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Original Article

Hypoadiponectemia is associated with metabolic syndrome in patients with type 2 diabetes

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Abstract: Adipose tissue-expressed adiponectin levels are inversely related to the degree of adiposity, and a reduction in adiponectin serum levels is accompanied by insulin resistance. The aim of this study was to evaluate the relationship between serum adiponectin concentration and metabolic syndrome (MetS) in patients with type 2 diabetes mellitus (DM). Fasting blood samples were obtained from 150 volunteers with type 2 DM. MetS and its components were defined according to diagnostic criteria from the International Diabetes Federation. Serum adiponectin concentrations were measured using a commercially available enzyme-linked immunosorbent assay. Among the 150 patients with type 2 DM, 102 (68.0%) had MetS. Female gender ($P = 0.007$), hypertension ($P = 0.005$), systolic blood pressure ($P < 0.001$), diastolic blood pressure (DBP, $P < 0.001$), waist circumference ($P < 0.001$), body weight ($P < 0.001$), body mass index (BMI, $P < 0.001$), fasting glucose ($P = 0.035$), triglyceride (TG) level ($P < 0.001$), glycated hemoglobin level (HbA1c, $P = 0.020$), insulin level ($P < 0.001$), and homeostasis model assessment of insulin resistance (HOMA-IR, $P < 0.001$) were higher in DM patients who had MetS, whereas high-density lipoprotein cholesterol (HDL-C) concentrations ($P < 0.001$) and adiponectin levels ($P < 0.001$) were lower. Univariate linear analysis revealed that logarithmically transformed age (log-age, $r = 0.279$; $P = 0.001$) and HDL-C ($r = 0.246$; $P = 0.002$) positively correlated, whereas height ($r = -0.183$; $P = 0.025$), body weight ($r = -0.282$; $P < 0.001$), BMI ($r = -0.237$; $P = 0.004$), waist circumference ($r = -0.249$; $P = 0.002$), DBP ($r = 0.252$; $P = 0.002$), log-TG ($r = 0.255$; $P = 0.002$), log-insulin ($r = -0.298$; $P < 0.001$), and log-HOMA-IR ($r = 0.288$; $P < 0.001$) negatively correlated with serum adiponectin levels in patients with type 2 DM. Multivariate forward stepwise linear regression analysis revealed that log-age (adjusted R^2 change = 0.069; $P < 0.001$) positively correlated, whereas log-insulin (adjusted R^2 change = 0.182; $P = 0.002$) and HDL-C (adjusted R^2 change = 0.037; $P = 0.006$) negatively correlated with serum adiponectin levels in patients with type 2 DM. This study showed that lower serum adiponectin levels were positively associated with MetS in patients with type 2 DM and significantly positively related to age but negatively related to serum insulin and HDL-C levels in these subjects.

Keywords: Metabolic syndrome, diabetes mellitus, adiponectin

Introduction

Adiponectin, first described in 1995, is a secretory protein specifically expressed by adipose tissue and plays a crucial role in the maintenance of metabolic homeostasis in the human body [1]. The major function of adiponectin is the control of glucose homeostasis, and it possesses insulin-sensitizing effects that can downregulate hepatic gluconeogenesis and increase fatty acid oxidation; meanwhile, it also functions in the inhibition of inflammation [2, 3]. The deficiency of adiponectin was found to be related to a wide spectrum of metabolic abnormalities, including obesity and associated disorders such as insulin resistance, hyperglycemia, dyslipidemia, and hypertension, collectively described as metabolic syndrome (MetS), which could directly increase the risk of cardiovascular diseases, type 2 diabetes mellitus (DM), and mortality [4, 5].

Previous studies have noted that serum adiponectin levels inversely correlated with MetS [6-8]. However, few studies have investigated such a correlation in patients with type 2 DM.

