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Plasma Adiponectin and Insulin Resistance in Korean Type 2 Diabetes Mellitus

Mi-Jin Kim[1], Kwang-Ha Yoo[1], Hyung-Suk Park[1], Sang-Man Chung[1], Choon-Jo Jin[1], Yoen Lee[2], Young-Goo Shin[2], and Choon-Hee Chung[2]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Konkuk University, Seoul, Korea;
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Wonju College of Medicine, Yonsei University, Wonju, Korea.

Insulin resistance, which implies impairment of insulin signaling in the target tissues, is a common cause of type 2 diabetes. Adipose tissue plays an important role in insulin resistance through the dysregulated production and secretion of adipose-derived proteins, including tumor necrosis factor-α, plasminogen activator inhibitor-1, leptin, resistin, angiotensinogen, and adiponectin. Adiponectin was estimated to be a protective adipocytokine against atherosclerosis, and also to have an anti-inflammatory effect. In this study, the relationship between fasting plasma adiponectin concentration and adiposity, body composition, insulin sensitivity (ITT, $HOMA_{IR}$, QUICK), lipid profile, fasting insulin concentration were examined in Korean type 2 diabetes. The difference in the adiponectin concentrations was also examined in diabetic and non-diabetic subjects, with adjustment for gender, age and body mass index. 102 type 2 diabetics and 50 controls were examined. After a 12-h overnight fast, all subjects underwent a 75gram oral glucose tolerance test. Baseline blood samples were drawn for the determinations of fasting plasma glucose, insulin, adiponectin, total cholesterol, triglyceride, LDL-cholesterol, and HDL-cholesterol. The body composition was estimated using a bioelectric impedance analyzer (Inbody 2.0). The insulin sensitivity was estimated using the insulin tolerance test (ITT), $HOMA_{IR}$ and QUICK methods. In the diabetic group, the fasting adiponectin concentrations were significantly lower in men than in women. They were negatively correlated with BMI (r=-0.453), hip circumference (r=-0.341), fasting glucose concentrations (r=-0.277) and $HOMA_{IR}$ (r=-0.233). In addition, they were positively correlated with systolic blood pressure (r=0.321) and HDL-cholesterol (r=0.291). The systolic blood pressure and HDL-cholesterol were found to be independent variables, from a multiple logistic regression analysis, which influenced the adiponectin concentration. Compared with the non-diabetic group, the adiponectin concentrations were significantly lower in the diabetic group, with the exception of obese males. In conclusion, the plasma adiponectin concentrations were closely related to the insulin resistance parameters in Korean type 2 diabetic patients.

Key Words: Diabetes mellitus, insulin resistance, adiponectin

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Reprint address: requests to Dr. Choon Hee Chung, Department of internal Medicine, Yonsei University, Wonju College of Medicine, 162 Ilsan-dong, Wonju, Kangwon-do, Korea. Tel: 82-33-761-0506, Fax: 82-33-731-5884, E-mail: cchung@wonju.yonsei.ac.kr

INTRODUCTION

Insulin resistance, which implies impairment of insulin signaling in the target tissues, is a common cause of type 2 diabetes. Adipose tissue plays an important role in insulin resistance through the secretion of adipose-derived proteins, including tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor-1, leptin, resistin, angiotensinogen and adiponectin.[1,2] Adiponectin was known as ACRP30, apM1, AdipoQ and GBP28. Recently, the plasma adiponectin levels were implicated in obesity and insulin resistance.[3-6] The plasma adiponectin concentrations were inversely correlated with fasting glucose, fasting insulin concentrations, triglyceride, and body mass index, but positively correlated with HDL-cholesterol.[7,8]

The role of adiponectin has been considered to have anti-inflammatory and anti-atherogenic effects. It accumulates in injured vessel walls, and dose-dependently inhibits the TNF-α signaling pathway in human aortic endothelial cells and reduces the TNF-α production in macrophages.[5,9]

The plasma adiponectin concentrations were decreased in obese and type 2 diabetic subjects and closely related to cerebro-vascular disease.[6,7] In this study, our intension was to observe the difference in the plasma adiponectin levels in diabetic and non-diabetic subjects, with adjustment for gender, age and body mass index. The relationship between fasting plasma adiponectin concentrations and insulin resistance parameters were also examined.

