Positive correlation of serum angiopoietin-like protein 3 levels with metabolic syndrome in patients with coronary artery disease

Sy-Harn Lian*, Bang-Gee Hsu a,b, Ji-Hung Wang c,d, Ming-Chun Chen a

ABSTRACT

Objectives: Angiopoietin-like protein 3 (ANGPTL3) regulates triglyceride metabolism by reversibly inhibiting the lipoprotein lipase activity. Metabolic syndrome (MetS) is an independent risk factor for further cardiovascular disease. This study evaluated the relationship between the fasting serum ANGPTL3 levels and MetS in patients with coronary artery disease (CAD). Materials and Methods: Fasting blood samples were obtained from 90 patients with CAD. Serum ANGPTL3 levels were measured using a commercial enzyme-linked immunosorbent assay kit. MetS and its components were defined using the diagnostic criteria of the International Diabetes Federation. Results: Fifty-three patients (58.9%) had MetS. The hypertension (P = 0.001), diabetes (P < 0.001), body weight (P = 0.027), body mass index (P = 0.001), waist circumference (P < 0.001), systolic blood pressure (P = 0.001), fasting glucose (P < 0.001), triglycerides (P < 0.001), blood urea nitrogen (P = 0.044), C-reactive protein (P = 0.010), insulin (P = 0.040), homeostasis model assessment of insulin resistance (P = 0.002), and ANGPTL3 level (P = 0.001) of CAD patients who had MetS were higher, and the high-density lipoprotein cholesterol (P = 0.001) and estimated glomerular filtration rate (P = 0.016) were lower. A binary logistic regression analysis of the significant variables also revealed that the ANGPTL3 level (odds ratio: 1.023, 95% confidence interval: 1.008–1.038, P = 0.002) was an independent predictor of MetS in patients with CAD. Conclusion: The results of our study indicated that the fasting ANGPTL3 level was positively associated with MetS among patients with CAD.

KEYWORDS: Angiopoietin-like protein 3, Coronary artery disease, Metabolic syndrome

INTRODUCTION

Coronary artery disease (CAD), one of the leading causes of disability and death worldwide, is a global health problem [1]. A data analysis from 2007 to 2010 in the United States indicated that 15.4 million adults had CAD, and its prevalence increased with age in both sexes [1]. In developing countries, the number of CAD-related deaths in 2005 was estimated up to 17.5 million, and this number is expected to increase by 137% in men and 120% in women by 2020 [2]. Metabolic syndrome (MetS), comprising interrelated risks of visceral obesity, hypertension, hyperglycemia, and dyslipidemia [3], is an independent risk factor for atherosclerosis and CAD [4,5]. In Western countries, the MetS prevalence in adults is 23.6% according to the NCEP ATP III definition [6]. With the growing incidence of the MetS and CAD worldwide [2,7], the identification of the risk factors affecting the occurrence of MetS among patients with CAD is of major importance.

Angiopoietin-like protein 3 (ANGPTL3), encoded by a gene containing seven exons located at chromosome 1 p31.1-p22.3, is a 70-kDa secretory glycoprotein with 460 amino acids mainly produced in the human liver [8]. It is composed of an N-terminal heparin-binding motif playing a key role in lipid transportation and metabolism, a coiled-coil domain, and a C-terminal fibrinogen-like domain involved in angiogenesis [9]. ANGPTL3 reversibly inhibits the activities of lipoprotein lipase and endothelial lipase in the capillaries of fat and muscle, thus inhibiting the hydrolysis of circulating chylomicrons and low-density lipoproteins [10-12]. ANGPTL3 has been suggested as a major liver-derived regulator of lipoprotein metabolism, MetS, and cardiovascular disease (CVD) [8]. In ApoE knock-out mice,

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The serum concentrations of fasting glucose, blood urea and were immediately centrifuged at 3000 g for 10 min. Approximately 5 mL were obtained from the study participants. Biochemical investigations

The body weight (BW) of each participant was measured in light clothing and without shoes to the nearest 0.5 kg, and the body height was measured to the nearest 0.5 cm. Waist circumference (WC) was assessed using a tape measure around the body height was measured to the nearest 0.5 cm. Waist in light clothing and without shoes to the nearest 0.5 kg, and

