Tzu Chi Medical Journal 2023; 35 (4): 348-354

Original Article

Serum adiponectin level is positively associated with vascular reactivity index by digital thermal monitoring in patients with coronary artery disease

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Submission : 10-Feb-2023
Revision : 16-Mar-2023
Acceptance : 18-Apr-2023
Web Publication : 01-Jun-2023

Abstract

Objectives: Adiponectin has anti-inflammatory and antiatherogenic effects and is important in the pathogenesis of cardiovascular diseases. In this cross-sectional study, our objective was to study the potential correlation between serum adiponectin levels and endothelial function in participants with coronary artery disease (CAD). **Materials and Methods:** We collected serum specimens from 125 fasting participants with CAD. The endothelial function was measured using the vascular reactivity index (VRI) determined by digital thermal monitoring, and VRI values of >2.0, 1.0–1.9, and <1.0 indicated good, intermediate, and poor vascular reactivity, respectively. A commercially available enzyme immunoassay kit was used to measure serum adiponectin levels. **Results:** The cohort included 55, 57, and 13 patients with good, intermediate, and poor vascular reactivity, respectively. Poor vascular reactivity was shown to be associated with older age, higher levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), C-reactive protein, and lower levels of serum albumin and adiponectin. The linear regression analysis with multivariable forward stepwise approach revealed that age ($\beta = -0.232$), serum LDL-C ($\beta = -0.264$), and serum adiponectin ($\beta = 0.574$) were correlated with the VRI in CAD patients significantly. **Conclusion:** Fasting serum adiponectin levels were associated with good endothelial function determined using the VRI in patients with CAD.

Keywords: *Adiponectin, Coronary artery disease, Endothelial dysfunction, Vascular reactivity index*

Introduction

Adiponectin is an adipokine, i.e., mainly secreted by white adipose tissue. It comprises 244 amino acids and possesses anti-inflammatory, insulin-sensitizing, and antiatherogenic properties [1]. In circulation, high-molecular-weight multimeric adiponectin is the major active form that contributes to its antidiabetic effect [2] and plays a protective role in the cardiovascular system [3]. Mechanistically, the cardiovascular effects of adiponectin are mediated by the activation of the 5' adenosine monophosphate-activated protein kinase and cyclooxygenase 2 pathways, which promote nitric oxide (NO) production in the endothelium, prevent endothelial apoptosis, reduce tumor necrosis factor-alpha activity, and inhibit smooth muscle migration [4-6]. Moreover, T-cadherin is an adiponectin-binding receptor which also attenuates stress-induced cardiac remodeling [7] and protects against the formation of atherosclerotic plaques [8]. Hypoadiponectinemia has been linked to hypertension [9], higher insulin resistance [10], obesity, metabolic syndrome [11], and left ventricular mass index [12] in previous studies. Decreased serum adiponectin levels have been predictive of myocardial infarction risk [13] and the severity of coronary artery disease (CAD) [14].

Digital thermal monitoring (DTM) is a validated, noninvasive, reproducible, and operator-independent technique to measure vascular reactivity [15]. Following a 5-min period of blood flow occlusion in the arm using a cuff, DTM measures temperature rebound at distal fingertips as a surrogate for reactive hyperemic response and subsequent vascular reactivity. The device then generates the vascular reactivity index (VRI) value automatically. The VRI assessed using DTM has been associated with risk factors of CAD [16],

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Access this article online
Quick Response Code:
Website: www.tcmjmed.com
DOI: 10.4103/tcmj.tcmj_30_23

How to cite this article: Hsiao CH, Hsu BG, Lu CW, Wang JH. Serum adiponectin level is positively associated with vascular reactivity index by digital thermal monitoring in patients with coronary artery disease. Tzu Chi Med J 2023;35(4):348-54.

calcified coronary arteries [17] and myocardial perfusion defect [18]. Nevertheless, the association between vascular reactivity and serum adiponectin levels has not been studied in CAD patients. Therefore, we performed a cross-sectional study investigating the correlation between serum adiponectin levels and endothelial function in participants with CAD using DTM.

