 had atherosclerotic infarction. The subjects with cerebral embolism were excluded. The diagnosis of cerebral infarction came from the abnormality of neurologic findings and was confirmed by computed tomography or diffusion-weighted magnetic resonance imaging. In the subjects with cerebral infarction, 31 subjects had diabetes mellitus, 46 had hypertension, 28 had dyslipidemia, 11 had obesity, and 32 had a smoking habit. Fifty-three control subjects were collected from the subjects who aimed to check their medical status in the outpatient clinic. They were 32 men and 21 women, with a mean age of 65.6 ± 18.1 years (range, 26-89 years). In the control subjects, 19 subjects had diabetes mellitus, 23 had hypertension, 19 had dyslipidemia, 11 had obesity, and 21 had a smoking behavior. All the 53 control subjects had no historical cerebral events. Subjects with advanced renal impairment (serum creatinine >2 mg/dL) and taking synthetic peroxisome proliferator–activated receptor γ ligands were excluded. Blood collections were made from the subjects in the supine position after an overnight fast to determine fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, plasma adiponectin, tumor necrosis factor (TNF) α, and RBP4 levels at the time of hospitalization or visit to the outpatient clinic. In the subjects with acute onset of cerebral infarction, blood samples were collected a day after the hospitalization. Risk factors for atherosclerosis were defined as follows: *Diabetes mellitus* was defined as a fasting plasma glucose level of greater than 126 mg/dL and a 2-hour postprandial glucose of more than 200 mg/dL, according to the criteria of the World Health Organization. *Dyslipidemia* was defined as a total cholesterol concentration of greater than 220 mg/dL, an HDL-C of less than 40 mg/dL, and a triglyceride level of more than 150 mg/dL, or the subjects' having either statin or fibrate. *Hypertension* was defined as systolic blood pressure of greater than 140 mm Hg, diastolic blood pressure of greater than 90 mm Hg, or the subjects' having taken antihypertensive agents. The present study was approved by the ethical committee of Jichi Medical University and Chichibu Municipal Hospital for human studies. We obtained informed consent from the subjects who joined the present protocol.

2.2. Measurements

Blood samples were collected into chilled tubes containing EDTA-Na_2 (1 mg/mL blood) and centrifuged at 3000 rpm at 4°C for 15 minutes. The supernatants were decanted and frozen at −80°C until assayed. Adiponectin was measured by enzyme-linked immunosorbent assay (ELISA) using Adiponectin ELISA kits (Otsuka Pharmaceutical, Osaka, Japan), and high–molecular-weight adiponectin was measured using high–molecular-weight adiponectin ELISA kits (Fuji Rebio, Tokyo, Japan). Intraassay and interassay coefficients of variation for Adiponectin ELISA kits were both less than 10%, respectively. Furthermore, intraassay and interassay coefficients of variation for high–molecular-weight Adiponectin ELISA kits were both less than 10%, respectively. Tumor necrosis factor α was determined by ELISA using TNFα ELISA kits (BioSource International, Camarillo, CA). Intraassay and interassay coefficients of variation for TNFα ELISA kits were less than 6% and less than 8.5%, respectively. Retinol-binding protein 4 was determined by the method of ELISA using RBP4 ELISA kits (AdipoGen, Seoul, Korea). Intraassay and interassay coefficients of variation for RBP4 ELISA kits were less than 5% and less than 7%, respectively.

2.3. Statistical analysis

All values are expressed as mean ± SEM. The values were analyzed by Student *t* test. Categorical data were analyzed by the χ^2 test. Simple linear regression analysis was performed to calculate correlation coefficients. The distributions of fasting plasma glucose, systolic blood pressure, and plasma TNFα levels were skewed; and Mann-Whitney

Table 1
Clinical features of the subjects with cerebral infarction and the control subjects

	Control	Cerebral infarction	*P* value
Subjects, n	53	58	
Age, y	65.6 ± 2.5	65.5 ± 1.3	.966
Sex, M/F	32/21	35/23	.997
BMI, kg/m^2	22.8 ± 0.5	22.9 ± 0.4	.875
Diabetes mellitus, n (%)	19 (35.8)	31(53.4)	.069
Hypertension, n (%)	23 (43.4)	46 (79.3)	<.001
Dyslipidemia, n (%)	19(35.8)	28 (48.3)	.190
Obesity, n (%)	11(20.8)	11 (19.0)	.955
Total cholesterol (mg/dL)	181.5 ± 5.4	190.6 ± 5.6	.249
Triglyceride (mg/dL)	117.7 ± 6.1	115.3 ± 7.0	.792
HDL-C (mg/dL)	54.1 ± 1.7	48.5 ± 1.6	.020
LDL-C (mg/dL)	105.1 ± 5.2	117.7 ± 5.4	.097
Fasting plasma glucose (mg/dL)*	127.8 ± 6.4	133.0 ± 7.0	.649
Systolic blood pressure (mm Hg)*	138.0 ± 2.4	144.1 ± 3.3	.113
Diastolic blood pressure (mm Hg)	75.7 ± 1.4	80.6 ± 2.0	.046

