Adiponectin Level Predicts HDL-Cholesterol Level in Type 2 Diabetes

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Abstract: *Background*: Atherosclerotic cardiovascular complications are the major causes of morbidity and mortality in Type 2 diabetic patients. Many studies have demonstrated that adiponectin has both anti-atherogenic and anti-diabetic properties. This study aims to examine the regulatory roles of serum adiponectin in a homogeneous Type 2 diabetic cohort.

Method: Of a population of 1256 registered diabetic patients, 116 subjects (1) aged between 40 and 70 years, (2) from the Chinese population, (3) having had Type 2 diabetes for more than one year, and (4) having been taking gliclazide and metformin for more than 6 months were enrolled in the study. All subjects were assigned to one of the plasma adiponectin level categories according to the quartiles. The main outcome evaluated is the associations of plasma adiponectin level; which were evaluated using multiple linear regression analysis.

Results: Adiponectin concentration was the only and main predictor of HDL-cholesterol level ($\beta = 0.321$, $p = 0.002$) after adjusting other factors for the homogeneous Type 2 diabetic subjects.

Conclusion: These initial findings seem to denote a positive association between adiponectin concentration and HDL-cholesterol level in Type 2 diabetes. Adiponectin concentration might be a valuable marker of artherosclerosis in Type 2 diabetic patients.

Keyword: Type 2 diabetes, Adiponectin, HDL-cholesterol, Atherosclerosis.

The risk of atherosclerotic cardiovascular disease in Type 2 diabetic patients is two to four folds higher than that in non-diabetic ones [1]. Atherosclerotic cardiovascular complications are among the major causes of morbidity and mortality in Type 2 diabetic patients [2]. This increased risk might be attributed to hyperglycemia, dyslipidemia, and inflammatory mechanism [3,4]. Monitoring a valuable marker on atherosclerotic pathogenesis and insulin resistance are desired and beneficial to these patients. Some related studies have been reported [5]. Adiponectin is a hormone produced in adipocytes, and appears to play a very important role in the above pathway [6-13]. HDL-cholesterol is known to have help prevent the development of atherosclerotic cardiovascular complications. We hypothesized that a strong association between adiponectin concentration and HDL-cholesterol level might exist in homogeneous Type 2 diabetic patients after adjusting the other factors. This study aims to examine the regulatory roles of serum adiponectin level in a homogeneous Type 2 diabetic cohort.

METHOD

Study Population

The trial was conducted from July 2005 through June 2006 in Taipei Hospital, Taiwan County, Taiwan. A total of 1256 registered diabetic patients were screened, among which 136 met the inclusion /exclusion criteria (Table **1**). A letter explaining the purpose of the study were sent to the 136 patients inviting their participation, and 116 accepted the invitation and were enrolled with informed consent. The protocol was approved by the Human Ethics Committee of Taipei Hospital.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
(1) Age between 40 and 70 years
(2) From Chinese population
(3) Having Type 2 diabetes for more than 1 year
(4) Taking gliclazide and metformin for more than 6 months
Exclusion Criteria
(1) AST, ALT > 80 U/L, serum creatinine > 2.0 mg/dl
(2) Breast feeding or pregnant women
(3) Heart failure, AMI stroke and serious injuries
(4) Any other conditions not suitable for trial as evaluated by the physician.

Abbreviations: AST: Alanine Aminotransferase; ALT: Aspartate Aminotransferase.

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Assessment

The main outcome evaluated is the associations of plasma adiponectin level; which were evaluated using multiple linear regression analysis. All subjects were assigned to one of the plasma adiponectin level categories according to the quartiles: quartile 1 (< 25%), quartile 2 (25-49%), quartile 3 (50-75%) and quartile 4 (> 75%) for further assessment and comparison. Measurements such as blood pressure, BMI, fasting glucose, hemoglobulin A_{1c} % (HbA_{1c}), insulin, and plasma lipoproteins (triglyceride, cholesterol, HDL-cholesterol (HDL) and LDL-cholesterol (LDL) were analyzed. All measurements were done using standardized methods between 0800-0900 after an overnight fast. Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm, waist circumference (WC) was measured mid-way between the lateral lower rib margin and the iliac crest to the nearest 0.1 cm, weight was measured on a calibrated balance beam scale to the nearest 0.1 kg, and BMI was calculated (BMI = body weight (BW)/height (kg/m^2)). A mercury sphygmomanometer with standard cuff was employed to measure the indirect auscultatory arterial blood pressure taken from the right arm with subjects in seated position.