Materials and Methods

Patients

We recruited 125 patients with CAD visiting the cardiology outpatient department at Hualien Tzu Chi Hospital in Taiwan from August 1, 2016, to April 30, 2017. CAD was defined by coronary angiography as more than 50% narrowing in any one of three epicardial coronary arteries and was counted as one, two, or three vessels CAD. Written informed consent before participation was obtained from all patients included in the study. Patients with active infection, acute myocardial infarction or pulmonary edema were excluded from the study. We defined hypertension as a systolic blood pressure (BP) of ≥140 mmHg, a diastolic BP of ≥90 mmHg, or treatment with any anti-hypertension drugs as outlined by the Eighth Joint National Committee guidelines. Diabetes mellitus (DM) was defined as a glycated hemoglobin level of ≥6.5%, a fasting serum glucose level of ≥126 mg/dL, a random glucose level of ≥200 mg/dL, or treatment with hypoglycemic agents [19]. The protocol for this research was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, under Project No. IRB104-27-B.

Anthropometric analysis

The participant's weight and height were determined while wearing light clothing, with a precision of 0.5 kg and 0.5 cm, respectively. The body mass index (BMI) was determined by the formula below: weight/height (kg/m^2) [20,21].

Biochemical investigations

In all patients, 5 mL of blood sample was obtained after a fasting period of 8–12 h. The samples were then centrifuged for 10 min at 3000 g. The concentration of serum triglycerides, total cholesterol (TCH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine, blood urea nitrogen (BUN), fasting glucose, albumin, globulin, and C-reactive protein (CRP) were measured using an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland) [20,21]. Serum adiponectin levels were measured with an enzymatic assay kit (SPI-BIO, Montigny le Bretonneux) [22]. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Measurement of endothelial function

The patients were asked to undergo an overnight fast and to refrain from consuming cigarettes, alcoholic beverages, caffeine, and medications with vasoactive effects before the evaluation. The DTM was performed using VENDYS-II (Endothelix, Houston, TX, USA; approved by the US FDA) to measure endothelial function. Before measurement, the patients had to lie down for 15 min in a controlled temperature laboratory room between 23°C and 25°C. The patient's right upper arm was fitted with a BP cuff. A pair of temperature sensors were positioned on the index fingers' skin, with the left side treated as the control. After stabilization for 5 min, we conducted the DTM of bilateral hands with the cuff quickly pumped up to a level 50 mmHg above the systolic BP and maintained for 5 min, followed by a rapid deflation to induce a reactive hyperemic response in the fingertips. A larger temperature rebound was interpreted as better vascular reactivity. The definition of VRI was the greatest difference in temperature observed between the rebound curves and zero reactivity curves in the reactive hyperemia phase. The VRI was computed using the VENDYS software. The usual range of VRI values was 0.0–3.5; and they were categorized as poor, intermediate, and good based on values <1.0, between 1.0 and 1.9, and >2.0, respectively [15,23,24].

Statistical analysis

Data were presented as means with standard deviation. The Kolmogorov–Smirnov test was used to analyzed for normal distribution. Differences in nonnormally distributed continuous variables (height, fasting glucose, triglycerides, HDL-C, BUN, creatinine, and CRP) were compared using the Kruskal–Wallis test, whereas normally distributed continuous variables were compared using one-way analysis of variance. Then, the values that were measured were examined through Fisher's protected *t*-test. The Chi-squared test was used to analyze categorical variables, which were then presented as numbers and percentages. Since the distribution of patient height and the levels of fasting glucose, triglycerides, HDL-C, BUN, creatinine, and CRP were skewed, they were log-transformed before analysis. The simple linear regression model was used to find variables correlated to the VRI. Then, the multivariable forward stepwise regression analysis was conducted to analyze significant variables. Vascular reactivity dysfunction was defined as intermediate vascular reactivity and poor vascular reactivity. Univariable and multivariable logistic regression analysis was used to analyze the adiponectin level for vascular reactivity dysfunction and poor vascular reactivity. After confirming the effect of adiponectin level on vascular reactivity dysfunction and poor vascular reactivity, we depict the receiver operating curve (ROC) to determine the power by the area under the curve (AUC). The relationship between adiponectin levels and clinical variables was assessed through the two-tailed, nonparametric Spearman's rank correlation coefficient. We defined statistical significance as $P < 0.05$. Data were analyzed using SPSS Statistics for Windows (version 19.0; SPSS, Chicago, IL, USA).