* Variables were skewed, and Mann-Whitney *U* test was applied for analyses.

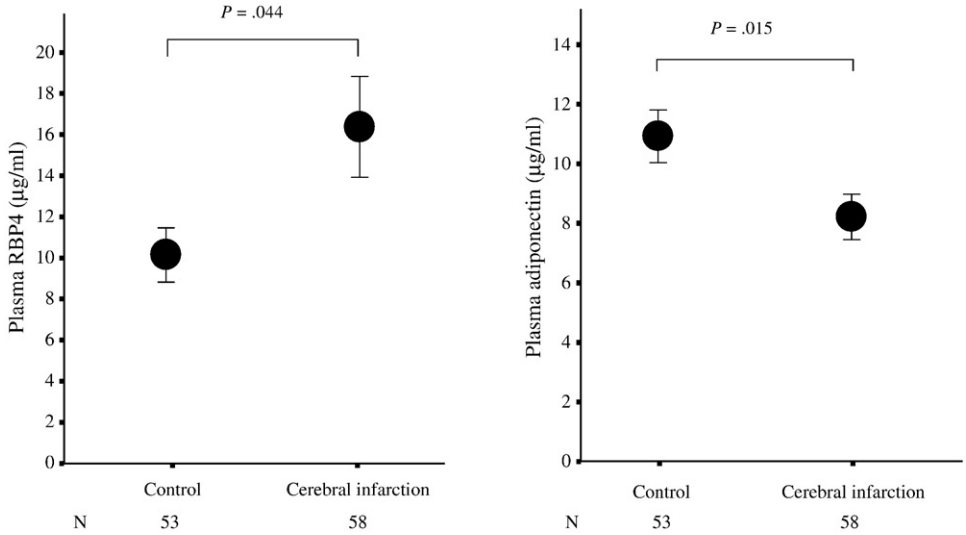

Fig. 1. Plasma RBP4 and adiponectin levels in the subjects with cerebral infarction and the control subjects.

U test was applied for analyses. Multiple regression analysis was applied to determine independent relation of clinical parameters with cerebral infarction. The Statistical Package of Social Science (SPSS for Windows, version 11.0; SPSS, Chicago, IL) was used for the present analysis. A *P* value less than .05 was considered significant.

3. Results

We compared clinical features in the 2 groups of subjects (Table 1). High-density lipoprotein cholesterol was significantly less and diastolic blood pressure was significantly higher in the subjects with cerebral infarction than in the control subjects. Otherwise, there was no difference in any parameter between the 2 groups of subjects. The prevalence of hypertension in the subjects with cerebral infarction was significantly greater than that in the control subjects.

Fig. 1 shows plasma RBP4 and adiponectin levels in the subjects with cerebral infarction and the control subjects. Plasma RBP4 level was 10.1 ± 1.2 μg/mL in the control subjects. Plasma RBP4 level of 16.4 ± 2.8 μg/mL in the subjects with cerebral infarction was significantly greater than that in the control subjects (*P* = .044). By contrast, the alteration in plasma adiponectin was totally inverse in the 2 groups of subjects. Namely, plasma adiponectin level was less in the subjects with cerebral infarction than in the control subjects (8.1 ± 0.8 vs 10.8 ± 0.7 μg/mL, *P* = .015). There was no difference in plasma high–molecular-weight adiponectin levels between the subjects with cerebral infarction and the control subjects (4.9 ± 0.5 vs 5.6 ± 0.4 μg/mL, *P* = .316). The hypertensive subjects with cerebral infarction had lower levels of plasma adiponectin than control subjects (7.4 ± 0.9 vs 10.8 ± 1.1 μg/mL, *P* = .028). However, in the nonhypertensive subjects, there was no difference in plasma adiponectin levels between subjects with cerebral infarction and controls (10.8 ± 1.4 vs 10.8 ± 1.0 μg/mL). In addition, plasma adiponectin and RBP4 levels were again analyzed because of sex difference [5,25]. As shown in Fig. 2, plasma adiponectin was significantly less in the female subjects with cerebral infarction than the female controls (*P* = .027). However, there was no significant difference in plasma

