Elevation of Plasma Malondialdehyde Levels Associated with The Severity of Coronary Atherosclerosis in Coronary Artery Disease Patients

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Abstracts: The present study aims to investigate the relationship between plasma MDA and the severity of coronary artery disease in CAD patients. A total of 159 newly diagnosed CAD patients were enrolled in the study with an average age of 65.5 ± 11.3 years old and 63% were male. Participants underwent an investigation of blood biochemistry and plasma MDA before the measurement of coronary artery angiography. They were then divided into four groups as control (non-CAD), single vessel disease (SVD), double vessel disease (DVD), and triple vessel disease (TVD) groups. The results showed high plasma MDA levels were observed in SVD, DVD, and TVD patients (1.64 ± 0.56, 2.32 ± 0.57, 2.52 ± 0.76, respectively) when compared with the control group (1.44 ± 0.54, P < 0.001). Interestingly, plasma MDA was associated with fasting blood glucose (r = 0.183, P = 0.024), total cholesterol (r = 0.231, P = 0.004), triglyceride levels (r = 0.269, P < 0.001), HDL-cholesterol levels (r = -0.221, P = 0.006), and LDL-cholesterol levels (r = 0.164, P = 0.044). ROC analysis was performed using both control and CAD patients as subjects. The cut-off for plasma MDA was 1.624 µmol/L with 83.6% sensitivity and 28.0% specificity. The findings of this research showed that plasma MDA levels were associated with the severity of CAD.

Keywords: Coronary Artery Disease, Severity, Plasma Malondialdehyde, Oxidative Stress, Atherosclerosis.

1. INTRODUCTION

An estimated 17.9 million people die from cardiovascular disease (CVD) each year and more than 75% of CVD deaths occur in low-income and middle-income countries (World Health Organization, 2022). Moreover, data indicates that 85% of the aforementioned deaths were due to heart attack and stroke. This number is steadily increasing in the Thai population [1]. An important cardiovascular risk factor is coronary artery disease (CAD). Atherosclerosis is a major key risk factor for coronary artery narrowing which causes a reduction or blockage of blood flow to the heart muscle [2,3]. Several CAD risk factors affect the development of atherosclerosis progressions such as age, gender, smoking, obesity, hypertension, diabetes mellitus, and abnormalities of serum cholesterol. Lipids or cholesterol are well-known as a big clue for plaque development, especially high LDL-cholesterol levels, and have been shown in several epidemiological studies [4-6]. Furthermore, HDL-cholesterol levels, a lipoprotein class promoting reverse cholesterol transportation, are significantly related to evaluating cardiovascular manufacturing risk factors.

The gold standard for diagnosis of CAD patients is coronary angiography which reports as the percentage of coronary artery occlusion in each major vessel. Luminal occlusion ≥ 50% in at least one of the epicardial coronary arteries is defined as significant CAD [7]. Previous studies observed that the severe type of CAD, triple vessel disease (TVD), is more related to the increasing rates of major adverse mortality and cardiac events than both

single vessel disease (SVD) and double vessel disease (DVD) [8,9]. Similarly, Yaghoubi et al. found that increasing serum MDA were significantly higher among CAD patient groups, especially SVD, DVD and TVD groups, compared to the control group or non-significant CAD group [10]. Therefore, MDA may be a useful predictor and biomarker for identification and further assessment in CAD patients [11,12].

Evidence of an imbalance between free radicals, which are unstable molecules, and antioxidant may cause increased oxidation of lipids, proteins, and nucleic acids resulting in cell damage, especially in endothelial cells [13]. Previous studies have found that oxidative stress may promote chronic inflammation and contribute to atherosclerosis in humans. Atherosclerosis or plaque was synthesized from both major mechanisms of oxidative stress and inflammation [14]. Recent studies have found that plasma malondialdehyde (MDA), which is well-known for lipid peroxidation, is at higher levels in elderly participants with CAD [11,12], and CAD with diabetes patients [15]. As we have known about the relationship between oxidative stress and atherosclerotic pathogenesis for a few decades. A few studies have evaluated the association between oxidative stress and the severity of CAD [16,17]. Therefore, this study aimed to evaluate the relationship between plasma MDA and the severity of coronary artery occlusion in CAD patients.