Results

The clinical and laboratory characteristics of the study patients are shown in Table 1. In the study cohort, 55 (44%) patients had DM and 67 (53.6%) patients had hypertension. In the entire cohort, 55 (44%), 57 (45.6%), and 13 (10.4%) patients had good, intermediate, and poor VRI values, respectively. Advanced age ($P = 0.029$), higher serum TCH ($P = 0.003$), higher LDL-C ($P < 0.001$), higher CRP ($P < 0.001$), lower serum albumin ($P = 0.033$), and lower adiponectin ($P < 0.001$) were associated with poor vascular reactivity. There were no significant differences in sex, DM,

Table 1: Clinical characteristics stratified by different vascular reactivity index of the 125 patients with coronary artery disease

Characteristics	All participants (*n*=125), *n* (%)	Good vascular reactivity (*n*=55), *n* (%)	Intermediate vascular reactivity (*n*=57), *n* (%)	Poor vascular reactivity (*n*=13), *n* (%)	*P*
Age (years)	62.49±9.07	60.43±8.96	63.39±8.95	67.27±8.16	0.029*
Height (cm)	167.00 (160.25–170.00)	165.00 (159.00–170.00)	168.00 (162.50–169.50)	166.00 (155.00–170.00)	0.262
Weight (kg)	72.33±11.88	71.51±10.94	73.49±12.96	70.64±11.12	0.589
BMI (kg/m^2)	26.56±3.74	26.57±3.64	26.53±3.953	26.64±3.56	0.995
VRI	1.86±0.64	2.40±0.33	1.64±0.236	0.52±0.21	<0.001*
SBP (mmHg)	131.84±17.05	133.49±15.85	129.44±17.50	135.38±19.73	0.334
DBP (mmHg)	76.82±12.91	77.82±14.71	76.35±11.31	74.69±11.84	0.688
TCH (mg/dL)	162.88±33.67	156.89±29.93	162.07±29.18	191.77±51.39	0.003*
Triglyceride (mg/dL)	134.00 (100.00–182.50)	131.00 (99.00–193.00)	131.00 (94.50–174.50)	159.00 (111.50–223.00)	0.469
HDL-C (mg/dL)	44.00 (38.00–54.00)	46.00 (39.00–57.00)	43.00 (37.50–52.50)	46.00 (38.00–54.00)	0.515
LDL-C (mg/dL)	94.75±30.09	89.33±22.91	91.91±28.97	130.15±39.32	<0.001*
Fasting glucose (mg/dL)	105.00 (91.00–134.50)	103.00 (91.00–136.00)	107.00 (91.50–137.50)	101.00 (90.50–119.50)	0.686
Albumin (mg/dL)	4.38±0.24	4.41±0.26	4.38±0.18	4.22±0.29	0.033*
Globulin (mg/dL)	3.00±0.39	2.98±0.35	3.01±0.40	3.06±0.53	0.779
BUN (mg/dL)	16.00 (13.00–20.00)	16.00 (13.00–19.00)	17.00 (13.50–21.50)	17.00 (12.50–23.50)	0.485
Creatinine (mg/dL)	1.00 (0.80–1.10)	1.00 (0.80–1.10)	0.90 (0.80–1.10)	1.00 (0.90–1.30)	0.814
eGFR (mL/min)	83.04±22.36	82.87±21.31	84.21±22.63	78.62±26.54	0.720
CRP (mg/dL)	0.11 (0.05–0.27)	0.06 (0.05–0.21)	0.07 (0.05–0.24)	0.35 (0.28–0.44)	<0.001*
Adiponectin (μg/mL)	16.67±6.75	19.95±6.71	15.26±5.42	8.95±2.67	<0.001*
Male	107 (85.6)	45 (81.8)	51 (89.5)	11 (84.6)	0.511
DM	55 (44.0)	26 (47.3)	24 (42.1)	5 (38.5)	0.785
Hypertension	67 (53.6)	32 (58.2)	30 (52.6)	5 (38.5)	0.431
Prior CVD	19 (15.2)	6 (10.9)	10 (17.5)	3 (23.1)	0.437
Smoking	25 (20.0)	13 (23.6)	9 (15.8)	3 (23.1)	0.559
ACE inhibitor use	25 (20.0)	12 (21.8)	12 (21.1)	1 (7.7)	0.501
ARB use	52 (41.6)	27 (49.1)	20 (35.1)	5 (38.5)	0.314
β-blocker use	63 (50.4)	26 (47.3)	30 (52.6)	7 (53.8)	0.823
CCB use	46 (36.8)	22 (40.0)	18 (31.6)	6 (46.2)	0.497
Statin use	102 (81.6)	43 (78.2)	48 (84.2)	11 (84.6)	0.682
Fibrate use	7 (5.6)	4 (7.3)	2 (3.5)	7 (7.7)	0.647
One vessel CAD	68 (54.4)	34 (61.8)	29 (50.9)	5 (38.5)	0.576
Two vessels CAD	41 (32.8)	15 (27.3)	20 (35.1)	6 (46.1)	
Three vessels CAD	16 (12.8)	6 (10.9)	8 (14.0)	2 (15.4)	