Anthropometric analysis

The study design was approved by the Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (IRB104-27-B). All participants provided written informed consent before their enrollment in this study. Between August 2016 and April 2017, a total of 90 patients with CAD (CAD was defined as >50% stenosis in any segment based on coronary angiography in medical records) in a medical center in Hualien, Eastern Taiwan, were enrolled. After the participants sat for at least 10 minutes in the morning, blood pressure (BP) was measured using standard mercury sphygmomanometers. Systolic BP (SBP) and diastolic BP (DBP) were taken at the points of appearance and disappearance, respectively, 3 times at 5-min intervals, and the results were averaged for analysis. Hypertension was defined by SBP ≥140 mmHg and/or DBP ≥90 mmHg or a prescription of antihypertensive medication in the preceding 2 weeks. If patients had an acute myocardial infarction, pulmonary edema, or acute infection at the time of blood sampling, or if they refused to provide informed consent for the study, they were excluded.

Biochemical investigations

After an 8-h overnight fast, venous blood samples of approximately 5 mL were obtained from the study participants and were immediately centrifuged at 3000 g for 10 min. The serum concentrations of fasting glucose, blood urea nitrogen (BUN), creatinine, TG, TCH, LDL-C, HDL-C, and C-reactive protein (CRP) were measured using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [17-19]. The serum ANGPTL3 (R and D Systems, Inc., Minneapolis, MN) levels were quantified using a commercial enzyme-linked immunosorbent assay [16]. Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405 [16,18,19]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Metabolic syndrome and its components

In accordance with previous studies, MetS was defined based on the International Diabetes Federation definition [20]. People who had central obesity, that is, with a WC of ≥90 cm in men or ≥80 cm in women (Chinese criteria) and met two or more of the following criteria: BP ≥130/85 mmHg, TG ≥150 mg/dL, HDL-C level ≤40 mg/dL in men or ≤50 mg/dL in women, or fasting serum glucose ≥100 mg/dL, were classified as having MetS. The use of antihypertensive drugs was considered as indicative of high blood pressure in this analysis. According to the World Health Organization criteria, a patient was considered as having Type 2 diabetes mellitus (DM) if their fasting plasma glucose was ≥126 mg/dL or if they were receiving antidiabetic therapy [21].

Statistical analysis

Analyses were performed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). The data were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data were expressed as the mean ± standard deviation and compared using the Student’s independent t-test (two-tailed). Non-normally distributed data were compared using the Mann–Whitney U test and expressed as medians and interquartile ranges (TG, fasting glucose, BUN, creatinine, CRP, ANGPTL3, insulin, and HOMA-IR) and then transformed to logarithms (base 10) to achieve normality. Categorical variables were compared using Chi-square test. Spearman’s rank-order correlation coefficient was used to examine associations between the ANGPTL3 and variables. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) to identify the cutoff value of ANGPTL3 level predicting MetS in patients with CAD. ANGPTL3 levels were tested for independency associated with MetS through a binary logistic regression analysis (adopted factors: DM, hypertension, WC, HDL-C, TG, eGFR, CRP, and ANGPTL3). P < 0.05 was considered statistically significant.

Results

The clinical characteristics, antihypertensive drug use, and antilipid drugs use of patients with CAD with or without MetS are presented in Table 1. A total of 44 patients (48.9%) had DM, and 73 patients (81.1%) had hypertension. Fifty-three patients (58.9%) were defined as having MetS. Patients in the MetS group had a higher percentage of hypertension (P = 0.001) and DM (P < 0.001) compared with patients with CAD without MetS. Patients with CAD with MetS...
had higher BW ($P = 0.027$), BMI ($P = 0.001$), WC ($P < 0.001$), SBP ($P = 0.001$), fasting glucose ($P < 0.001$), TG ($P < 0.001$), BUN ($P = 0.044$), CRP ($P = 0.010$), insulin level ($P = 0.040$), HOMA-IR ($P = 0.002$), and ANGPTL3 level ($P = 0.001$), but had lower eGFR ($P = 0.016$) and HDL-C ($P = 0.001$) compared with patients with CAD without MetS. The drugs used by the patients included angiotensin-converting enzyme inhibitors (ACEis; $n = 24$; 26.7%), angiotensin receptor blockers (ARBs; $n = 37$; 41.1%), β-blockers ($n = 52$; 71.2%), calcium channel blockers (CCBs; $n = 32$; 35.6%), statins ($n = 67$; 74.4%), and fibrates ($n = 13$; 14.4%). No statistically significant difference was noted in sex and use of ACEis, ARBs, β-blockers, CCBs, statins, or fibrates between the two groups. The correlation between ANGPTL3 values and clinical variables among patients with CAD is shown in Table 2. In Spearman’s rank-order correlation coefficient model, we found that female ($P = 0.031$), TG ($P = 0.014$), and LDL-C ($P = 0.032$) were positively correlated, while serum HDL-C levels ($P = 0.030$) were negatively with ANGPTL3 values.