MATERIALS AND METHODS

Subjects

The subjects of this study were 102 type 2 diabetic and 50 control subjects with normoglycemic conditions. All subjects were ambulatory patients seen at the Won-ju Christian Hospital between October 2002 and January 2003. Diabetes was defined according to the diagnostic criteria recommended by ADA in 1997.

Anthropometric and biochemical measurement

All the subjects' heights, weights, and waist and hip circumferences were recorded, and their adiposity checked by a bioelectrical method (Inbody 2.0, Biospace®). The body mass index (BMI) was defined as weight (kg)/height (m^2).

A dietitian asked about their daily protein, carbohydrate and fat intakes using a Food Questionnaire. All subjects had their blood pressure measured. No subjects was using any antihypertensive, antihyperglycemic, or lipid-lowing drugs before the study evaluation. After 10 hours, all subjects were given a 75g oral glucose tolerance test (OGTT). The plasma insulin levels were measured with a radioimmunoassay kit (Linco Research Inc., Missouri, USA) and the plasma adiponectin levels an enzyme-linked immunosorbent assay by human adiponectin ELISA kit (B-Bridge International, Inc., San Jose, CA, USA). The intra and inter assay coefficients of variation for adiponectin were 4.6 and 3.2% respectively. The total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride were checked after 10 hours fasting.

Insulin resistance measurement

The insulin resistance was measured by the insulin tolerance test (ITT), $HOMA_{IR}$ (Homeostasis model assessment) and QUICK (Quantitative insulin sensitivity check).

Insulin tolerance test

After 12 hours fasting, all subjects were administrated a bolus of Humulin R® 0.1 units per kilogram into an antecubital vein, with blood sampled from a vein on the dorsum of the same hand. To arterialize the venous blood, the hand was placed in a water bath held at a constant temperature of 43℃ for 20 min prior to the start of the infusion and kept there until the end of the study. Sampling was carried out 0, 3, 6, 9, 12, and 15 minute after the insulin injection. After 15 minutes of sampling, the test was terminated by injection of glucose (20% D/W). Blood samples were analyzed for whole blood glucose using a Yellow Springs analyzer (YSI, Yellow Springs, OH, USA). Linear regression was used to estimate the slope of the decline in the log transformed blood glucose concentration. The slope was multiplied by -100 to derive the glucose disposal rate (Kitt). The Kitt was equivalent to the percentage decline in blood glucose per min, as calculated by the formula: $69.3/t_{1/2}$. Where $t_{1/2}$ was the time taken for the blood glucose to fall from a certain value at 3 minutes to half that value [Kitt(%/min)=0.693t1/2 × 100]. $HOMA_{IR}$ was applied to estimate the degree of insulin resistance [$HOMA_{IR}$=Insulin/$22.5e^{-In(glucose)}$]. QUICK[10] was applied to estimate the degree of insulin resistance [1/log(fasting insulin) + log(fasting glucose)], where the insulin and glucose were expressed in μU/mL and mmol/L, respectively.

Statistical analysis

All data were expressed as the mean ± SD. The SPSS 10.0 (Chicago, USA) programs were used for the statistical analyses. Differences in the means of the plasma adiponectin between the male and female groups were tested by the Mann-Whitney U test. Correlations of the adiponectin and metabolic parameters were calculated by Pearson's correlation method. Multiple linear regression

analyses were used to identify independent determinants of adiponectin. A significant level of 5% was chosen for all the tests (p value < 0.05).

RESULTS

Clinical data and basic laboratory parameters in diabetes

The height, weight, total body fat percent, fat mass, lean mass, waist circumference, and waist to hip ratio measurements and plasma adiponectin levels were significantly different between the male and female groups (Table 1).

Insulin resistance parameters in diabetes

There were no differences in the insulin tolerance test, HOMAIR, and QUICK between the male and female groups (Table 2).