*P<0.05 was defined as statistical significance. Results for continuous variables are expressed as means±SD and tested by one-way analysis of variance; nonparametric variables are expressed as medians and IQR and tested by Kruskal–Wallis analysis; values are expressed as *n* (%) and analyzed by the Chi-squared test. SD: Standard deviation, IQR: Interquartile range, CAD: Coronary artery disease, CCB: Calcium channel blockers, ARB: Angiotensin receptor blockers, ACE: Angiotensin-converting enzyme, CRP: C-reactive protein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, BUN: Blood urea nitrogen, BMI: Body mass index, VRI: Vascular reactivity index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CVD: Cardiovascular disease, DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, TCH: Total cholesterol

hypertension, different vessels of CAD, prior cardiovascular disease, smoking status, or anti-hypertensive medication use among the three vascular reactivity groups.

The association of the VRI with clinical variables using simple and multivariable linear regression models of the entire cohort is illustrated in Table 2. Briefly, the simple linear regression models indicated that age (r = −0.201, P = 0.025) and the levels of serum TCH (r = −0.280, P = 0.002), LDL-C (r = −0.365, P < 0.001), and log-transformed CRP (log-CRP, r = −0.329, P < 0.001) had a negative association with the VRI and that hypertension (r = 0.189, P = 0.035), the levels of serum albumin (r = 0.193, P = 0.031) and adiponectin (r = 0.617, P < 0.001) had a positive association with the VRI in patients with CAD. In addition, after adjusting for these significant variables (hypertension, age, TCH, LDL-C, albumin, log-CRP, and adiponectin) using linear regression analysis with multivariable forward stepwise approach, age (β = −0.232, adjusted R^2 change = 0.051; P < 0.001), serum LDL-C level (β = −0.264, adjusted R^2 change = 0.058; P < 0.001), and serum adiponectin level (β = 0.574, adjusted R^2 change = 0.376; P < 0.001) were significantly and independently associated with the VRI in patients with CAD. Figure 1 shows the two-dimensional scatter plots illustrating the correlation of the VRI with age [Figure 1a], LDL-C [Figure 1b], log-CRP [Figure 1c], and adiponectin [Figure 1d] in patients with CAD. There were no significant differences in VRI with different vessels of CAD (P = 0.226 by one-way analysis of variance) (VRI value in one vessel CAD: 1.95 ± 0.64, in two vessels CAD: 1.74 ± 0.64, in three vessels CAD: 1.78 ± 0.67, respectively).