The plotting of the ROC curve for MetS prediction revealed that the AUC for ANGPTL3 level was 0.708 (95% confidence interval [CI], 0.603–0.799; $P < 0.001$) [Figure 1]. According to the Youden index, the optimal cutoff point of ANGPTL3 level for predicting MetS was 309.88 ng/mL (sensitivity: 33.96%; specificity: 97.30%). After adjusting for factors associated with MetS by binary logistic regression, serum ANGPTL3 levels (odds ratio [OR] = 1.008–1.036; $P = 0.002$), DM (OR = 26.982; 95% CI, 2.672–272.419; $P = 0.005$), hypertension (OR = 6.611; 95% CI, 1.081–40.437; $P = 0.041$), WC (OR = 1.192; 95% CI, 1.048–1.356; $P = 0.008$), and CRP (each increase 0.1 mg/dL, OR: 3.095, 95% CI: 1.050–9.118, $P = 0.040$) were found to be independent predictors for MetS in patients with CAD [Table 3].

**DISCUSSION**

The present study revealed that the fasting ANGPTL3 level was an independent predictor of MetS in patients with CAD. Higher percentages of hypertension and DM, higher BW, BMI, WC, SBP, fasting glucose, TG, BUN, CRP, insulin level, HOMA-IR, and ANGPTL3 level, as well as lower eGFR and HDL-C values, were observed in patients with CAD with MetS, a group of multiple risk factors for atherosclerosis [4,5]. The positive correlation between the fasting ANGPTL3 level and MetS in patients with CAD is in accordance with several

| Table 1: Clinical variables of the 90 coronary artery disease patients with or without metabolic syndrome |
|-----------------------------------------------|
| **Items** | **All patients (n=90)** | **No metabolic syndrome group (n=37)** | **Metabolic syndrome group (n=53)** | **P** |
| Age (years) | 65.59±8.63 | 66.70±8.78 | 64.81±8.52 | 0.309 |
| Height (cm) | 161.31±7.79 | 162.35±6.09 | 160.92±8.79 | 0.395 |
| Body weight (kg) | 68.37±11.94 | 65.05±9.81 | 70.69±12.80 | 0.027* |
| Waist circumference (cm) | 92.88±10.09 | 87.81±8.57 | 96.42±9.61 | <0.001* |
| BMI (kg/m²) | 26.12±3.49 | 24.63±3.06 | 27.15±3.43 | 0.001* |
| Systolic blood pressure (mmHg) | 131.80±19.44 | 124.14±14.20 | 137.15±20.89 | 0.001* |
| Diastolic blood pressure (mmHg) | 71.96±9.57 | 70.76±8.59 | 72.79±10.19 | 0.323 |
| Total cholesterol (mg/dL) | 162.61±33.69 | 161.32±32.58 | 163.51±34.72 | 0.764 |
| Triglyceride (mg/dL) | 119.00 (89.75-168.00) | 101.00 (77.00-125.00) | 148.00 (94.50-219.50) | <0.001* |
| HDL-C (mg/dL) | 44.60±11.86 | 49.65±12.58 | 41.08±10.03 | 0.001* |
| LDL-C (mg/dL) | 93.93±27.19 | 91.65±26.46 | 95.53±27.83 | 0.508 |
| Fasting glucose (mg/dL) | 108.00 (94.75-142.00) | 98.00 (90.00-115.00) | 129.00 (104.50-169.50) | <0.001* |
| Blood urea nitrogen (mg/dL) | 16.00 (13.00-19.00) | 15.00 (12.50-17.00) | 17.00 (13.00-20.50) | 0.044* |
| Creatinine (mg/dL) | 1.10 (0.90-1.30) | 1.00 (0.90-1.20) | 1.10 (0.90-1.45) | 0.066 |
| eGFR (mL/min) | 67.94±19.59 | 73.86±14.05 | 63.81±21.85 | 0.016* |
| CRP (mg/dL) | 0.19 (0.14-0.27) | 0.17 (0.14-0.21) | 0.24 (0.15-0.36) | 0.010* |
| Insulin (μIU/mL) | 10.65 (6.80-19.62) | 9.33 (5.96-16.55) | 13.21 (9.08-21.61) | 0.040* |
| HOMA-IR | 3.54 (2.03-6.46) | 2.21 (1.42-4.19) | 4.23 (2.88-8.49) | 0.002* |
| ANGPTL3 (mg/mL) | 240.31 (164.40-294.29) | 200.32 (116.17-271.33) | 264.02 (191.60-346.31) | 0.001* |
| Female, n (%) | 23 (25.6) | 26 (6.2) | 17 (32.1) | 0.090 |
| Hypertension, n (%) | 73 (81.1) | 64 (46.9) | 49 (92.5) | 0.001* |
| Diabetes, n (%) | 44 (48.9) | 9 (24.3) | 35 (66.0) | <0.001* |
| ACE inhibitor use, n (%) | 24 (26.7) | 6 (16.2) | 18 (34.0) | 0.061 |
| ARB use, n (%) | 37 (41.1) | 13 (35.1) | 24 (45.3) | 0.336 |
| β-blocker use, n (%) | 52 (71.2) | 19 (51.4) | 33 (62.3) | 0.302 |
| CCB use, n (%) | 32 (35.6) | 10 (27.0) | 22 (41.5) | 0.158 |
| Statin use, n (%) | 67 (74.4) | 26 (70.3) | 41 (77.4) | 0.448 |
| Fibrate use, n (%) | 13 (14.4) | 5 (13.5) | 8 (15.1) | 0.834 |