Daily protein, carbohydrate and fat intake in diabetes

The daily protein, carbohydrate and fat intakes

Table 1. Clinical and Biochemical Characteristics in Diabetic Patients

	Total	Male	Female
Number	102	61	41
Age (year)	53.4 ± 12.1	51.3 ± 13.1	56.4 ± 9.8
Height (cm)	160.9 ± 10.3	160.7 ± 7.9	152.3 ± 7.3†
Weight (kg)	66.3 ± 11.9	69.5 ± 10.2	61.6 ± 12.9†
BMI (kg/m^2)	25.6 ± 3.5	25.1 ± 2.9	26.3 ± 4.2
Total body fat (%)	29.2 ± 7.9	26.0 ± 6.0	33.9 ± 8.1†
Fat mass (kg)	20.4 ± 7.2	19.0 ± 7.1	22.4 ± 6.9*
Lean mass (kg)	44.9 ± 10.8	49.1 ± 10.7	38.7 ± 7.7†
Waist (cm)	88.4 ± 8.4	86.8 ± 7.9	91.2 ± 8.6*
Hip (cm)	94.5 ± 7.3	94.0 ± 7.3	94.7 ± 7.3
Waist to hip ratio	0.93 ± 0.09	0.92 ± 0.08	0.97 ± 0.07*
Systolic BP (mmHg)	137.1 ± 20.5	135.8 ± 20.6	139.1 ± 20.4
Diastolic BP (mmHg)	81.7 ± 13.6	80.7 ± 13.2	83.0 ± 4.1
Fasting plasma glucose (mol/L)	11.1 ± 4.0	11.2 ± 4.6	10.3 ± 3.6
Fasting plasma insulin (mU/L)	6.7 ± 5.1	6.4 ± 5.2	7.1 ± 5.0
Adiponectin (μg/mL)	5.0 ± 3.7	4.5 ± 3.9	5.9 ± 3.2†
Total cholesterol (mmol/L)	5.3 ± 1.2	5.3 ± 1.0	5.4 ± 1.4
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.4	1.2 ± 0.3
LDL-cholesterol (mmol/L)	3.9 ± 1.3	4.0 ± 1.1	3.7 ± 1.4
Triglyceride (mmol/L)	4.9 ± 2.2	4.9 ± 2.9	4.7 ± 3.1
HbA1c (%)	9.8 ± 2.4	10.2 ± 2.3	9.3 ± 2.5

Data express mean ± SD.
BMI, Body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
* $p<0.05$ between male and female groups.
† $p<0.001$ between male and female groups.

Table 2. Insulin Resistance Parameters in Type 2 Diabetes

	Total	Male	Female
Kitt	2.17 ± 1.2	2.20 ± 1.2	2.14 ± 1.3
HOMAIR	3.26 ± 3.1	3.70 ± 3.6	2.72 ± 2.1
QUICKI	0.63 ± 0.3	0.63 ± 0.3	0.65 ± 0.2

Table 3. Daily Protein, Carbohydrate, and Fat Intakes of the Type 2 Diabetics

	Total	Male	Female
Protein (%)	14.5 ± 2.8	13.9 ± 2.7	15.0 ± 2.7*
Carbohydrate (%)	66.6 ± 8.5	66.8 ± 8.5	66.1 ± 8.7
Fat (%)	19.4 ± 7.8	19.8 ± 8.3	19.0 ± 7.1

*p<0.05 between male and female groups.

Table 4. Daily Protein, Carbohydrate and Fat Intakes of the Type 2 Diabetics in Relation to Obesity

	Male		Female	
	BMI < 25kg/m^3	BMI ≥ 25kg/m^3	BMI < 25kg/m^3	BMI ≥ 25kg/m^3
Protein (%)	14.1 ± 3.2	14.0 ± 2.6	14.7 ± 2.2	15.9 ± 2.6
Carbohydrate (%)	65.0 ± 9.1	66.2 ± 7.9	66.9 ± 6.0	64.9 ± 10.3
Fat (%)	21.0 ± 6.4	21.1 ± 10.0	18.6 ± 5.0	19.1 ± 8.5

in the diabetics were 14.5 ± 2.8, 66.6 ± 8.5 and 19.4 ± 7.8%, respectively (Table 3). Diabetic patients ate more carbohydrate than recommended by the 'Korea Diabetes Diet Guideline': 15 - 20% protein, 55 - 60% carbohydrate, and 20 - 25% fat.[11] There was no intake difference between the male and female groups, regardless of obesity (Table 4).

The daily protein intake was significantly correlated with $HOMA_{IR}$ (r=0.370, p < 0.001) and QUICK (r=-0.289, p < 0.05). Neither the daily carbohydrate nor fat intakes were significantly correlated with the Kitt, $HOMA_{IR}$ or QUICK, nor the daily protein, carbohydrate and fat intakes with the plasma adiponectin concentration.

