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Meteorin-like protein decreases in acute coronary syndrome

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Abstract. – OBJECTIVE: This study aims to investigate the level of Meteorin-like protein (METRNL) and C-reactive protein (CRP), total antioxidant status (TAS), total oxidant status (TOS), and oxidative Stress Index (OSI) which are known to be related with inflammation in patients with acute myocardial infarction (AMI).

PATIENTS AND METHODS: A total of 64 patients diagnosed with AMI at the emergency service and 56 healthy controls were included in this study. Levels of METRNL, CRP, TAS, TOS, OSI, and other basic biochemical parameters and hemograms of the study groups were analyzed.

RESULTS: A significant difference was found between groups in terms of level of glucose (GLU) (p<0.001), urea (p<0.001), creatinine (CRE) (p<0.001), Troponin-I (TROP) (p<0.001), CRP (p<0.001), white blood cell (WBC) (p<0.001), TAS (p<0.001), TOS (p<0.001), OSI (p<0.001) and METRNL (p<0.001). It was determined that there was a significant negative correlation between the level of METRNL with the time from the onset of chest pain until emergency department admission (r=-0.345, p=0.005) and the level of troponin (r=-0.372, p=0.002) in 64 patients diagnosed with the acute coronary syndrome (ACS). However, it was determined that a significant correlation was not present with age (r=-0.058, p=0.650), BMI (r=0.092, p=0.472), TAS (r=0.079, p=0.533), TOS (r=0.113, p=0.374), OSI (r=0.042, p=0.740), CRP (r=-0.192, p=0.129) level. When we accept the cut-off value of METRNL ≤2.55 ng/mL in ROC analysis, its sensitivity and specificity were determined as 82.81% and 80.36%, respectively in differentiating AMI patients from the healthy control group.

CONCLUSIONS: It was found that the level of METRNL decreased in AMI patients and a negative correlation was present between the level of METRNL with the time from the onset of chest pain until emergency department admission and the level of troponin. In addition, it was determined that the level of TOS and OSI were significantly increased and the level of TAS decreased considerably compared to the healthy control.

Key Words:

Acute myocardial infarction, Meteorin-like protein, Total antioxidant status, Total oxidant status, Oxidative stress index.

Introduction

Coronary heart disease (CHD), stable or unstable angina, myocardial infarction, and sudden cardiac death are the leading causes of death in developed countries[1,2]. CHD is a condition characterized by inflammation and deposition of plaques primarily composed of lipids, calcium, and inflammatory cells in the walls of the coronary arteries. Inflammatory cells accumulate in the damaged vascular area and secrete inflammatory mediators that contribute to plaque formation. ST-Segment-Elevation Myocardial Infarction (STEMI) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) are differentiated from unstable angina among acute coronary syndromes because of the release of specific markers of myocardial necrosis (Troponin-I, CK-MB) that define themselves clinically as Acute Myocardial Infarction (AMI). Diagnosis and classification of AMI are based on a detailed examination of electrocardiogram findings, biochemical markers of myocardial necrosis, and clinical manifestation of patients[3,4]. The most common mechanism responsible for AMI is the rupture of atherosclerotic plaque, an inflammatory condition[5-7]. Inflammatory factors can be considered biomarkers for atherosclerosis and CHD. Research on biomarkers and their clinical applications has been recently increasing[8]. It has been shown that oxidative stress, which occurs because of increased production of reactive oxygen species (ROS) and which plays a role in atherogenesis and vascular inflammation, also plays a role in atherosclerosis and cardiovascular diseases[9-11].

Meteorin-like protein (METRNL) is a myokine that regulates energy expenditure and inflammation in adipose tissue. It is highly expressed in white adipose tissue. It is also found in the liver, spleen, muscle tissue, heart, thymus, omental adipose tissue, subcutaneous adipose tissue, and interscapular adipose tissue[12-14].