2. MATERIEL AND METHODS

2.1. Study Population

One hundred and fifty-nine stable chest pain subjects (aged between 39 to 90 years old and comprising 100 men and 59 women) were included in this study in which each participant was first requested to provide informed consent. The participants were recruited from the Outpatient Clinic of the Thammasat Heart Center, Thammasat Hospital, and Thammasat University between October 2016 and March 2018. Demographic data was sought through questionnaires including age, gender, waist circumference, smoking status, weight, height (to calculate body mass index [BMI]), and history of chronic diseases and medications utilizing a retrospective chart review. The measurements of the midline between the last rib of the inferior margin and the iliac crest were presented to waist circumference. Systolic and diastolic blood pressure were obtained with an automatic sphygmomanometer.

Forty-three participants who matched the exclusion criteria were excluded from the study. The exclusion criteria of this study included (1) valvular heart disease, unstable angina, acute myocardial infarction, atrial fibrillation, cardiomyopathy, valvular disease, congenital heart disease, heart failure, end-stage renal disease or acute infection; (2) systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg; (3) chronic kidney disease (serum creatinine > 2 mg/dL); (4) severe left ventricular dysfunction (ejection fraction < 40%); (5) ABI > 1.4, (6) plasma MDA ≥ 5.0 μmol/L; and (7) failure to provide consent to participate in the study. The study protocol was approved by the Human Ethics Committee of the Faculty of Medicine, Thammasat University (MTU-EC-OO-6-055/59), and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

2.2. Blood Collection and Plasma MDA Measurements

Following a 12-hour fast, a venous blood sample was collected from all subjects for routine laboratory tests such as lipid profile levels, fasting blood glucose, and others measured via standard laboratory techniques at the Laboratory Unit, Thammasat University Hospital. The plasma was stored at -80°C before MDA measurement in the research laboratory room, 8th floor, Cooperative Learning Center building, Chulabhorn International College of Medicine, Thammasat University. The thiobarbituric acid reactive substance was evaluated by measuring a colored complex from the reaction of MDA with thiobarbituric acid in boiling water following previously described methods [18].

2.3. Coronary Angiography

After all patients completed their routine blood examinations, they underwent coronary angiography for evaluation of coronary atherosclerosis at the Thammasat Heart Center, Thammasat Hospital, Thammasat University. In

patients with coronary artery occlusion in the major lumen (including the left anterior descending artery, left circumflex artery, and right coronary artery), more than 50% were diagnosed with coronary artery disease. All subjects were divided into four groups as shown in the demographic and clinical characteristic information in Table 1. The control group was defined as participants who presented coronary artery occlusion less than 50%. In contrast, single vessel disease (SVD), double vessel disease (DVD), and triple vessel disease (TVD) are presented as one, two, and three-vessel occlusion of more than 50% in the major coronary arteries, respectively.