Analysis of Blood Samples

A sample of whole blood was drawn and centrifuged at 4°C, and a 1 ml aliquot of serum was rapidly frozen (-80°C) for subsequent hormone analysis. The plasma leptin and adiponectin concentration was measured with a human leptin and adiponectin RIA assay (Linco Research, Inc, St. Charles, MO, USA). The limit of sensitivity is 0.5 ng/ml. There is no cross-reactivity with human insulin and pro-insulin. Plasma insulin levels were measured using a commercially available RIA (Linco Research, Inc). Fasting glucose, HbA1c, cholesterol, triglyceride, LDL and HDL were performed at the clinical laboratories at the hospital and analyzed.

Statistical Analysis

One-way analysis of variance (ANOVA) and linear trend test were employed to evaluate the trend among the plasma adiponectin level quartile groups. Chi-square test was used for gender (male/female) comparison. Multiple linear regression analysis with stepwise method was applied to adiponectin concentrations. All *p* values were two-tailed and

Table 2. Comparison of Characteristics Among Quartiles of Adiponectin

Variable	Quartiles of Adiponectin				P for Trend
	1 Mean (SD)	2 Mean (SD)	3 Mean (SD)	4 Mean (SD)	
Adiponectin, μg/ml	9.3 (1.3)	13.2 (1.3)	17.2 (1.4)	25.7 (5.3)	
Basic Data					
Male/Female	16/13	10/19	13/16	10/19	0.21
Age, year	55.8 (6.1)	55.2 (8.9)	56.9 (7.6)	57.1 (6.9)	0.85
G, mg/day	179.3 (46.1)	171.0 (51.2)	168.3 (32.7)	179.3 (40.9)	0.94
M, mg/day	1722.4 (665.2)	1731.0 (629.1)	1563.8 (595.1)	1763.8 (517.9)	0.93
BMI, kg/m^2	26.2 (3.0)	27.5 (5.2)	25.7 (3.1)	25.4 (4.9)	0.23
WC, cm	88.1 (7.5)	87.7 (11.2)	85.4 (8.1)	84.7 (12.7)	0.14
SBP, mmHg	137.8 (15.2)	129.6 (15.4)	134.2 (16.7)	139.5 (17.8)	0.48
DBP, mmHg	82.8 (8.8)	76.8 (9.7)	80.4 (10.6)	82.1 (10.5)	0.86
Fasting Serum Factors					
Glucose, mg/dl	199.6 (48.4)	185.3 (57.1)	198.3 (49.9)	208.6 (63.0)	0.38
HbA_{1c},%	9.3 (1.5)	9.2 (1.7)	9.3 (1.6)	9.3 (2.0)	0.92
Insulin, IU/ml	11.9 (8.0)	13.2 (12.8)	8.9 (5.6)	7.0 (4.1)	0.03
Leptin, ng /ml	6.0 (3.9)	7.3 (4.2)	6.7 (3.6)	7.3 (5.5)	0.62
AST, IU/L	23.7 (11.5)	26.1 (8.7)	28.0 (12.6)	22.9 (9.7)	0.97
ALT, IU/L	29.3 (15.3)	37.9 (17.3)	34.0 (33.1)	28.0 (16.8)	0.66
Creatinine, mg/dl	0.9 (0.2)	0.8 (0.3)	0.9 (0.3)	0.9 (0.4)	0.46
Triglyceride, mg/dl	219 (229)	239 (451)	167 (121)	128 (81)	0.12
Cholesterol, mg/dl	175 (42)	182 (45)	171 (631)	178 (37)	0.99
HDL, mg/dl	40 (9)	43 (7)	43 (9)	48 (11)	0.01
LDL, mg/dl	106 (32)	113 (33)	105 (32)	114 (30)	0.63

Abbreviation BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL: HDL-cholesterol; LDL: LDL-cholesterol; G: gliclazide, M: metformin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

α level of significance was set at 0.05. The data were analyzed with SPSS software (version11.5).