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It is reported that METRNL, which is known to increase anti-inflammatory cytokines by stimulating IL-4 expression, is abundantly expressed in the heart and plays a critical role in the pathogenesis of cardiovascular diseases[15-17]. Although studies[18,19] have found that serum METRNL concentrations are decreased in patients with CHD, there are limited studies on the level of METRNL in AMI.

In our study, we aimed to examine the level of METRNL, C-reactive protein (CRP), Total antioxidant status (TAS), Total oxidant status (TOS) and Oxidative Stress Index (OSI), which are known to be associated with inflammation, in patients who had an acute myocardial infarction.

Patients and Methods

Subjects

The study was started after complying with the Helsinki Committee requirement protocol and receiving approval from Harran University Clinical Research Ethics Committee (Date: 08/01/2019 Decision No.: 12/22). This case-control study included 64 patients who were diagnosed with AMI and sent from the emergency department to the catheterization laboratory with the diagnosis of ACS within three months from the ethics approval date and 56 healthy controls. The diagnosis of AMI was made in accordance with the criteria set out in the 2020 European Society of Cardiology Guidelines[20]. Accordingly, patients who had acute and persistent chest pain (>20 min), ST-segment elevation, patients who did not have permanent ST-segment elevation but had transient ST-segment elevation, permanent or transient ST-segment depression, T-wave inversion, pseudo normalization of T waves or flat T waves, or normal electrocardiograms and patients who had dynamic cardiac troponin elevation greater when compared to the 99% of healthy individuals were accepted as AMI.

Laboratory Measurements

Blood samples were collected from all patients at admission. These blood samples were centrifuged for 10 min at 3,000 rpm, and the serum was divided into aliquots and stored at -80°C until the day of analysis. White blood cell (3.7-10.1 $10e^3$/µL), hemoglobin (12-18 g/dL), hematocrit (35-53.7%), and platelet (142-424 $10e^3$/µl) counts were determined with the Alinity HQ (Abbott Laboratories, IL, USA). Serum glucose (70-105 mg/dL), urea (10-50 mg/dL), and creatinine (0.2-1.11 mg/dL) levels were measured by conventional laboratory methods on Atellica Solution (Siemens Healthineers, Erlangen, Germany).

Meteorin-Like Protein Assay

All patients gave blood samples at the hospital admission. These blood samples were then centrifuged for 10 min at 3,000 rpm, were aliquoted and stored at -80°C until analysis. The level of METRNL was measured with enzyme-linked immunosorbent assays (Catalogue No.: YLA-3736HU, Shanghai YL Biotech Co., Ltd., Shanghai, China) in accordance with the manufacturer's instructions. The 96-microplate is pre-coated with human METRNL antibodies in this kit protocol. METRNL binds to the antibodies in the 96-plate, which is previously added with METRNL antibodies. Molecules, that are not bounded, are removed by washing. Then biotinylated human METRNL antibodies are added to the wells, ensuring that they can bind to the meteorite in the sample. After that, Streptavidin-HRP is added for binding the biotinylated METRNL antibodies. After incubation, the unbound Streptavidin-HRP is removed by the washing step. Then the substrate solution is added, and the color develops in proportion to the amount of human METRNL. The reaction is terminated by adding an acidic cessation solution and the absorption is measured at 450 nm in the microplate reader (Cytation-1, Biotek, Winooski, VT, USA). Assay range was 0.05-15 ng/mL.

Total Antioxidant Level

The TAS level were measured with the Rel Assay branded commercial kits developed by Erel (LOT: HN20106A Rel Assay Kit Diagnostics, Mücahitler, Şehitkamil/Gaziantep, Turkey)[21]. Trolox, a water-soluble analogue of vitamin E, was used as a calibrator. The results were expressed in mmol Trolox Equiv./Lt.

Total Oxidant Level

The TOS level of the samples was measured with the Rel Assay branded commercial kits developed by Erel (Rel Assay Kit Diagnostics, Mücahitler, Şehitkamil/Gaziantep, Turkey)[22]. Hydrogen peroxide was used as a calibrator. The results were expressed in µmol H_2O_2 Equiv./Lt.