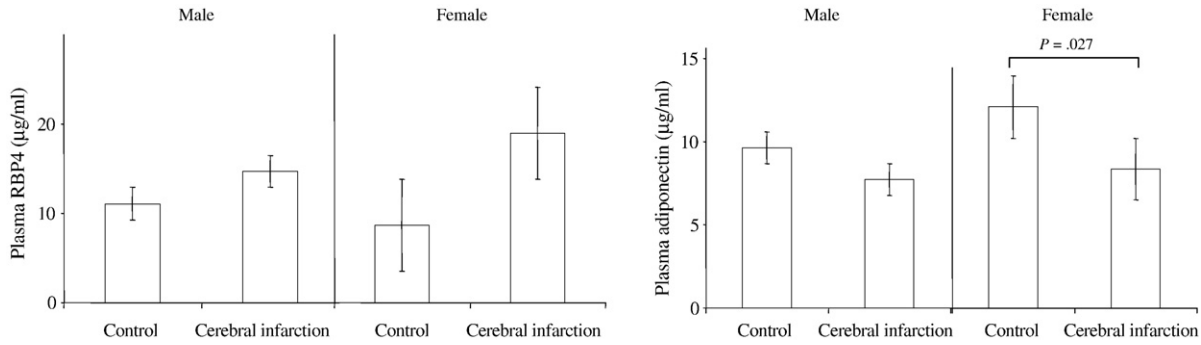

Fig. 2. Sex difference in plasma RBP4 and adiponectin levels in the subjects with cerebral infarction and the control subjects.

Table 2
Linear regression analysis of varying parameters in the subjects with cerebral infarction and the control subjects

	Control subjects		Cerebral infarction	
	r	*P* value	*r*	*P* value
vs BMI				
Age	0.132	.345	−0.216	.104
T-chol	0.322	.021	0.155	.253
TG	0.045	.753	0.156	.251
HDL-C	−0.191	.180	−0.431	.001
LDL-C	0.32	.022	0.246	.068
FPG	−0.074	.605	0.37	.004
SBP	0.232	.094	−0.077	.565
DBP	0.138	.323	0.098	.463
RBP4	0.366	.007	0.425	.001
HMW adiponectin	−0.374	.009	−0.326	.025
Total adiponectin	−0.472	<.001	−0.38	.003
TNFα	−0.234	.109	0.114	.462
vs RBP4				
Age	−0.174	.213	−0.053	.690
T-Chol	0.062	.664	−0.044	.749
TG	−0.085	.553	−0.039	.776
HDL-C	0.108	.450	−0.304	.023
LDL-C	0.018	.900	0.013	.924
FPG	0.144	.314	0.109	.417
SBP	−0.036	.799	−0.134	.315
DBP	0.168	.228	0.081	.546
HMW adiponectin	−0.344	.017	−0.026	.861
Total adiponectin	−0.363	.008	−0.094	.482
TNFα	−0.216	.140	0.075	.628

T-Chol indicates total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HMW, high molecular weight.

adiponectin levels in the male subjects. When the results were subgrouped by sex, there was no significant difference in plasma RBP4 between subjects with cerebral infarction and controls. There was no difference in plasma TNFα between subjects with cerebral infarction and controls (2.3 ± 0.2 vs 2.3 ± 0.3 pg/mL, not significant).

Table 2 shows the relationship of plasma RBP4 level and body mass index (BMI) with various variables in the subjects with cerebral infarction and the control subjects. In both groups of subjects, plasma RBP4 levels had a positive correlation, and plasma adiponectin and high–molecular-weight adiponectin had negative correlations, with BMI. Plasma RBP4 had negative correlations with plasma adiponectin and high–molecular-weight adiponectin levels in the control subjects ($P = .008$ and $P = .017$, respectively) (Fig. 3); however, they totally disappeared in the subjects with cerebral infarction. In addition, neither BMI nor plasma RBP4 levels correlated with plasma TNFα in both subjects with cerebral infarction and control subjects. Otherwise, in control subjects, total cholesterol and low-density-lipoprotein cholesterol (LDL-C) had negative correlations with BMI. In the subjects with cerebral infarction, HDL-C had negative correlation with BMI and plasma RBP4 levels. Fasting plasma glucose had a positive correlation with BMI.