RESULTS

Demographics

Among the 1256 screened patients, 136 met the inclusion criteria, of which 116 (85.3%) agreed to participate. There are 49 men (age 55.3 ± 8.0 years) and 67 women (age 56.8 ± 6.9 years). There are no significant gender difference in means of age, BMI, WC, blood pressure, fasting glucose, lipid profile, insulin, HOMA-IR, aminotransferases alanine, aminotransferases aspartate and creatinine. Female have significiantly higher leptin level than male (8.2(3.9) ng/ml; 4.4(2.3) ng/ml; $p < 0.001$).

Measurements Among Plasma Adiponectin Level Quartile Categories

Table **2** shows the comparison of characteristics among quartiles of adiponectin categories. Results of linear trend test show significant statistical difference in insulin level and HDL-cholesterol level ($p = 0.03$, $p = 0.01$) but not in other characteristics among quartiles of adiponectin levels.

Coefficiences of Linear Multiple Regression on Adiponectin Level

Table **3** shows the coefficients of linear multiple regression on adiponectin level using stepwise method. Adiponectin concentration was the main predictor of HDL-cholesterol level ($\beta = 0.321$, $p = 0.002$) in all Type 2 diabetic subjects. Fig. (**1**) shows the relationship **(Scatter)** of HDL-cholesterol level and adiponectin concentration in this Type 2 diabetic cohort.

DISCUSSION

Previous studies have shown that adiponectin levels are significantly lower in Type 2 diabetic patients [14]. Circulating adiponectin levels and adiponectin gene expression in adipose tissues are also found to be lower in such patients [15, 16]. Adiponectin levels are positively correlated with insulin sensitivity and negatively correlated with fasting insulin concentrations [17]. Insulin levels and sensitivity play very important roles in regulating adiponectin concentration. However, related studies conducted on homogeneous Type 2 diabetic cohorts have been scarce. Our previous study showed the level of insulin is the main predictor of leptin level [18].

Previous research has also revealed that plasma adiponectin concentration in Type 2 diabetes might be changed by taking oral antidiabetic drugs [19-23]. To understand the regulatory roles of plasma adiponectin level in a homogeneous diabetic cohort, we conducted this study on Chinese adult subjects who have had Type 2 diabetes for more than one year, have been taking gliclazide and metformin for more than six months, and are aged 40-70 years. Subjects with abnormal renal, liver function impairment, prolaction or pregnancy, heart failure, stroke and heavy injuries were excluded to avoid the possible bias or confounder. We attempted to examine the regulatory roles of serum adiponectin level in a homogeneous Type 2 diabetic cohort. We hypothesized that there would be a strong association between adiponectin concentration and HDL-cholesterol level among our subjects after adjusting the other factors.

Table 3 .Multiple Regression Analysis of Serum Adiponectin Level Using Stepwise Method

	β	p
Factors		
Gender (male = 1 / female = 0)	-0.08	0.44
Family history of Type 2 DM (yes = 1 / no = 0)	-0.09	0.40
Basic data		
Age	0.05	0.64
Body mass index	-0.11	0.31
Waist circumference	-0.11	0.31
Systolic blood pressure	0.09	0.40
Diastolic blood pressure	0.07	0.48
Fasting serum factors		
Glucose	0.16	0.13
HbA_{1c}	0.11	0.30
Insulin	-0.15	0.15
Leptin	0.14	0.17
Creatinine	0.11	0.30
Alanine Aminotransferase	0.01	0.95
Aspartate Aminotransferase	-0.07	0.53
Fasting triglycerides	-0.08	0.47
Fasting cholesterol	-0.04	0.72
HDL-cholesterol	0.321	0.002
LDL-cholesterol	0.01	0.93

Results of linear trend test shown in Table **2** reveal significant difference in insulin level and HDL-cholesterol level ($p = 0.03$, $p = 0.01$). Subjects with the greatest plasma adiponectin concentration also had the highest plasma HDL-cholesterol levels but lowest insulin levels. However, there was no statistical difference in other characteristics among quartiles of adiponectin levels. Our data recomfirmed that the adiponectin levels are negatively correlated with fasting insulin concentrations but positively correlated with HDL-cholesterol level, which have been reported in other non-homogeneous Type 2 diabetic cohorts [17, 24-29]. The study by Zietz *et al.,* also showed similar results; adiponectin represented an independent cardiovascular risk factor predicting serum HDL-cholesterol levels in type 2 diabetes [30]. Our research showed the detail comparisons, related variable and a homogenous 40-70 years type 2 diabetes cohort.