Oxidative Stress Index

The mmol unit of the TAS value was converted to the µmol, as for the TOS value unit, during

Table I. General data of the study groups.

	Control	AMI	*p*-value
N (F/M)	56 (32/24)	64 (33/31)	0.334
Age/year	60.54 ± 9.34	59.25 ± 15.24	0.574
BMI (kg/m^2)	24.25 ± 3.87	24.61 ± 4.07	0.622
Glucose (mg/dL)	99.75 ± 19.67	182.64 ± 102.89	< 0.001
Urea (mg/dL)	25.69 ± 10.33	40.52 ± 24.15	< 0.001
Creatinine (mg/dL)	0.62 ± 0.18	0.98 ± 0.40	< 0.001
TROP	0.03 ± 0.02	1.70 ± 2.62	< 0.001
CRP	0.16 ± 0.22	2.23 ± 3.80	< 0.001
White Blood Count (10e^3/µl)	7.64 ± 1.36	11.93 ± 4.98	< 0.001
Hemoglobin (g/dL)	13.61 ± 1.65	13.94 ± 1.80	0.298
Hematocrit (%)	41.99 ± 5.03	43.33 ± 5.31	0.162
Platelet (10e^3/µl)	297.86 ± 60.31	283.61 ± 116.42	0.412
TAS (mmol Trolox Equiv./Lt)	1.59 ± 0.29	1.00 ± 0.19	< 0.001
TOS (µmol H_2O_2 Equiv./Lt)	9.46 ± 1.88	16.83 ± 3.97	< 0.001
OSI (Arbitrary Unit)	0.62 ± 0.21	1.72 ± 0.50	< 0.001
METRNL (ng/mL)	2.78 ± 0.63	2.09 ± 0.53	< 0.001

F: Female, M: Male, AMI: Acute myocardial infarction BMI: Body Mass Index METRNL: Meteorin-like protein, TAS: Total Antioxidant Status, TOS: Total Oxidant Status, OSI: Oxidative Stress Index, TROP: Troponin-I, CRP: C-reactive protein, *p*-value < 0.05 was considered statistically significant.

the calculation of OSI, which was expressed as the percentage of the ratio of TOS to the TAS levels[22]. The results were expressed as "Arbitrary Unit" and calculated according to the following formula: TOS, µmol H_2O_2 Equiv./Lt OSI=TAS, mmol Trolox Equiv./Lt × 1.

Statistical Analysis

The data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) v. 21.0 (IBM Corp., Armonk, NY, USA) and the MedCalc v. 10.1.6.0 (Ostend, West-Vlaanderen, Belgium) software package. The Receiver Operating Characteristic (ROC curve) analysis was used to determine the difference in METRNL level between AMI patients and healthy controls. The results of the analysis were expressed as % specificity, % sensitivity [Area under the ROC curve (AUC), *p*, 95% Confidence Interval (CI)]. A *p*-value <0.05 was considered statistically significant.

Results

There was no difference in gender, age and BMI at the groups included in the study. However, the level of GLU (p<0.001), URE (p<0.001), CRE (p<0.001), TROP (p<0.001), CRP (p<0.001), WBC (p<0.001), TAS (p<0.001), TOS (p<0.001), OSI (p<0.001) and METRNL (p<0.001) were found to be significantly different (Table I, Figure 1).

The mean time of onset of chest pain in the patients was 5.53±3.82/hour. It was determined that the level of METRNL in the 64 patients with the acute coronary syndrome has a significant negative correlation with time from the onset of chest pain to admission to the emergency department (r=-0.345, p=0.005) and Troponin levels (r=-0,372, p=0,002). However, there was no significant correlation with age (r=-0.058, p=0.650), BMI (r=0.092, p=0.472), TAS (0.079, p=0.533), TOS (r=0.113, p=0.374), OSI (r=0.042, p=0.740), and the level of CRP (r=-0.192, p=0.129).