Table 1. Baseline characteristics of the study subjects

Parameters	Controls (n = 25)	SVD (n = 31)	DVD (n = 44)	TVD (n = 59)
Age (year)	65.8 ± 10.6	67.8 ± 10.1	63.5 ± 11.1	65.8 ± 121.3
Gender (male (%))	13 (52)	18 (58)	33 (75)	36 (61)
Waist circumference (cm)	92.1 ± 12.9	91.2 ± 9.9	92.9 ± 10.0	90.7 ± 10.5
Body mass index (kg/m^2)	26.9 ± 5.6	25.5 ± 3.6	26.2 ± 4.7	25.6 ± 4.0
Systolic blood pressure (mmHg)	133.4 ± 18.0	136.7 ± 20.8	132.3 ± 19.6	133.8 ± 19.0
Diastolic blood pressure (mmHg)	74.8 ± 13.6	75.7 ± 13.3	73.6 ± 12.9	78.1 ± 11.8
Fasting glucose (mg/dL)	111.7 ± 39.9	112.8 ± 38.3	126.1 ± 41.8	124.9 ± 44.9
Total cholesterol (mg/dL)	154.1 ± 39.5	169.2 ± 46.7	174.4 ± 52.2	184.2 ± 51.2
Triglyceride (mg/dL)	118.2 ± 71.5	143.4 ± 52.0	142.4 ± 56.6	147.7 ± 66.0
HDL-cholesterol (mg/dL)	54.7 ± 13.7	47.1 ± 10.4	45.2 ± 14.0	44.3 ± 11.0*
LDL-cholesterol (mg/dL)	88.3 ± 41.7	102.8 ± 43.9	102.5 ± 44.1	113.2 ± 44.3
Current smoking (*n* (%))	3 (12)	4 (13)	12 (27)	8 (14)
Medications				
Clopidogrel (*n* (%))	13 (52)	25 (81)	32 (72)	39 (66)
Aspirin (n (%))	21 (84)	29 (94)	40 (91)	54 (92)
Nitrates (*n* (%))	7 (28)	15 (48)	19 (43)	31 (53)
Statin (n (%))	19 (76)	26 (84)	41 (93)	50 (85)
Beta-blocker (*n* (%))	18 (72)	28 (90)	33 (75)	43 (73)
ACEI & AT1 blocker (*n* (%))	12 (48)	17 (55)	25 (57)	40 (68)
Calcium channel blocker (*n* (%))	10 (40)	8 (26)	11 (25)	13 (22)
Diuretics (*n* (%))	9 (36)	7 (23)	10 (23)	14 (24)
Anti-diabetic drugs (*n* (%))	5 (20)	10 (32)	16 (36)	18 (31)

All data are expressed as mean ± SD or number (%).SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACEI & AT1, angiotensin-converting-enzyme inhibitor and angiotensin II type 1 receptor. *P < 0.001.

2.4 Statistical Analyses

Data is presented as mean with standard deviation or number and percentage appropriately. One-way analysis of variance (ANOVA) was used to determine the statistical comparison among four groups. The association between plasma MDA levels and blood biochemical parameters was evaluated using Pearson correlation analysis. Identification of the optimal cutoff point between CAD and plasma MDA levels was used in a receiver operator characteristic (ROC) curve analysis. Stata version 11 was used for the analysis in this study (Stata Corp., College Station, Texas, USA). P value < 0.05 was considered as significant.

3. Results

There were no significant differences in age, sex, waist circumference, body mass index, blood pressure, fasting glucose, total cholesterol, triglyceride, LDL-cholesterol between groups. However, HDL cholesterol levels were significantly lower in CAD patients with more number of coronary artery occlusions (P < 0.001; Table 1). Twenty-seven males were identified as current smokers, and 64% of all subjects were being treated with clopidogrel, 91%

with aspirin, 44% with nitrates, 86% with statins, 72% with beta-blockers, 62% with angiotensin-converting-enzyme inhibitors and angiotensin II type 1 receptor blockers, 26% with calcium channel blockers, 24% with diuretic drugs, and with 30% anti-diabetic medications.

Table 2 Correlation of plasma MDA levels and blood chemistry variables in all participants

Parameters	Plasma MDA	
	r	P
Fasting glucose (mg/dL)	0.183	0.024
Total cholesterol (mg/dL)	0.231	0.004
Triglyceride (mg/dL)	0.269	<0.001
HDL-cholesterol (mg/dL)	-0.221	0.006
LDL-cholesterol (mg/dL)	0.164	0.044

MDA; malondialdehyde; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Plasma MDA levels were higher in patients with SVD (1.64 ± 0.56; P = 0.050), DVD (2.32 ± 0.57; P = 0.013), and TVD (2.52 ± 0.76; P = 0.009) when compared with the control group (1.44 ± 0.54; Figure 1). Interestingly, Table 2 shows that plasma MDA was associated with blood chemistry including fasting blood glucose (r = 0.183, P = 0.024), total cholesterol (r = 0.231, P = 0.004), triglyceride (r = 0.269, P < 0.001), HDL-cholesterol (r = -0.221, P = 0.006), and LDL-cholesterol (r = 0.164, P = 0.044). Moreover, plasma MDA was associated with the number of coronary artery occlusions (r = 0.546, P < 0.001; Figure 1), which is defined as no vessel occlusion of more than 50%, and occlusion of more than 50% in one, two, and three vessels, respectively.