In the multiple regression analysis, plasma adiponectin level and the presence of hypertension were independent factors for contributing to cerebral infarction (adiponectin: r=0.440, $P < .001$; hypertension: r=0.378, $P < .001$); but plasma RBP4 level was not.

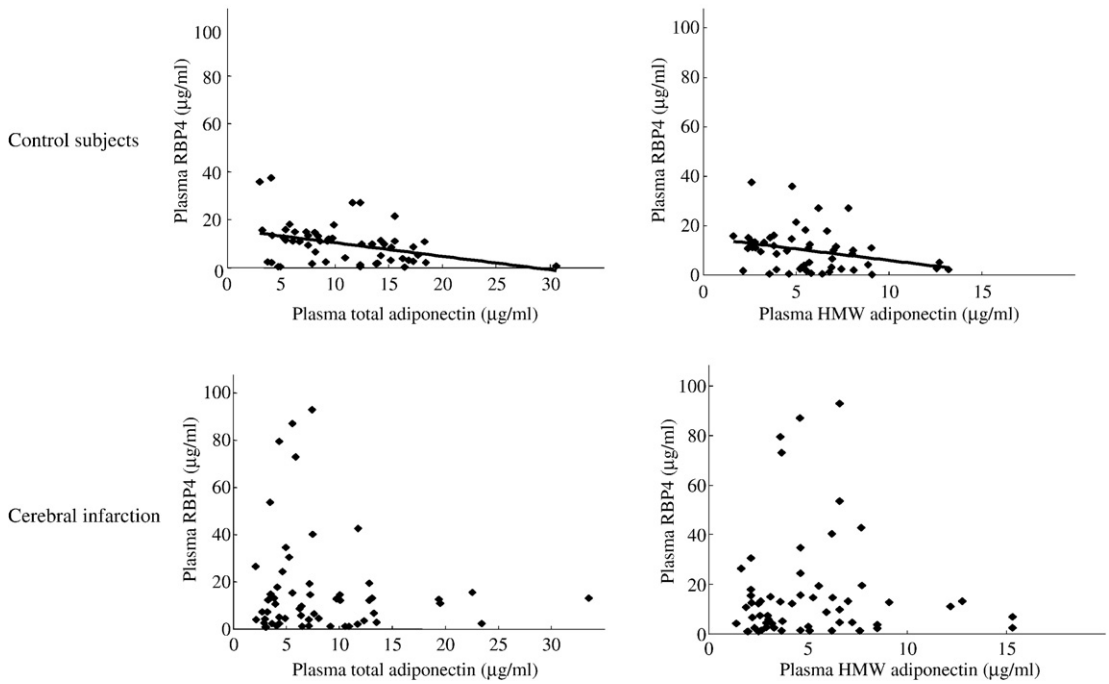

Fig. 3. Relationships of plasma RBP4 with plasma adiponectin and high–molecular-weight adiponectin levels in the control subjects and the subjects with cerebral infarction.

4. Discussion

The present study examined plasma RBP4 and adiponectin in subjects with cerebral infarction. Plasma RBP4 was significantly greater and, inversely, plasma adiponectin was less in subjects with cerebral infarction than in control subjects. Elevation in plasma RBP4 levels in cerebral infarction was initially found in the present study. The findings were basically similar in the individual male and female subgroups of the subjects with cerebral infarction and controls. In the enrollment of subjects, the prevalence of diabetes mellitus, hypertension, and dyslipidemia was somewhat different in the subjects with cerebral infarction and the controls. Namely, their prevalence was greater in the subjects with cerebral infarction than the control subjects. We could not totally rule out a possibility that control subjects might had old cerebral infarction or lacunae because magnetic resonance imaging examination was not carried out in all the control subjects. This is the limitation of the present study.