* $P<0.05$ was considered statistically significant. Values for continuous variables given as means±SD and are test by Student’s $t$-test; variables not normally distributed given as medians and interquartile range and are test by Mann-Whitney U test; values are presented as, n (%) and analysis was done using the Chi-square test. HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, HOMA-IR: Homeostasis model assessment of insulin resistance, ANGPTL3: Angiopoietin-like protein 3, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-receptor blocker, CCB: Calcium-channel blocker, SD: Standard deviation, BMI: Body mass index.
studies that have indicated the critical role of ANGPTL3 in lipid metabolism and MetS [8,9].

Individuals with MetS are at a higher risk of CAD events [4,5] and increased CVD mortality [5]. With the growing prevalence of obesity and sedentary lifestyles, the prevalence of MetS and CAD is also increasing worldwide [2,7]. Therefore, identifying the risk factors affecting MetS occurrence among patients with CAD is of major importance. As expected, the present study revealed that patients with CAD with MetS have significantly higher BW, WC, BMI, and SBP, higher prevalence of hypertension and DM, and high TG and fasting glucose levels, as well as lower HDL-C values than patients with CAD without MetS.

Previous epidemiological studies have demonstrated that MetS prominently increases the prevalence of CKD, and a significant relationship between the number of MetS components and CKD occurrence was noted [22,23]. A systematic review and meta-analysis also revealed that MetS and its components have been associated with microalbuminuria or overt proteinuria and impaired renal function [24]. Predictably, MetS increased the occurrence of DM and CVD and established cardiometabolic risk factors that promote CKD development [25]. Our study also confirmed significantly impaired renal function with increased BUN and decreased eGFR values in patients with CAD with MetS compared with those without MetS. In addition, a chronic low-grade inflammation state causing a proinflammatory environment has been associated with insulin resistance, diabetes, MetS, and CVD [26,27]. Systemic inflammatory markers, such as CRP, interleukin-6 (IL-6), and TNFz, are widely present in MetS [27]. A recent study by Kawada and coworkers revealed that a high CRP level was associated with MetS in 5102 working individuals aged 30–60 years without metabolic diseases [28]. In line with previous studies, our study revealed that patients with CAD with MetS had significantly higher CRP levels than with CAD without MetS, indicating that the proinflammatory state could induce metabolic disturbances and MetS development over time.