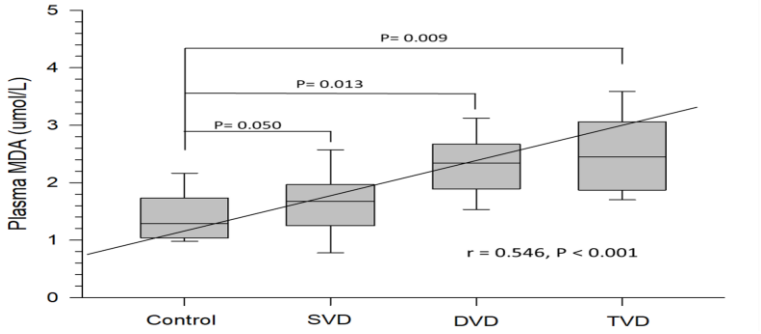

Figure 1. The comparison and relationship between plasma malondialdehyde (MDA) and the category of coronary artery disease diagnosis; control group, single-vessel disease (SVD), double-vessel disease (DVD), and triple-vessel disease (TVD) groups.

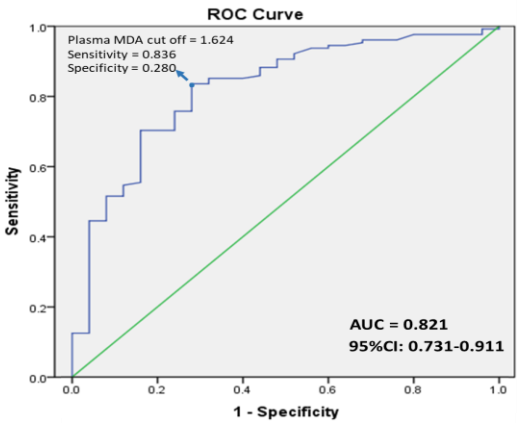

Figure 2. Receiver operator characteristic (ROC) curve analysis of plasma malondialdehyde predicts coronary artery disease.

The critical value of plasma MDA was determined by ROC curve analysis in both CAD and non-CAD patients, which is presented in Figure 2. The area under the curve value in predicting CAD was 0.821 (95% CI: 0.731-0.911, $P < 0.001$), and the optimal cut-off point for plasma MDA was obtained as 1.624 μmol/L with 83.6% sensitivity and 28.0% specificity.

4. DISCUSSIONS

We observed the relationship between plasma MDA and multiple coronary artery occlusion in patients with CAD. The data reveals that patients diagnosed with TVD presented as the highest number of coronary artery stenosis showed the highest plasma MDA levels, while HDL-cholesterol levels were lowest. Furthermore, plasma MDA was found to be very strongly related to the number of coronary artery stenosis vessels ($P<0.001$). Plasma MDA also presented 1.624 μmol/L as the optimal cut-off point for CAD prediction.

Atherosclerosis slowly builds up inside the arterial wall and is mainly developed from hyperlipidemia and lipid oxidation. The first sign of atherosclerosis is fatty streaks which present in four steps: (i) low-density lipoprotein-cholesterol (LDL-cholesterol) trapped in the intima of the arterial walls; (ii) dysfunction of endothelial cells allowing monocytes and T-lymphocytes influx into vascular walls; (iii) leukocyte activation leading to pro-inflammatory cytokines binding to their receptors on the endothelial surface and smooth muscle cells, playing a pivotal role in leukocyte activation and migration; and (iv) foam cell formation which is the process by which phagocytosis of lipids increase the size of plaque resulting in arterial wall narrowing [19]. LDL-cholesterol levels can therefore be an independent predictor for CAD. Moreover, increasing blood triglyceride and reduction of high-density lipoprotein cholesterol (HDL-cholesterol) levels are well-known risk factors for coronary atherosclerosis and cardiovascular disease [2,20]. Lipid profiles include total cholesterol, triglyceride, LDL-cholesterol, and HDL-cholesterol and have been widely used as a core value for prevention and treatments in clinical practice for a few decades [2]. In the present study, there were no statistically significant total cholesterol, triglyceride, and LDL-cholesterol among groups, whereas low HDL-cholesterol was observed in patients with multi-vessel occlusion in coronary artery disease ($P < 0.001$).