Table 1. Clinical variables of the 150 diabetic patients with or without metabolic syndrome

Items	All participants (n = 150)	No metabolic syndrome (n = 48)	Metabolic syndrome (n = 102)	*P* value
Age (years)	65.50 (57.00-71.00)	62.00 (57.00-67.75)	66.00 (56.75-71.00)	0.198
Height (cm)	162.22 ± 8.42	163.38 ± 8.07	161.67 ± 8.57	0.250
Body weight (kg)	71.60 ± 13.45	63.40 ± 9.16	75.46 ± 13.44	< 0.001*
Body mass index (kg/m^2)	27.10 ± 3.96	23.68 ± 2.35	28.72 ± 3.52	< 0.001*
Waist circumference (cm)	91.11 ± 9.42	83.06 ± 7.08	94.89 ± 7.89	< 0.001*
Systolic blood pressure (mmHg)	141.89 ± 18.96	129.46 ± 14.76	147.75 ± 17.91	< 0.001*
Diastolic blood pressure (mmHg)	82.77 ± 11.27	76.52 ± 9.12	85.72 ± 11.02	< 0.001*
Total cholesterol (mg/dl)	162.13 ± 30.62	163.85 ± 29.75	161.31 ± 31.13	0.637
Triglyceride (mg/dl)	116.50 (84.75-173.25)	91.00 (60.25-125.75)	129.00 (96.50-193.75)	< 0.001*
HDL-C (mg/dl)	46.57 ± 12.75	53.02 ± 13.99	43.53 ± 10.93	< 0.001*
LDL-C (mg/dl)	99.83 ± 26.48	97.98 ± 24.20	100.71 ± 27.56	0.558
Fasting glucose (mg/dl)	138.50 (121.00-175.00)	125.50 (116.25-157.75)	143.00 (126.00-183.50)	0.035*
Glycated hemoglobin (%)	7.45 (6.60-9.05)	7.00 (6.40-8.25)	7.90 (6.70-9.25)	0.020*
Blood urea nitrogen (mg/dl)	16.00 (12.00-18.25)	15.00 (12.00-18.00)	16.00 (13.00-19.00)	0.209
Creatinine (mg/dl)	0.90 (0.70-1.00)	0.90 (0.70-1.08)	0.80 (0.70-1.00)	0.979
Glomerular filtration rate (ml/min)	87.16 ± 27.06	92.86 ± 28.56	84.48 ± 26.04	0.077
Insulin (uIU/ml)	6.79 (3.59-13.23)	3.65 (1.99-5.66)	9.81 (5.37-17.80)	< 0.001*
HOMA-IR	2.52 (1.16-5.04)	1.15 (0.77-1.90)	3.63 (1.99-6.89)	< 0.001*
Adiponectin (ng/ml)	29.73 ± 11.01	34.68 ± 11.03	27.40 ± 10.26	< 0.001*
Female (n, %)	61 (40.7)	12 (25.0)	49 (48.0)	0.007*
Hypertension (n, %)	78 (52.0)	17 (35.4)	61 (59.8)	0.005*

Values for continuous variables given as means ± standard deviation and are tested by Student's *t*-test; variables not normally distributed given as medians and interquartile range and are tested by Mann-Whitney U test; values are presented as number (%) and analysis was done using the chi-square test. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *$P < 0.05$ was considered statistically significant after the Student's *t*-test or Mann-Whitney U test.

Therefore, the aim of this study was to evaluate the relationship between serum adiponectin concentration and MetS in patients with type 2 DM.

Materials and methods

Patients

A total of 150 patients with type 2 DM were enrolled from a medical center in Hualien, Taiwan, from November 2014 through March 2015. The Protection of the Human Subjects Institutional Review Board of Tzu Chi University and Hospital approved this study. All patients provided their informed consents before participating in this study. Blood pressure (BP) was measured by trained staff in the morning using standard mercury sphygmomanometers with appropriate cuff sizes after making the patient sit for at least 10 min. Systolic BP (SBP) and diastolic BP (DBP) were measured three times at 5-min intervals and were averaged for analysis. Patients who were diagnosed with hypertension were defined based on SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or having received any antihypertensive medication in the past 2 weeks. Patients were excluded if they had an acute infection, acute myocardial infarction, heart failure, and malignancy at the time of blood sampling or if they refused to provide informed consent for the study.

Anthropometric analysis

Body weight of each participant was measured in light clothing and without shoes to the nearest 0.5 kg, and body height was measured to the nearest 0.5 cm. Waist circumference was measured using a tape measurement around the waist from the point between the lowest ribs and the hip bones with the hands on the hips. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters [9-11].