Compensatory hyperinsulinemia due to insulin resistance plays a central etiological role in MetS [18]. A recent study reported that insulin resistance, estimated through the HOMA-IR, increased more than additively by clustering the components of MetS cross-sectionally and over time among

### Table 2: Correction between log-transformed angiopoietin-like protein 3 level and clinical variables

| Variables                      | Spearman’s correlation coefficient | P    |
|--------------------------------|-----------------------------------|------|
| Age (years)                    | −0.160                            | 0.132|
| Height (cm)                    | −0.176                            | 0.098|
| Body weight (kg)              | −0.081                            | 0.449|
| Waist circumference (cm)       | 0.075                             | 0.481|
| BMI (kg/m²)                   | 0.019                             | 0.861|
| Systolic blood pressure (mmHg) | 0.124                             | 0.243|
| Diastolic blood pressure (mmHg)| 0.007                             | 0.950|
| Total cholesterol (mg/dL)      | 0.111                             | 0.296|
| Log-triglyceride (mg/dL)       | 0.258                             | 0.014*|
| HDL-C (mg/dL)                 | −0.230                            | 0.030*|
| LDL-C (mg/dL)                 | 0.226                             | 0.032*|
| Log-glucose (mg/dL)           | 0.088                             | 0.412|
| Log-BUN (mg/dL)               | 0.037                             | 0.728|
| Log-creatinine (mg/dL)        | 0.020                             | 0.853|
| eGFR (mL/min)                 | −0.054                            | 0.612|
| Log-CRP (mg/dL)               | 0.082                             | 0.442|
| Log-insulin (uIU/mL)          | 0.049                             | 0.649|
| Log-HOMA-IR                   | 0.078                             | 0.465|
| Female, %                     | 0.227                             | 0.031*|
| Hypertension, %               | 0.115                             | 0.281|
| Diabetes, %                   | 0.148                             | 0.163|

*P<0.05 was considered statistically significant (two-tailed). Data of triglyceride, glucose, blood urea nitrogen, creatinine, CRP, ANGPTL3, insulin, and HOMA-IR levels showed skewed distribution, and therefore were log-transformed before analysis. HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HOMA-IR: Homeostasis model assessment of insulin resistance, ANGPTL3: Angiopoietin-like protein 3, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-receptor blocker, CCB: Calcium-channel blocker, BMI: Body mass index.

### Table 3: Odds ratio for metabolic syndrome by binary logistic regression analysis of angiopoietin-like protein 3 levels among the 90 coronary artery disease patients

| Variables                      | OR       | 95% CI    | P    |
|--------------------------------|----------|-----------|------|
| Angiopoietin-like protein 3 (1 ng/mL) | 1.023    | 1.008-1.038 | 0.002*|
| Diabetes mellitus, present      | 26.982   | 2.672-272.419 | 0.005*|
| Hypertension, present           | 6.611    | 1.081-40.437 | 0.041*|
| Waist circumference (1 cm)      | 1.192    | 1.048-1.356 | 0.008*|
| CRP (0.1 mg/dL)                 | 3.095    | 1.050-9.118 | 0.040*|
| HDL-C (1 mg/dL)                 | 0.974    | 0.902-1.053 | 0.508|
| eGFR (1 mL/min)                 | 0.982    | 0.940-1.025 | 0.400|
| Triglyceride (1 mg/dL)          | 1.009    | 0.998-1.019 | 0.112|

*P<0.05 was considered statistically significant in the binary logistic regression analysis (adopted factors: diabetes mellitus, hypertension, waist circumference, HDL-C, triglyceride, eGFR, CRP, and ANGPTL3). ANGPTL3: Angiopoietin-like protein 3, HDL-C: High density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein.
reported that the expression of ANGPTL3 led to the inactivation of lipoprotein lipase, resulting in severe dyslipidemia [30]. Dyslipidemia plays a pivotal role in the pathophysiology of CAD by inducing platelet aggregation and the production of plasminogen activator-inhibitor-1, increasing macrophages, and promoting the proliferation and migration of vascular smooth muscle cells [31,32]. Therefore, insulin resistance could be considered as the missing link between MetS and CAD.

Beyond conventional factors, growing evidence suggests that increased circulating ANGPTL3 levels are linked to the occurrence of MetS and CVD in human studies [10,15,16]. Serum ANGPTL3 levels are associated with human BP and lipid parameters, which are risk factors for both MetS and CAD [33]. A recent study by Fu et al. reported that the circulating ANGPTL3 level had a positive correlation with the aortic augmentation index, a marker of arterial stiffness and the degree of CVD, among the CAD population [16]. Our study also indicated that serum ANGPTL3 level had a positive correlation with TG level and LDL-C level and a negative correlation with HDL-C level. Moreover, high ANGPTL3 levels independently increased the risk of MetS in patients with CAD.