Retinol-binding protein 4 is the primary carrier for vitamin A (retinol) in plasma and is synthesized by hepatocytes. Its expression is also present in extrahepatic tissues, including skeletal muscles and white adipose tissues [1]. Retinol-binding protein 4 delivers retinol to tissues. Elevated circulatory RBP4 increases insulin resistance by inhibiting insulin signaling in muscular tissues and increasing hepatic glucose output [1]. Persistent insulin resistance may develop arteriosclerotic disorders, including ischemic heart disease, cerebrovascular diseases, and arteriosclerosis obliterans [26-29]. Negative correlations of plasma RBP4 levels with plasma adiponectin and high–molecular-weight adiponectin levels were obtained in the control subjects, but these correlations totally disappeared in the subjects with cerebral infarction. We further analyzed plasma adiponectin, high–molecular-weight adiponectin, and RBP4 by dividing into the degree of cerebral infarction, namely, lacunar state and atherosclerotic infarction. However, there were no differences between the 2 subgroups of cerebral infarction. This may indicate that elevation of plasma RBP4 levels is related with the development of atherosclerosis. As we specially focused on the relation of plasma RBP4 with atherosclerosis in the present study, we unfortunately did not measure serum insulin and thus could not evaluate insulin resistance directly. Further study will be necessary to elucidate the exact mechanism.

We have reported that plasma adiponectin levels are significantly reduced in subjects with cerebral infarction [17]. Besides, hypoadiponectinemia is also found in atherosclerotic disorders [18-20]. Adiponectin has various potential properties, such as anti-inflammatory effect, antidiabetic effect, and antiatherogenic effect [30,31]. Furthermore, adiponectin produces nitric oxide synthesis and angiogenesis [32,33]. As plasma adiponectin rapidly accumulates in the subendothelial space of the injured artery [34] and inhibits the atherogenic process [31,35-38], adiponectin could be accumulated into the obstructive artery and may result in hypoadiponectinemia. Basically, plasma adiponectin levels change in several pathologic states; that is, plasma adiponectin levels decrease in conditions of diabetes mellitus, hypertension, dyslipidemia, and obesity [16,39-43]. In the present study, hypoadiponectinemia was found in the hypertensive subjects with cerebral infarction, but not in the hypertensive controls. However, there was no difference in high–molecular-weight adiponectin between the subjects with cerebral infarction and the control subjects. In the present study, blood samplings were carried out after an overnight fast in the subjects with cerebral infarction, that is, a day after the hospitalization. Under the present design of blood collections, cerebral infarction itself may have affected plasma levels of RBP4 and adiponectin in the subjects with cerebral infarction. On the contrary, the alteration in plasma adiponectin levels seemed peculiar in the advanced impairment of kidney and heart. We demonstrated that plasma adiponectin levels are elevated in congestive heart failure and end-stage renal diseases [44,45], although atherosclerosis is fully developed.

In conclusion, the present study is the first report that demonstrated that plasma RBP4 levels were greater and, inversely, plasma adiponectin levels were less in the subjects with cerebral infarction than the control subjects. There were negative correlations of plasma RBP4 with plasma high–molecular-weight adiponectin and total adiponectin levels in the control subjects, but they totally disappeared in the subjects with cerebral infarction. These findings indicate that hypoadiponectinemia is concomitantly involved in the pathogenesis of atherosclerotic disorders, and that an elevation of plasma RBP4 may be a useful marker for the development of atherosclerosis, in subjects with cerebral infarction.

References

[1] Yang Q, Graham TE, Mody N, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005;436:356-62.
[2] Quadro L, Blaner WS, Salchow DJ, et al. Impaired retinal function and vitamin A availability in mice lacking retinol-binding protein. EMBO J 1999;18:4633-44.
[3] Graham TE, Yang Q, Blüher M, et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 2006;354:2552-63.
[4] Takebayashi K, Suetsugu M, Wakabayashi S, et al. Retinol binding protein–4 levels and clinical features of type 2 diabetes patients. J Clin Endocrinol Metab 2007;92:2712-9.
[5] Cho YM, Youn BS, Lee H, et al. Plasma retinol-binding protein-4 concentrations are elevated in human subjects with impaired glucose tolerance and type 2 diabetes. Diabetes Care 2006;29:2457-61.
[6] Qi Q, Yu Z, Ye X, et al. Elevated retinol-binding protein 4 levels are associated with metabolic syndrome in Chinese people. J Clin Endocrinol Metab 2007;92:4827-34.
[7] Janke J, Engeli S, Boschmann M, et al. Retinol-binding protein 4 in human obesity. Diabetes 2006;55:2805-10.
[8] Mody N, Graham T, Tsuji Y, et al. Decreased clearance of serum retinol binding protein and elevated levels of transthyretin in insulin-