Serum adiponectin was independently associated with vascular reactivity dysfunction (odds ratio [OR] = 0.831;

Table 2: Simple or multivariable linear regression analyses for investigating association between vascular reactivity index levels and clinical variables among 125 coronary artery disease patients

Variables	VRI				
	Simple regression		Multivariable regression		
	r	*P*	Beta	Adjusted R^2 change	*P*
DM	0.098	0.279	-	-	-
Hypertension	0.189	0.035*	-	-	-
Male	0.064	0.481	-	-	-
Age (years)	−0.201	0.025*	−0.232	0.051	<0.001*
Log-height (cm)	−0.047	0.603	-	-	-
Body weight (kg)	−0.088	0.329	-	-	-
BMI (kg/m^2)	−0.068	0.454	-	-	-
SBP (mmHg)	0.054	0.553	-	-	-
DBP (mmHg)	0.131	0.146	-	-	-
TCH (mg/dL)	−0.280	0.002*	-	-	-
Log-triglyceride (mg/dL)	−0.093	0.303	-	-	-
Log-HDL-C (mg/dL)	0.075	0.404	-	-	-
LDL-C (mg/dL)	−0.365	<0.001*	−0.264	0.058	<0.001*
Log-glucose (mg/dL)	0.093	0.301	-	-	-
Albumin (mg/dL)	0.193	0.031*	-	-	-
Globulin (mg/dL)	−0.038	0.676	-	-	-
Log-BUN (mg/dL)	−0.036	0.688	-	-	-
Log-creatinine (mg/dL)	−0.050	0.577	-	-	-
eGFR (mL/min)	0.034	0.704	-	-	-
Log-CRP (mg/dL)	−0.329	<0.001*	-	-	-
Adiponectin (μg/mL)	0.617	<0.001*	0.574	0.376	<0.001*

*P<0.05 was defined as statistical significance. Adjusted R^2=0.485 for vascular reactivity index. Data of height, triglyceride, HDL-C, fasting glucose, blood urea nitrogen, creatinine, and CRP were log-transformed before analysis due to skewed distribution. Simple linear regression analyses or multivariable stepwise linear regression analyses were used for analyzing data (adapted factors were hypertension, age, total cholesterol, LDL-C, albumin, log-CRP, and adiponectin). CRP: C-reactive protein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, BUN: Blood urea nitrogen, BMI: Body mass index, VRI: Vascular reactivity index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DM: Diabetes mellitus, TCH: Total cholesterol, eGFR: Estimated glomerular filtration rate

95% confidence interval [CI] = 0.764–0.905; P < 0.001) and poor VRI (OR = 0.507, 95% CI = 0.330–0.780, P = 0.002) in CAD patients by logistic regression analysis adjusted data for significant factors of poor vascular reactivity as shown in Table 1 including age, TCH, LDL-C, albumin, and CRP levels [Table 3]. The ROC curve for predicting vascular reactivity dysfunction by adiponectin revealed that the AUC was 0.770 (95% CI = 0.686–0.841, P < 0.001) and poor vascular reactivity by adiponectin demonstrated the AUC was 0.929 (95% CI = 0.869–0.907, P < 0.001), respectively [Table 4].