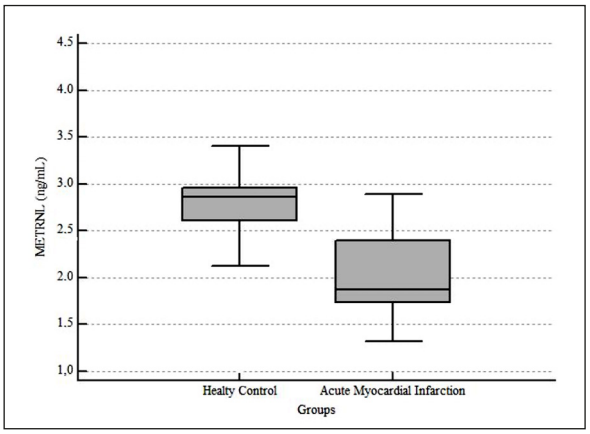

Figure 1. MERNL levels of AMI and healthy control groups.

Table II. ROC analysis results for METRNL in the differentiation of acute myocardial infarction.

	Cut-off (ng/mL)	AUC	95% CI	Sensitivity	Specificity	PPD	NPD	p
Meteorin	≤ 2.55	0.832	0.753-0.894	82.81	80.36	82.8	80.4	< 0.001
Troponin-I	> 0.06	0.846	0.769-0.906	71.87	98.21	97.9	75.3	< 0.001

AUC: Area under the ROC curve, PPD: Positive Predictive Value, NPD: Negative Predictive Value, CI: Confidence Interval.

When we accept the cut-off value of METRNL as ≤2.55 ng/mL in ROC analysis, its sensitivity and specificity were determined as 82.81% and 80.36%, respectively in differentiating AMI patients from the healthy control group. In addition, the sensitivity and specificity of Troponin I level were determined as 71.87% and 98.21%, respectively in differentiating AMI patients from the healthy control group when we take the cut-off value of Troponin I level as 0.06 ng/mL (Table II) (Figure 2).

Discussion

Inflammation is an important factor in the development and progression of atherosclerosis[23,24]. Circulating low-density lipoprotein (LDL) invades and oxidizes the endothelium, which is regulated by enzymes such as Lp-LpA2 and free radicals in the endothelium[25,26]. Thus, atherosclerosis is a chronic inflammatory disease mainly caused by LDLs and leukocytes[27]. C-Reactive Protein is a systemic inflammatory mediator and an acute phase reactant produced mainly by hepatocytes after stimulation by cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)[28]. Clinical studies have reported that CRP levels are associated with endothelial dysfunction and CHD stages[29,30]. CRP reduces the transcription of endothelial nitric oxide synthase in endothelial cells, resulting in decreased nitric oxide release[31]. In addition, it has been reported that CRP increases the expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in human umbilical vein endothelial cells[29]. Another study reported that CRP and WBC increased more in STEMI patients than in NSTEMI patients. In our study, it was found that CRP levels were significantly increased in AMI patients[32].

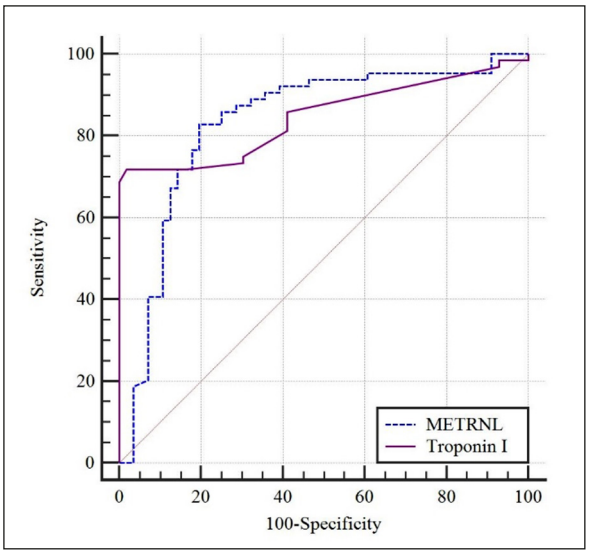

Figure 2. ROC analysis graph for the use of METRNL and Troponin I in differentiation of AMI.