Biochemical investigations

Fasting blood samples (approximately 5 ml) of all participants were immediately centrifuged

Table 2. Clinical characteristics and fasting serum adiponectin levels of 150 diabetic patients

Characteristic		Number (%)	Adiponectin (ng/ml)	*P* value
Gender	Male	89 (55.7)	29.43 ± 10.10	0.695
	Female	61 (44.3)	30.16 ± 12.29	
Hypertension	No	72 (47.9)	29.15 ± 10.47	0.542
	Yes	78 (52.1)	30.26 ± 11.53	
Statin	No	79 (50.9)	30.32 ± 10.49	0.492
	Yes	71 (49.1)	29.07 ± 11.60	
Fibrate	No	141 (94.5)	29.93 ± 11.24	0.371
	Yes	9 (5.5)	26.53 ± 5.87	
Metformin	No	67 (44.8)	29.63 ± 11.42	0.921
	Yes	83 (55.2)	29.81 ± 10.74	
Sulfonylureas	No	69 (46.7)	30.27 ± 10.60	0.583
	Yes	81 (53.3)	29.27 ± 11.40	
DDP-4 inhibitor	No	60 (39.4)	29.92 ± 10.36	0.860
	Yes	90 (60.6)	29.60 ± 11.48	
Thiazolidinediones	No	148 (97.0)	29.55 ± 10.95	0.083
	Yes	2 (3.0)	43.13 ± 9.26	
Insulin	No	109 (73.9)	30.14 ± 11.75	0.451
	Yes	41 (26.1)	28.62 ± 8.77	

Data are expressed as means ± standard deviations. **P* < 0.05 was considered statistically significant after Student's *t*-test. DDP-4, dipeptidyl peptidase 4.

at 3000 g for 10 min. Serum levels of blood urea nitrogen (BUN), creatinine, fasting glucose, glycated hemoglobin (HbA1c), total cholesterol (TCH), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an autoanalyzer (Siemens Advia 1800; Siemens Healthcare GmbH, Henkestr, Germany) [9-11]. Serum adiponectin (SPI-BIO, Montigny le Bretonneux, France) and insulin (Labor Diagnostika Nord, Nordhorn, Germany) concentrations were determined using a commercially available enzyme-linked immunosorbent assay [9, 12]. Insulin resistance was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting plasma glucose (mg/dl × fasting serum insulin (μU/ml)/405 [9]. The estimated glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease (MDRD) equation in this study.

MetS and its components

The prevalence of MetS was defined using the International Diabetes Federation definition [13]. People were classified as having MetS if they had central (abdominal) obesity with a waist circumference ≥ 90 cm (men) or ≥ 80 cm (women) (Chinese criteria) and matched two or more of the following criteria: fasting serum glucose ≥ 100 mg/dL, TGs ≥ 150 mg/dL, HDL-C level < 40 mg/dL in men or < 50 mg/dL in women, or BP ≥ 130/85 mmHg. The use of antihypertensive drugs was considered as indicative of high BP in this analysis. Type 2 DM was determined according to the World Health Organization criteria [14]. A patient was considered as having DM if the fasting plasma glucose was ≥ 126 mg/dL or if he/she was undergoing antidiabetic therapy.

Statistical analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD), and comparisons between patients were performed using the Student's independent t-test (two-tailed). Data not normally distributed were expressed as medians and interquartile ranges, and comparisons between patients were performed using the Mann-Whitney U test (age, TGs, fasting glucose, HbA1c, BUN, creatinine, insulin, and HOMA-IR). Data expressed as the number of patients were analyzed by the χ^2 test. Because age, TGs, fasting glucose, HbA1c, BUN, creatinine, insulin, and HOMA-IR were not normally distributed, they underwent base 10 logarithmic transformations to achieve normality. Clinical variables that correlated with serum adiponectin levels in patients with DM were evaluated using univariate linear regression analysis. Variables that were significantly associated with adiponectin levels in patients with DM were tested for independency by multivariate forward stepwise regression analysis. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A *P* value < 0.05 was considered as statistically significant.

Results

The clinical characteristics of the 150 patients with type 2 DM are presented in **Table 1**. Among

Table 3. Correlation of fasting serum adiponectin levels and clinical variables by univariable linear regression analyses among the 150 diabetic patients