Generating high oxidative stress, an imbalance between free radicals and antioxidant properties has been known as a cause of lipid, protein, and DNA damage for several decades. Plasma MDA, a product of lipid peroxidation, is a breaking down production from long-chain fatty acids in cellular membranes and tissues [21]. Moreover, MDA epitopes the major marker of lipid peroxidation have been identified as mediators of atherosclerosis, which is characterized by chronic inflammation and endothelial dysfunction [22]. Madisetty et al. found that plasma MDA was significantly higher in CAD patients than in healthy controls and non-CAD patients [23]. Other studies have demonstrated that plasma MDA could play a potential biomarker for the early-onset detection of atherosclerosis [12,24]. All of these data support our finding that plasma MDA levels increased in CAD patients, especially in patients with multi-occlusion of coronary artery vessels. Moreover, there was a significant correlation of both fasting blood sugar and lipid variables with plasma MDA (Table 2), which was supported by a previous study that found a significant increase in plasma MDA levels in diabetes patients with hyperglycemia [25]. They demonstrated that raised blood glucose concentration results in excess generation of free radicals, leading to lipid damage [25]. This indicates that not only high blood sugar levels, but also dyslipidemia, play a major role in lipid peroxidation and oxidative stress elevation by increased plasma MDA.

The result of this study shows an elevation of plasma MDA levels in CAD patients with multiple coronary artery occlusion. The satisfactory diagnostic power of all plasma MDA for predicting CAD was analyzed by ROC curve. Previous studies report that serum MDA was higher in CAD patients and the cut-off point showed 5.49 mmol/mL [26], while another study presented the optimal cut-off for serum MDA was 2.59 nmol/ml with 83.2% sensitivity and 62.0% specificity [27]. Amaki et al. revealed that the optimal cut-off level of circulating malondialdehyde-modified low-density lipoprotein (MDA-LDL) was 85.6 U/l with 64% sensitivity and 65% specificity and the Odds ratio showed

a 3.3-fold likeliness for patients with high MDA-LDL levels to have coronary atherosclerosis [11]. Moreover, Kotani et al. observed that a level of MDA-LDL concentration ≥ 110 U/l was related to a significantly higher prevalence of cardiac events than MDA-LDL < 110 U/l in CAD patients with type 2 diabetes mellitus [15]. Our study shows that the optimal cut-off point for plasma MDA obtained was 1.624 μmol/L with 83.6 % sensitivity and 28.0% specificity. Even though there are different methods for MDA investigation (plasma MDA, serum MDA, and circulating MDA-LDL), all of them are useful prognostic tools for future cardiac events in CAD patients.

The limitations of the present study should be considered. First, all baseline characteristics of this study showed no significant difference among control and CAD categories groups, except HDL-cholesterol levels. Increasing the sample size might affect the results of this study. Second, medications potentially affect the biochemical laboratories. Third, the differences in the numbers among the CAD category groups occurred in soft endpoints. Last, plasma MDA is only one representation of oxidative stress, other oxidants and antioxidant variables should be measured.

CONCLUSIONS

This study showed higher plasma MDA levels in CAD patients with multiple coronary artery occlusion vessels. A high level of plasma MDA may indicate the severity of coronary atherosclerosis by increasing the number of coronary artery occlusions. Further studies with a larger patient sample size and a comparison of techniques for MDA measurements will help to develop a deeper understanding of the pathogenesis of lipid peroxidation and atherosclerotic properties.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper. The funding source had no role in the collection of the data or in the decision to submit the manuscript for publication. No other potential conflicts of interest relevant to this article were reported.

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