The mechanism by which ANGPTL3 affects the pathogenesis of MetS and CAD is likely to be multifactorial. Dyslipidemia is a major contributor to MetS [8]. ANGPTL3 regulates lipid metabolism, and ANGPTL3 deficiency-related hypolipidemia is driven by enhanced lipoprotein turnover and the resulting altered energy substrate distribution among tissues [34]. Animal studies have indicated that KK/Snk mice with ANGPTL3 deficiency exhibited reduced circulating TG levels due to their accelerated catabolism [35]. In addition, through the introduction of the functioning Angptl3 gene or the injection of human recombinant ANGPTL3, the plasma TG level of KK/Snk mice was reported to increase to normal values [36]. The Dallas Heart Study revealed that multiple loss-of-function alleles in ANGPTL3 were associated with lower plasma TG levels [37]. In the DiscovEHR study, heterozygous ANGPTL3 loss-of-function carriers had significantly lower circulating levels of TG (27%), LDL-C (9%), and HDL-C (4%) than noncarrier individuals [38]. In addition, a dose-dependent reduction of TG, with maximal reduction of 80%, and decreased plasma LDL-C levels were observed in both intravenous and subcutaneous injections of evinacumab, an antibody of ANGPTL3 investigated by a randomized, double-blinded, placebo-controlled trial in 2017 [38]. In the present study, the ANGPTL3 level and TG level were both higher in patients with MetS than in those without MetS among the CAD population. Ando et al. reported that the expression of ANGPTL3 was positively regulated by the liver X receptor (LXR)/retinoid X receptor (RXR) complex and LXR ligands. Moreover, the LXR-mediated induction of ANGPTL3 led to the inactivation of lipoprotein lipase, resulting in severe hypertriglyceridemia [13,39,40]. Our results may be explained by the LXR/RXR dysregulation and the decreased lipoprotein lipase when the ANGPTL3 status is increased. In addition, dyslipidemia is strongly associated with inflammation [41], which may aggravate MetS initiation and progression as aforementioned.

As a hepatokine, ANGPTL3 plays an essential role in not only lipid metabolism but also glucose metabolism and insulin sensitivity, owing to the crosstalk between the liver and adipose tissue [42]. Previous animal studies have revealed that in insulin-resistant diabetic mice, the plasma ANGPTL3 levels and hepatic ANGPTL3 mRNA expression increased [43]. Furthermore, decreased angptl3 gene expression and protein secretion were noted after the insulin was injected or after the treatment of hepatocytes, suggesting that insulin resistance conditions may be associated with an increased ANGPTL3 production [44]. Higher insulin sensitivity and lower plasma glucose and insulin levels were observed in humans with homozygous loss-of-function mutations in ANGPTL3 compared with those with heterozygotes and noncarrier individuals [42]. Yilmaz et al. also reported that serum ANGPTL3 levels were independently associated with insulin resistance based on the HOMA-IR [45]. Taken together, insulin resistance-related compensatory hyperinsulinemia plays a central role in MetS [18], and ANGPTL3 secretion and action are interrelated with insulin metabolism [46], indicating that an increased circulating ANGPTL3 level is involved in the pathophysiology of MetS.

Although several medications used by patients with cardiometabolic syndrome may influence the underlying inflammatory status, our study revealed that ACEis, ARBs, β-blockers, CCBs, statins, and fibrates had no influence on MetS occurrence among the CAD population. Further longitudinal studies are warranted to evaluate the effect of these medications on MetS in patients with CAD.

Our study has some limitations. First, this was a cross-sectional study with a relatively small sample size; therefore, it did not elucidate the causal relationship between circulating ANGPTL3 values and the presence of MetS in the CAD population. That is, our findings should be investigated in long-term prospective studies before a causal relationship between serum ANGPTL3 levels and MetS in patients with CAD can be established. Second, whether lower plasma ANGPTL3 levels equal to the intracellular inactivation of ANGPTL3 mRNA expression remains unknown. Moreover, the possible mechanism between lower ANGPTL3 levels and other components of MetS, such as blood glucose and BP, in CAD needs further assessment.

**Conclusions**

The present study revealed that the serum ANGPTL3 level, an emerging potential surrogate biochemical marker for MetS, was an independent positive predictor of MetS in patients with CAD. Further prospective studies are warranted to confirm the mechanisms underlying this association.
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Conflicts of interest
Dr. Bang-Gee Hsu, an editorial board member 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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