Items	Beta	*P* value
Log-Age (years)	0.279	0.001*
Height (cm)	-0.183	0.025*
Body weight (kg)	-0.282	< 0.001*
Body mass index (kg/m^2)	-0.237	0.004*
Waist circumference (cm)	-0.249	0.002*
Systolic blood pressure (mmHg)	-0.105	0.199
Diastolic blood pressure (mmHg)	-0.252	0.002*
Total cholesterol (mg/dl)	0.017	0.839
Log-Triglyceride (mg/dl)	-0.255	0.002*
HDL-C (mg/dl)	0.246	0.002*
LDL-C (mg/dl)	-0.088	0.282
Log-Glucose (mg/dl)	-0.051	0.537
Log-HbA1c (%)	-0.031	0.710
Log-BUN (mg/dl)	0.135	0.100
Log-Creatinine (mg/dl)	0.027	0.742
Glomerular filtration rate (ml/min)	-0.096	0.243
Log-insulin (uIU/ml)	-0.298	< 0.001*
Log-HOMA-IR	-0.288	< 0.001*

Data of age, triglyceride, glucose, HbA1c, BUN, and creatinine levels showed skewed distribution, and therefore were log-transformed before analysis. *$P < 0.05$ was considered statistically significant after univariable linear analyses. HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; HOMA-IR, homeostasis model assessment of insulin resistance.

them, 102 patients (68.0%) had MetS and 48 (32.0%) did not have MetS. Patients who had MetS had significantly lower serum fasting adiponectin levels than the levels of those without MetS ($P < 0.001$). Compared with DM patients without MetS, those with MetS showed a much higher proportion of females ($P = 0.007$) and as expected more hypertension ($P = 0.005$), higher SBP ($P < 0.001$) and DBP ($P < 0.001$), higher waist circumference ($P < 0.001$), higher body weight ($P < 0.001$) and BMI ($P < 0.001$), higher fasting glucose ($P = 0.035$) and TGs ($P < 0.001$), and lower HDL-C concentrations ($P < 0.001$). Moreover, DM patients with MetS had higher HbA1c levels ($P = 0.020$), insulin levels ($P < 0.001$), and HOMA-IR ($P < 0.001$).

The clinical characteristics and serum adiponectin values of the 150 patients with DM are presented in **Table 2**. No statistically significant differences in adiponectin levels were found in terms of gender distribution; presence of hypertension; or use of statins, fibrates, or antidiabetic drugs.

Results of the univariate linear analysis of the clinical variables associated with fasting serum adiponectin levels in patients with DM are presented in **Table 3**. Logarithmically transformed age (log-age, $r = 0.279$; $P = 0.001$) and HDL-C ($r = 0.246$; $P = 0.002$) positively correlated, whereas height ($r = -0.183$; $P = 0.025$), body weight ($r = -0.282$; $P < 0.001$), BMI ($r = -0.237$; $P = 0.004$), waist circumference ($r = -0.249$; $P = 0.002$), DBP ($r = 0.252$; $P = 0.002$), log-TG ($r = 0.255$; $P = 0.002$), log-insulin ($r = -0.298$; $P < 0.001$), and log-HOMA-IR ($r = 0.288$; $P < 0.001$) negatively correlated with serum adiponectin levels in patients with type 2 DM.

Multivariate forward stepwise linear regression analysis of the variables significantly associated with fasting serum adiponectin levels revealed that log-insulin (adjusted R^2 change = 0.182; $P = 0.002$), log-age (adjusted R^2 change = 0.069; $P < 0.001$), and HDL-C (adjusted R^2 change = 0.037; $P = 0.006$) were independent predictors of these values for patients with type 2 DM (**Table 4**).

Discussion

In our study, serum adiponectin level negatively correlated with MetS in patients with type 2 DM. DM patients with MetS were mostly females and had higher BMI, HbA1c, and HOMA-IR but lower serum adiponectin levels. Serum insulin levels, age, and HDL-C levels were independent predictors of fasting serum adiponectin levels among the 150 diabetic patients.

The prevalence of MetS in patients with type 2 DM was 68% in our study, which was much higher than that of normal population [15]. Previous studies have reported the prevalence of MetS in patients with type 2 DM as 70%-80% in the study population [16, 17]. Other studies have reported the prevalence of MetS in patients with type 2 DM as 86% in the Nigerian population and 60.4%-71.7% with different criteria in patients with type 2 DM in Cameroon [18, 19].