resistant *ob*/*ob* mice. Am J Physiol Endocrinol Metab 2008;294: E785-93.
[9] Stefan N, Hennige AM, Staiger HE, et al. Circulating retinol-binding protein–4, insulin sensitivity, insulin secretion, and insulin disposition index in obese and nonobese subjects: response to Broch et al. Diabetes Care 2007;30:e91 [author reply e92].
[10] Promintzer M, Krebs M, Todoric J, et al. Insulin resistance is unrelated to circulating retinol binding protein and protein C inhibitor. J Clin Endocrinol Metab 2007;92:4306-12.
[11] Lewis JG, Shand BI, Elder PA, et al. Plasma retinol-binding protein is unlikely to be a useful marker of insulin resistance. Diabetes Res Clin Pract 2008;80:e13-5.
[12] Yao-Borengasser A, Varma V, Bodles AM, et al. Retinol binding protein 4 expression in humans: relationship to insulin resistance, inflammation, and response to pioglitazone. J Clin Endocrinol Metab 2007;92:2590-7.
[13] Bajzová M, Kovaciková M, Vitková M, et al. Retinol-binding protein 4 expression in visceral and subcutaneous fat in human obesity. Physiol Res 2009;57:927-34.
[14] von Eynatten M, Lepper PM, Liu D, et al. Retinol-binding protein 4 is associated with components of the metabolic syndrome, but not with insulin resistance, in men with type 2 diabetes or coronary artery disease. Diabetologia 2007;50:1930-7.
[15] Maeda K, Okubo K, Shimomura I, et al. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996; 221:286-9.
[16] Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
[17] Sasaki M, Kawano T, Saito T, et al. Hypoadiponectinemia in patients with cerebral infarction: comparison with other atherosclerotic disorders. Am J Med Sci 2007;333:140-4.
[18] Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
[19] Pischon T, Girman CJ, Hotamisligil GS, et al. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7.
[20] Kawano T, Saito T, Yasu T, et al. Close association of hypoadiponectinemia with arteriosclerosis obliterans and ischemic heart disease. Metabolism 2005;54:653-6.
[21] Chen MP, Tsai JC, Chung FM, et al. Hypoadiponectinemia is associated with ischemic cerebrovascular disease. Arterioscler Thromb Vasc Biol 2005;25:821-6.
[22] Efstathiou SP, Tsioulos DI, Tsiakou AG, et al. Plasma adiponectin levels and five-year survival after first-ever ischemic stroke. Stroke 2005;36:1915-9.
[23] Kubo M, Kiyohara Y, Kato I, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke 2003;34:2349-54.
[24] Kitamura A, Iso H, Iida M, et al. Trends in the incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994. Am J Med 2002;112:104-9.
[25] Nishizawa H, Shimomura I, Kishida K, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002;51:2734-41.
[26] Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective d\ata from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135-41.
[27] Hanley AJ, Williams K, Stern MP, et al. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177-84.
[28] Folsom AR, Rasmussen ML, Chambless LE, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Diabetes Care 1999;22:1077-83.
[29] Matsumoto K, Miyake S, Yano M, et al. Insulin resistance and arteriosclerosis obliterans in patients with NIDDM. Diabetes Care 1997;20:1738-43.
[30] Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 2000;102:1296-301.
[31] Ouchi N, Kihara S, Arita Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001;103:1057-63.
[32] Chen H, Montagnani M, Funahashi T, et al. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003;278:45021-6.
[33] Ouchi N, Kobayashi H, Kihara S, et al. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. J Biol Chem 2004;279: 1304-9.
[34] Okamoto Y, Arita Y, Nishida M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 2000;32:47-50.
[35] Ouchi N, Kihara S, Arita Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
[36] Arita Y, Kihara S, Ouchi N, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002;105:2893-8.
[37] Yokota T, Oritani K, Takahashi I, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000;96:1723-32.
[38] Matsuda M, Shimomura I, Sata M, et al. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002;277:37487-91.
[39] Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
[40] Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
[41] Duncan BB, Schmidt MI, Pankow JS, et al. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2004;53:2473-8.
[42] Kazumi T, Kawaguchi A, Sakai K, et al. Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. Diabetes Care 2002;25:971-6.
[43] Iwashima Y, Katsuya T, Ishikawa K, et al. Hypoadiponectinemia is an independent risk factor for hypertension. Hypertension 2004;43: 1318-23.
[44] Nakamura T, Funayama H, Kubo N, et al. Association of hyperadiponectinemia with severity of ventricular dysfunction in congestive heart failure. Circ J 2006;70:1557-62.
[45] Saito T, Saito O, Kawano T, et al. Elevation of serum adiponectin and CD146 levels in diabetic nephropathy. Diabetes Res Clin Pract 2007; 78:85-92.