Insulin resistance parameters and adiponectin

The Kitt value was highly correlated with the hemoglobin A1c (r=-0.404, p < 0.001), and correlated with the fasting glucose, hip circumference, and HDL-cholesterol. $HOMA_{IR}$ was highly correlated with QUICK (r=-0.594, p < 0.001), and correlated with the lean mass, daily protein intake, weight, height, age, plasma adiponectin concentration, body mass index and fat mass. QUICK was highly correlated with $HOMA_{IR}$ (r=-0.594, p < 0.001), fat mass (r=-0.447, p < 0.001), and waist circumference (r=-0.429, p < 0.001), and correlated with the body mass index, weight, hip circumference, daily protein intake, hemoglobin A1c, and lean mass.

Correlation of adiponectin and metabolic parameters in type 2 diabetes

The plasma adiponectin concentration was negatively correlated with the body mass index (r=-0.453, p < 0.001), hip circumference (r=-0.341, p < 0.001), fasting glucose (r=-0.277, p < 0.001) and $HOMA_{IR}$ (r=-0.233, p < 0.05), and positively correlated with the systolic blood pressure (r=0.321, p < 0.001) and HDL-cholesterol (r=0.291, p < 0.001).

In the multiple logistic regression analysis, the systolic blood pressure and HDL-cholesterol were

Table 5. Multiple Linear Regression Analysis for the Fasting Adiponectin Concentration, and the Anthropometric, and Metabolic Parameters in the Diabetics

Independent variable	Standardized coefficient(Beta)	t
Sex	0.311	1.582
Age	0.064	0.336
Weight	0.121	0.279
BMI	-0.244	-0.851
Lean mass	-0.111	-0.488
Waist	0.007	0.037
Hip	-0.013	-0.062
Systolic BP	0.297	2.081*
Fasting glucose	0.015	0.122
HDL-cholesterol	0.450	3.299*
HOMAIR	-0.127	-0.892
R^2	0.548	
F	3.526*	

Dependent variables: Fasting adiponectin concentration.
*$p < 0.05$.

significant independent variables for the plasma adiponectin concentration (Table 5).

Plasma adiponectin concentrations according to obesity

The plasma adiponectin concentration was significantly lowered in the diabetic group compared to the non diabetic group, with the exception for obese males, after adjustment for age, gender and BMI (Fig. 1).

DISCUSSION

Obesity is commonly associated with insulin resistance and hyperinsulinemia, and is a major risk factor in the development of type 2 diabetes and cardiovascular disease. Free fatty acids, derived from adipose tissue, have long been implicated in the development of these obesity-related complications.[12] TNF-α, which is also derived from adipose tissue, has direct effects on the insulin signaling cascade, and inhibits GLUT4 gene expression.[1,2,12,13] Plasminogen activator inhibitor type[1,11,14] interleukin 6[15] and complement 3[16] cause insulin resistance and diabetes related cardio-vascular complications.

Adiponectin is a 244-amino acid protein, with high structural homologies to collagen VIII, X and complement C1q[17-20] as well as TNF-α.[21] Although the physiological role of adiponectin remains to be fully determined, this protein accumulates in injured vessel walls, and dose-dependently inhibits TNF-α induced cell adhesion in human aortic endothelial cells.[5,8] Furthermore, adiponectin has recently been reported to have an inhibitory effect on the proliferation of myelomonocytic progenitors, as well as on the phagocytic activity and TNF-α production by macrophage.[22]

The plasma adiponectin levels were decreased in obese Caucasians[23] and Japanese[6,7] with type 2 diabetes. Recently, an intra venous injection of the c-terminus globular domain of the mouse homologue of adiponectin was demonstrated to reduce the plasma fatty acid levels and diet induced weight gain in mice.[24] This indicated that adiponectin may participate in fatty acid metabolism