Table 4. Multivariable stepwise linear regression analysis of log-age, height, body weight, body mass index, waist circumference, diastolic blood pressure, HDL-C, log-triglyceride, log-insulin and log-HOMA-IR: correlation to fasting serum adiponectin level among 150 diabetic patients

Items	Beta	Adjusted R square	Adjusted R square change	*P* value
Log-insulin (uIU/ml)	-0.240	0.082	0.082	0.002*
Log-age (year)	0.289	0.151	0.069	< 0.001*
HDL-C (mg/dl)	0.211	0.188	0.037	0.006*

*$P < 0.05$ was considered statistically significant after multivariable stepwise linear regression analyses. HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

Insulin and its signaling cascade control cell growth and cell metabolism. Impaired insulin signaling or insulin resistance could result in type 2 DM and MetS [20]. In addition, insulin resistance has even been reported as the best predictor of MetS [21]. Patients with type 2 DM with a greater number of MetS components have a higher risk of developing insulin resistance [22]. Our results also demonstrated a higher proportion of hypertension, SBP, DBP, waist circumference, body weight, BMI, fasting glucose, TGs, HbA1c, insulin level, and HOMA-IR, whereas HDL-C concentrations were lower in patients with DM who had MetS, since MetS represents a constellation of hypertension, abdominal obesity, impaired fasting glucose, and dyslipidemia.

Adiponectin has antidiabetic, antiatherosclerotic, and anti-inflammatory functions, and its level in plasma would decrease with the accumulation of visceral adipose tissue [2, 3, 23]. Therefore, hypoadiponectinemia plays an important role in the development of MetS [6, 7]. Koh et al. reported that plasma adiponectin level in subjects with MetS was significantly lower than that in non-MetS subjects in a non-diabetic Korean population [24]. Adiponectin was inversely associated with MetS in 284 individuals aged > 30 years from the general population in Greece [8]. Our results also showed that hypoadiponectinemia is associated with MetS in patients with type 2 diabetes. In a cross-sectional study on 210 healthy Caucasians, adiponectin levels increased with age in both male and female participants [25]. A large-scale study recruiting 21,100 healthy subjects and 1,833 patients with type 2 DM in Japan reported that adiponectin levels were found to be positively and independently correlated to age in both group of subjects [26]. The mechanism of this phenomenon has not been well established. However, the possible explanation was that sex hormone could be responsible for the increased adiponectin in aging people, because recent studies found that androgen and estrogen could inhibit the production of adiponectin, and it was known that both hormones dramatically decreased with age [27-29]. An animal study supported that hypoadiponectinemia plays a role in the development of obesity-related hypertension [30]. Previous studies have reported that increased body weight and BMI were associated with lower adiponectin level [31, 32], which may result from decreased mRNA expression in adipocytes [33]. Moreover, adiponectin was shown to be significantly and inversely associated with waist circumference [8]. Studies have shown that adiponectin correlated with lipid profiles, and adiponectin concentration negatively correlated with TG levels but positively correlated with HDL-C levels [34, 35]. Adiponectin can induce an increase in serum HDL-C levels by altering the amount and activity of lipoprotein lipase and hepatic lipase, which are responsible for the catabolism of HDL-C [36]. Meanwhile, HDL-C elevates plasma adiponectin concentrations and increases adiponectin expression in adipocytes through the phosphatidylinositol-3-kinase-dependent pathway [37]. Adiponectin plays an important role in insulin resistance and insulin secretion [38, 39]. Adiponectin has antidiabetic and antiatherogenic effects because it could improve insulin sensitivity by enhancing fatty acid oxidation and inhibiting hepatic glucose production [2, 22]. Adiponectin is an insulin sensitizer, and reduced adiponectin levels are linked to insulin resistance [3]. Our results showed that age and HDL-C positively correlated, whereas height, body weight, BMI, waist circumference, DBP, TG, insulin, and HOMA-IR negatively correlated with serum adiponectin levels in patients with type 2 DM. Multivariate forward stepwise linear regression analysis after adjusting for significant confounders demonstrated that age, insulin, and HDL-C were independent predictors of serum adiponectin levels in patients with type 2 DM.

There are limitations in our study. First, this study was conducted using a cross-sectional design with a small sample size, and hence, we cannot draw a causal inference until further prospective study is conducted. Second, some drugs may affect serum adiponectin levels. For example, statins and thiazolidinediones were found to increase circulating adiponectin levels in a previous study [40]. In our study, there were no significant differences in serum adiponectin in terms of the medications used, including statins, metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin, or thiazolidinediones. Further studies are needed to investigate the relationship between these medications and adiponectin levels in patients with type 2 DM.

In conclusion, this study showed that lower serum adiponectin level was positively associated with MetS in patients with type 2 DM and significantly positively correlated to age but negatively related to serum insulin and HDL-C levels in these subjects.

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Disclosure of conflict of interest

None.

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