Oxidative modification of LDL in the arterial wall (Ox-LDL) can be derived from both normal LDL locally oxidized in the arterial intima and Ox-LDL in plasma. Accumulation of Ox-LDL in the arterial wall initiates monocyte and smooth muscle cell migration and transforms macrophages and smooth muscle cells into cholesterol-laden foam cells, which are the major cell components found in atherosclerotic plaque[33-35].

However, mammalian cells are protected from free radicals by a wide variety of antioxidants such as vitamin E, glutathione, carotenoids, and antioxidant enzymes. Antioxidants have been found to prevent chain reactions and repair biomolecules damaged by free radicals. In a study, oxidative stress markers were compared in patients with CHD and a healthy control group. It was reported in that study that the level of plasma vitamin C and red blood cell glutathione peroxidase (R-GPx), which are antioxidants, in ACS patients were significantly decreased. However, no significant change was found in the level of red blood cell glutathione (R-GSH), plasma vitamin E and plasma total antioxidant status (P-TAS). In the same study, it was reported that oxidative damage products, such as plasma malondialdehyde and red blood cell malondialde-

hyde, increased significantly[36]. In another study consisting of ACS patients, patients with chronic CHD and healthy subjects as a control group, a significant decrease in plasma TAS level in patients with ACS and chronic CHD compared to healthy controls has been found. It has been also found a significant reduction in plasma TAS levels of ACS patients compared to those with chronic CHD[37]. In our study, it was found that TOS and OSI were significantly increased in AMI patients compared to healthy controls whilst TAS levels were significantly decreased.

One of the adipokines in the adipose tissue that has an effect on the regulation of many metabolic functions in the body is METRNL[12]. It was reported that while METRNL increased the expression of anti-inflammatory genes such as interleukin-10 (IL-10), and TGF-Beta, it caused a decrease in the expression of pro-inflammatory genes such as TNF-α, Interferon-gamma and IL-1β[17]. In addition, it has been shown that the decrease of METRNL in circulation causes an increase in insulin resistance, which is accepted as a critical risk factor for cardiovascular diseases including metabolic syndrome and type 2 diabetes[38]. There are limited studies showing an association between METRNL and atherosclerosis and coronary artery disease. In one study, they reported that the levels of METRNL decreased significantly in patients with CHD and DM[18]. METRNL was found to have a sensitivity of 68.3% and a specificity of 66.7% in differentiating the healthy control group from those with CHD[18]. In addition, Yilmaz et al found that the sensitivity and specificity of METRNL were 63.64% and 69.39%, respectively in differentiating patients with AMI from control patients without AMI[19]. In our study, it has been found that serum METRNL levels were significantly decreased in AMI in the emergency department and its sensitivity and specificity were 82.81% and 80.36%, respectively in differentiating those with AMI from the healthy control group. Also, it has been found that Troponin I had a sensitivity and specificity of 71.87% and 98.21%, respectively.

Previous experimental studies have shown that METRNL is increased in obese mice[17]. However, different results have been obtained in studies with humans. One study reported no significant association between METRNL and BMI[39]. In our study, it was determined that there was a significant negative correlation between the level of METRNL with the time from the onset of chest pain until emergency department admission and the level of troponin in 64 patients diagnosed with ACS. However, no significant correlation was found with BMI, age, level of TAS, TOS, OSI, CRP.

Limitations

The main limitations of our study are the fact that the METRNL levels of the patients were not controlled before and after AMI, and the drugs used were not defined.

Conclusions

METRNL levels decrease in AMI patients. TOS and OSI levels were significantly increased compared to the healthy control. It was determined that TOS and OSI levels increased significantly compared to the healthy control, and TAS levels were significantly decreased. In addition, it was determined that there was a significant negative correlation between the level of METRNL with the time from the onset of chest pain until emergency department admission and the level of troponin.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

Harran University Rectorate Non-Interventional Research Ethics Committee granted approval for the study (date and approval No.: 09.11.2020-HRU/20.19.32).

Informed Consent

A voluntary consent form was obtained from each participant.

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