Table 5 displays the results of the Spearman correlation analysis examining the association between clinical variables, VRI, and serum adiponectin. First, serum adiponectin had a strong and significant correlation with VRI (r = 0.602, P < 0.001). Second, serum adiponectin was significantly positively correlated with log-HDL-C (r = 0.283, P = 0.001), but negatively associated with BMI (r = −0.182, P = 0.042), log-triglycerides (r = −0.209, P = 0.019), LDL-C (r = −0.215, P = 0.015), and log-CRP (r = −0.387, P < 0.001).

Discussion

In this study of patients with CAD, our analyses indicated that the VRI determined using DTM was negatively associated with age and serum levels of TCH, LDL-C, and CRP and positively associated with serum levels of albumin and adiponectin. Furthermore, older age, higher serum LDL-C levels, and lower adiponectin levels were independently and significantly associated with poor vascular reactivity in patients with CAD after controlling for significant confounding variables.

The arterial endothelium is a dynamic site that plays important roles in the regulation of vascular tone, permeability, angiogenesis, inflammation, and thrombogenesis [25]. Endothelial dysfunction arises from the dysregulation of these tightly balanced functions and is characterized by oxidative damage, vasoconstriction, inflammation, and thrombosis. In older endothelial cells, inflammation and increased production of reactive oxygen species lead to a reduction in NO bioavailability and subsequent endothelium-dependent dilatation [26]. Age was shown to be inversely correlated with brachial artery flow-mediated dilatation in the Framingham Heart Study [27]. In a previous study, we also reported that older age was associated with lower VRI in patients with kidney transplants [23]. In the present study, we also found an independent and inverse association between age and vascular reactivity in patients with CAD.

Hyperlipidaemia has deleterious effects on endothelial function due to increased oxidative and endoplasmic reticulum stress, inflammation, mitochondrial dysfunction, and subsequent endothelial cell apoptosis [28]. High cholesterol levels are associated with impaired endothelium-dependent vasodilation, which may contribute to the increased risk of cardiovascular diseases [29]. Moreover, oxidized LDL-C promotes the binding of macrophages to the arterial wall and their uptake of the oxidized LDL-C, with the subsequent formation of foam cells, accounting for the endothelial pro-atherogenic effect of LDL-C [30]. A systematic review and meta-analysis found that more intense interventions to lower serum LDL-C levels were associated with a greater reduction in the risk of total and cardiovascular mortality compared to less intense interventions [31]. Consistent with these reports, we found that higher LDL-C levels were correlated with poorer vascular reactivity determined using DTM in patients with CAD.

The endothelial glycocalyx, a complex and dynamic structure lining the vascular endothelium, is composed of proteoglycans, glycosaminoglycans, glycolipids, and glycoproteins, which incorporate plasma or endothelium-derived soluble molecules such as albumin [32]. The endothelial glycocalyx has a crucial function in the regulation of vascular permeability, exhibits antithrombotic and anti-adhesive effects, and protects the endothelium from oxidative stress while maintaining NO bioavailability [33].