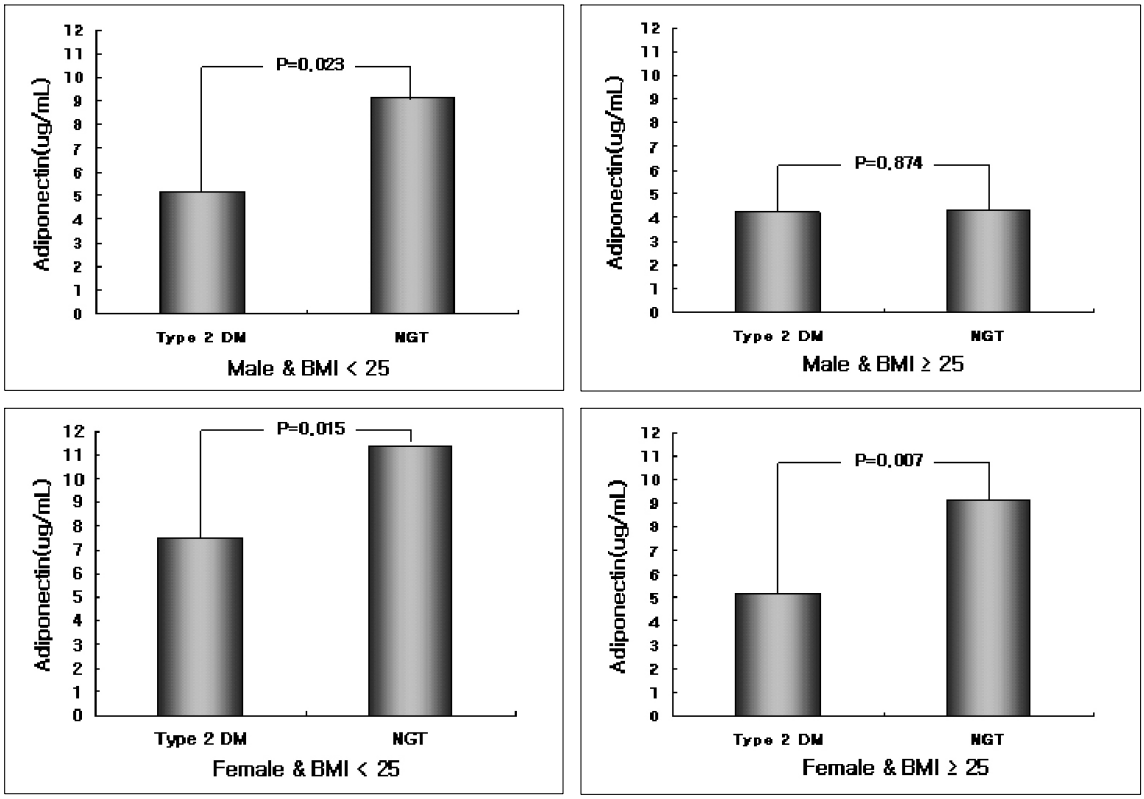

Fig. 1. Adiponectin concentration difference between diabetic and non-diabetic patients, with adjustment for age, gender and BMI.

and energy homeostasis.[24] Treatment of adiponectin increased muscle free fatty acid β-oxidation and decreased gluconeogenesis in the liver.[9,24,25] The plasma adiponectin level was found to be lower in obese human subjects.[9,19,26] In ob/ob mice, the steady state mRNA of adipoQ was also found to be down regulated.[19] The expression of adiponectin is considered to be activated during adipogenesis, but a feedback inhibition of its production may be imposed in the development of obesity. Yang et al.[26] reported a change in the plasma adiponectin levels with body weight reduction among 22 obese patients who received gastric portion surgery. A 46 percents increase in the mean plasma adiponectin levels was accompanied by a 21% reduction in the mean body mass index. As a result, the plasma triglyceride was significantly decreased and the insulin resistance recovered. They insisted that weight reduction of obese patients increased the adiponectin levels and has a protective effect against cardio-vascular disease and diabetes related complications.

Nishizawa et al.[27] indicated that androgens decreased the plasma adiponectin level and that androgen-induced hypoadiponectinemia may be related to a high risk of insulin resistance and atherosclerosis in men. In our study, the plasma adiponectin concentration was observed to be lowered further in men than in women (4.5 ± 3.9 vs. 5.9 ± 3.2μ/mL). Hypoadiponectinemia in men is thought to be partially responsible for the effect of androgen. However, the total body fat may affect the plasma adiponectin levels. So there is a need to carefully interpret only the androgen effects on hypoadiponectinemia in men.

DeFranzo et al.[28] reported that the hyperinsulinemic euglycemic clamp technique is currently regarded as the gold standard for measuring insulin sensitivity. However, this method requires a proficient technique and highly trained personnel. The insulin tolerance test (ITT) is a well known technique for measuring insulin resistance.[29-31] Park et al.[32] reported highly significant correlations between the Kitt value, which is

derived from the ITT and the M (kg/kg/min) or M/I (mg/kg/min/μU/mL × 100) derived from the hyperglycemic euglycemic clamp test. QUICK is also known as a reliable index of insulin sensitivity.[10]

In our study, neither Kitt, $HOMA_{IR}$, nor QUICK was significantly different between males and females. For the purpose of data accuracy, Kitt must be checked repeatedly. However, the Kitt value was not repeated checked in this study, which is a possible limitation of the data accuracy.