We also observed that adiponectin concentration was the only and main predictor of HDL-cholesterol level after adjusting other factors for homogeneous Type 2 diabetic subjects. In multiple regression analysis using stepwise

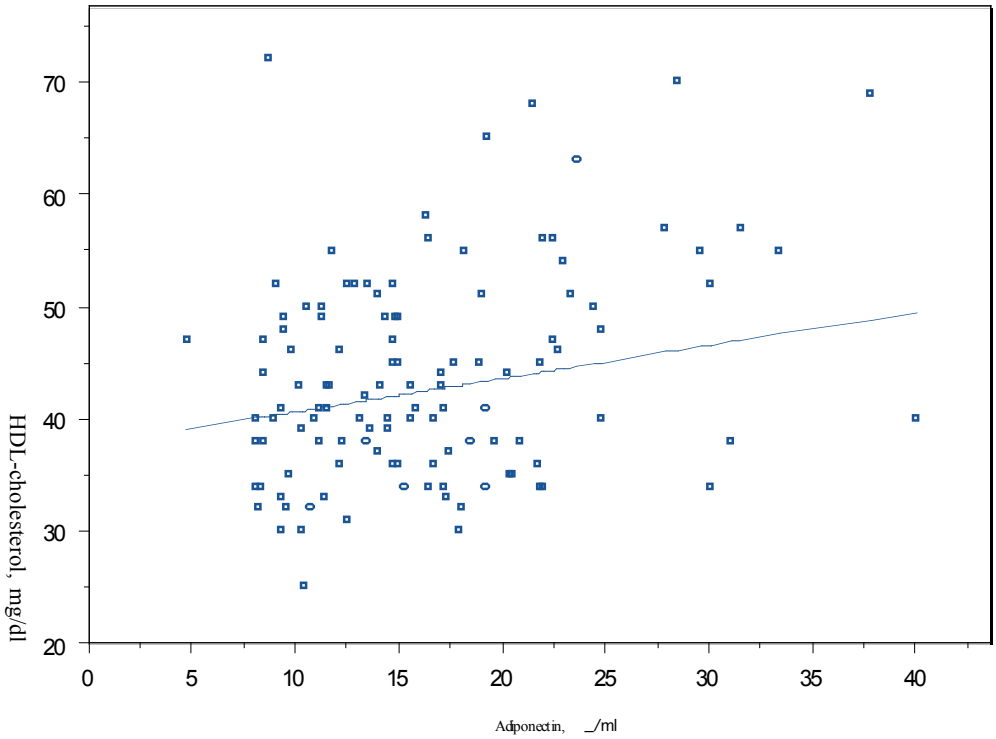

Fig. (1). Relationship (scatter) between HDL-cholesterol level and adiponectin concentration in Type 2 diabetes.

model, adiponectin level as a predictor of insulin level did not reach statistical significance. This may be attributed to the homogeneous insulin sensitivity in this Type 2 diabetic cohort. HDL-cholesterol has been known for its role in preventing atherosclerotic cardiovascular disease, which can benefit Type 2 diabetes. The anti-atherogenic and anti-diabetic properties of adiponectin are also worth further investigation. It was a preliminary data and a detailed relationship cannot be concluded if control of confounding factors was not comprehensive.

In conclusion, this study demonstrated that adiponectin concentration is strongly associated with HDL-cholesterol level among homogeneous Type 2 diabetes. Hence, adiponectin concentration might be a valuable marker to be monitored in Type 2 diabetic patients.

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CONFLICT OF INTEREST

None declared.

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