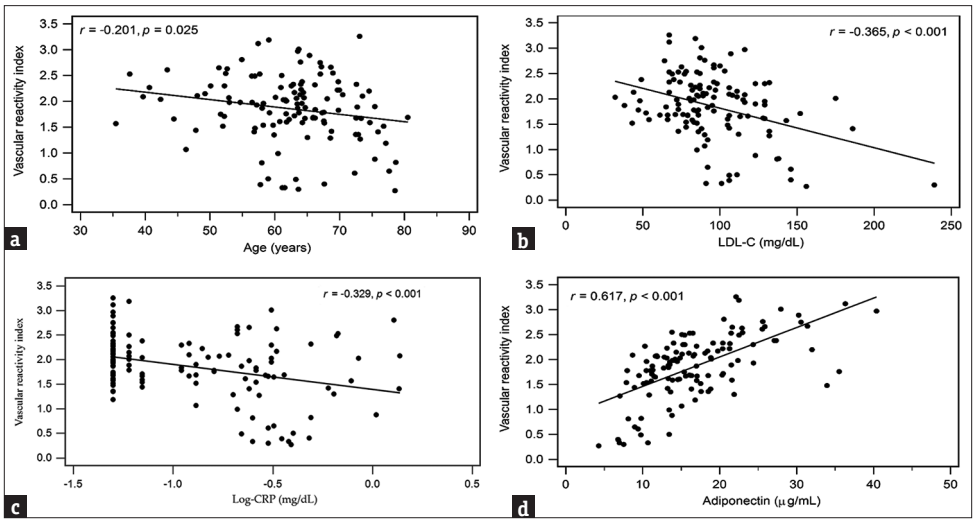

Figure 1: Relationships between VRI and (a) age, (b) LDL-C, (c) log-transformed CRP (log-CRP), and (d) adiponectin among 125 patients with coronary artery disease. LDL-C: Low-density lipoprotein cholesterol, VRI: Vascular reactivity index, CRP: C-reactive protein

Table 3: Univariable and multivariable logistic regression analysis for vascular reactivity dysfunction or poor vascular reactivity among 125 coronary artery disease patients

Model	Adiponectin (per 1 μg/mL of increase) for vascular reactivity dysfunction		Adiponectin (per 1 μg/mL of increase) for poor vascular reactivity	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Crude model	0.848 (0.786–0.914)	<0.001*	0.540 (0.396–0.737)	<0.001*
Adjusted model	0.831 (0.764–0.905)	<0.001*	0.507 (0.330–0.780)	0.002*

**P*<0.05 was defined as statistical significance. Adjusted model: Age, TCH, LDL-C, albumin, and CRP. OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, LDL-C: Low-density lipoprotein cholesterol, TCH: Total cholesterol

Physiologically, albumin is bound within the glycocalyx, maintaining its stability. Furthermore, several preclinical studies have shown that albumin plays a crucial part in maintaining the glycocalyx integrity, protecting the endothelial function through transporting sphingosine-1-phosphate to the surface of endothelium and functioning as an anti-inflammatory and anti-oxidative molecule [34-37]. In the present study, serum albumin levels were positively associated with better vascular reactivity determined using the VRI, although the observed association was not significant after the adjustment for confounders using multivariable linear regression. Further studies are required to clarify the role of albumin in the endothelial function of CAD patients.

Adiponectin, an adipokine best known for its insulin-sensitizing effects, exhibits an inverse relationship with obesity, DM, and metabolic syndrome [38]. Our results also noted serum adiponectin was positively associated with log-HDL-C and negatively associated with BMI, log-triglycerides, and LDL-C. In addition, adiponectin plays a crucial role in maintaining endothelial function demonstrated in several experimental studies [4,5,39-41]. For example, adiponectin promotes the phosphorylation of 5' adenosine monophosphate-activated protein kinase, which subsequently activates the endothelial NO synthase, increases NO production, and prevents endothelial apoptosis [4,5]. In addition, oxidative stress in the vascular wall in an *ex vivo* model of DM-associated vascular injury is reduced by adiponectin through the inhibition of the nicotinamide adenine dinucleotide phosphate oxidase through the phosphoinositide 3-kinase/Akt-mediated pathway [39]. Adiponectin also decreases the endothelial synthesis of interleukin 8 stimulated by tumor necrosis factor-alpha, contributing to its anti-inflammatory effect [40]. Low serum adiponectin levels are associated with decreased vasodilation by endothelium in diabetic patients [41]. Hypoadiponectinemia shows an inverse relationship with carotid arterial intimal-medial thickness, which indicates early atherosclerosis [42]. In the present study, serum adiponectin levels were positively associated with the VRI in patients with CAD. Moreover, a low adiponectin level could independently predict poorer vascular reactivity in the multivariable logistic regression models.