Our study showed that the hemoglobin A1c was correlated with Kitt, and inversely correlated with the fasting insulin concentrations, but not significantly. The body mass index, fat amount, and waist circumference were significantly correlated $HOMA_{IR}$ and QUICK, which were same results previously reported by Laaksonen.[33] Kitt was significantly correlated with fasting glucose and hemoglobin A1c; therefore, the fasting glucose and glucose control status were considered good parameters for insulin resistance measurements in this study.

Neither the daily protein, carbohydrate nor fat intakes was correlated with the plasma adiponectin concentrations. However, these intakes were affected by age, gender, diet habit and seasonal variation, so there is a limit to the interpretation. Separate studies found the adiponectin concentration in the plasma correlated negatively with the fasting insulin levels in Caucasian,[34] Pima Indian[34] and Japanese.[7] In addition, the plasma adiponectin levels was negatively correlated with the plasma triglyceride concentration as well as the fasting and postprandial plasma glucose concentration. Christian et al.[3] also reported that hypoadiponectinemia was correlated with hyperinsulinemia and insulin resistance. Berg et al.[25] showed that treatment of thiazolidinedione, a PPARγ agonist, to db/db mice increased the plasma adiponectin concentration and improved insulin resistance. In our study, the plasma adiponectin concentration was negatively correlated with the body mass index, hip circumference, fasting glucose and $HOMA_{IR}$, but was not significantly correlated with abdominal obesity, has represented by the waist circumference. Park et al.[35] reported that the serum adiponectin levels was inversely correlated with the subcutaneous adipose tissue area (SAT), visceral adipose tissue area (VAT), and waist to hip ratio (WHR). This study agrees with the result published by Yatagai et al.,[36] which showed that hypoadiponectinemia was associated with visceral fat accumulation. It seems likely that the discrepancies among this and several other studies may have resulted from the different degrees of obesity of subjects, as well as the difference in gender, degree of hyperglycemia, and duration of diabetes. Additional studies are necessary to elucidate the association the adiponectin concentration with the abdominal obesity determined by computed tomography.

The plasma adiponectin level was positively correlated with the HDL-cholesterol and systolic blood pressure. In multiple regression analyses, the systolic blood pressure and HDL-cholesterol were significant independent variables for adiponectin. The correlations between adiponectin and blood pressure was different from those of other studies. Hypoadiponectinemia has been reported in essential hypertensive patients.[37] However, Mallamari et al.[38] reported that hypertensive men had significantly higher plasma adiponectin levels than normotensive men. They explained that the hyperadiponectinemia in hypertensive men was likely due to the expression of high levels of essential hypertensives as a counter-regulatory response aimed at mitigating the endothelial damage and cardiovascular risk associated with high arterial pressure. The plasma adiponectin levels may be affected by arterial pressure, but may also be affected by total body fat, hormones and so on.

Adiponectin, derived from adipose tissue, was inversely correlated with the amount of body fat.[3,19,23] Furthermore, the adiponectin level was correlated with leptin resistance.[9] Both hyperleptinemia and leptin resistance inhibit adiponectin synthesis in the adipose tissue.[9] Miyao et al.[39] found an inversely correlation between the plasma adiponectin and leptin concentrations in both normal weight and obese women. The correlation between adiponectin and leptin was also reported by a recent genomic scan study, which revealed a linkage of the metabolic syndrome to both a region on chromosome 3q27, where the gene encoding adiponectin is located, and to regions on chromosome 17q12 that are strongly linked to the plasma leptin concentration.[20]

In this study, the adiponectin concentrations, in relation to the glucose levels, was lower in the diabetic than non-diabetic subjects, with the exception of obese males. Some of the obese male group with a high body mass index had only a little amount of fat. To obtain exact data, the total body fat as well as body mass index must be adjusted in future studies.

In conclusion, the plasma adiponectin concentration was closely related to the insulin resistance parameters in Korean type 2 diabetic patients, but further study will be needed to clarify the relationship between the adiponectin level and diabetes related complications.

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