However, whether adiponectin could be targeted as a modifiable factor to improve clinical outcomes is still debatable in the literature. A Mendelian randomization trial conducted with more than 280,000 participants showed that genetic variants with higher adiponectin levels did not associate with decreased coronary heart disease [43]. Patients who have undergone kidney transplantation and have increased adiponectin levels are more likely to experience increased mortality [44]. This discrepancy is commonly referred to as the "adiponectin paradox." Some explanations have been proposed. First, the existence of residual confounding factors may present between adiponectin levels and mortality rates, such as BMI, renal dysfunction, and overtreated medications for cardiovascular diseases in old and frail patients [45]. Second, adiponectin may paradoxically produce proinflammatory cytokines in certain chronic inflammatory conditions such as colitis and rheumatoid arthritis in basic research [46,47]. Whether these unexpected deleterious effects of adiponectin would occur in other chronic inflammatory

Table 4: Diagnostic value of adiponectin on vascular reactivity dysfunction or poor vascular reactivity

Vascular reactivity dysfunction	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Adiponectin (μg/mL)	0.770 (0.686–0.841)	14.76	64.3	78.2	87.3	48.4
Poor vascular reactivity	**AUC (95% CI)**	**Cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
Adiponectin (μg/mL)	0.929 (0.868–0.907)	10.68	84.6	90.2	50.1	98.1

All $P<0.001$. AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Table 5: Spearman correlation coefficients between serum adiponectin and clinical variables in 125 coronary artery disease patients

Variables	Spearman coefficient of correlation	*P*
Male	−0.112	0.214
Age (years)	0.048	0.597
BMI (kg/m^2)	−0.182	0.042*
VRI	0.602	<0.001*
SBP (mmHg)	0.105	0.245
DBP (mmHg)	0.096	0.288
TCH (mg/dL)	−0.128	0.154
Log-triglyceride (mg/dL)	−0.209	0.019*
Log-HDL-C (mg/dL)	0.283	0.001*
LDL-C (mg/dL)	−0.215	0.015*
Log-glucose (mg/dL)	−0.005	0.956
eGFR (mL/min)	−0.155	0.085
Log-CRP (mg/dL)	−0.387	<0.001*

*$P<0.05$ was defined as statistically significant. Log transformation was performed before analysis due to the skewed distribution of data, including triglyceride, HDL-C, glucose, and CRP levels. The Spearman correlation analysis was used for data analysis. CRP: C-reactive protein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, BMI: Body mass index, VRI: Vascular reactivity index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TCH: Total cholesterol, eGFR: Estimated glomerular filtration rate

environments like atherosclerosis in cardiovascular diseases is unknown. Further trials are needed to solve the paradox due to the lack of solid evidence supporting these hypotheses.

It is important to note several limitations to the present study. First, this was a cross-sectional study performed in a single medical center and the causality between adiponectin levels and endothelial dysfunction could not be determined. Second, the cohort size was relatively small and only restricted to patients with CAD and did not include a healthy control group. Further subgroup analysis according to mortality or other morbidities could not be performed. Third, all patients were Taiwanese individuals, therefore the generalizability of the findings to other races or patients without CAD may be limited. Nevertheless, this is the first study showing that serum adiponectin levels positively correlate with the VRI in patients with CAD. Fourth, anti-hypertensive drugs and statins might exert protective effects on the endothelium and might act as potential confounders in the correlation between serum adiponectin levels and the VRI [48]. In the present study, the rates of patients taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, statins and fibrates were not significantly different among the three VRI groups. However, other medications might still act as unmeasured confounders, which could not be determined in the present study.

Conclusions

Adiponectin is secreted by white adipose tissue and plays an important role in the protection of endothelial function and the pathogenesis of atherosclerosis. The present study revealed a positive correlation between serum adiponectin levels and the VRI determined using thermal monitoring in patients with CAD. Further longitudinal research is needed to establish the causality between serum adiponectin levels and endothelial function in CAD patients.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

This work was supported by Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, Grant Number TCRD110-41.

Conflicts of interest

Dr. Bang-Gee Hsu, an editorial board members at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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