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MOTS-c as a predictor of coronary lesions and complexity in patients with stable coronary artery disease

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Abstract. – OBJECTIVE: Atherosclerosis plays a major role in the development of coronary artery disease (CAD). It has been shown that mitochondrial open-reading-frame of the twelve S rRNA-c (MOTS-c), a mitochondrial-derived peptide, has preventive effects on atherosclerosis. The aim of this study was to determine the relationship between MOTS-c levels and CAD presence and severity using SYNTAX score (SS) in patients with stable angina pectoris.

PATIENTS AND METHODS: Ninety-two consecutive patients with stable coronary artery disease (CAD+) and ninety-two consecutive patients with normal coronary artery (CAD-) were included. Presence and severity of coronary artery disease were determined using the SS.

RESULTS: We observed that the MOTS-c levels was lower in the CAD group (111±13 *vs.* 161±23, $p<0.001$). The MOTS-c levels were also found to be significant independent predictors for CAD in multiple regression analysis ($p<0.001$). A MOTS-c levels ≥130.9 had 80.3% sensitivity and 73.2% specificity (area under the curve [AUC]: 0.858, 95% CI: 0.895-0.999, $p<0.001$) for predicting CAD.

CONCLUSIONS: The authors revealed that there is a strong correlation between MOTS-c levels and CAD. Therefore, MOTS-c may help identify patients with CAD, thus allowing for early preventive treatment.

Key Words:
Coronary artery disease, MOTS-c, SYNTAX score.

Introduction

Coronary artery disease (CAD) is the most common cause of mortality and morbidity worldwide[1]. Atherosclerosis plays an important role in the occurrence and prevalence of CAD[2]. Numerous factors contribute to the pathogenesis of atherosclerosis, including endothelial dysfunction, dyslipidaemia, inflammatory and immunological factors, plaque rupture and smoking[3,4]. Among them, endothelial dysfunction occurs before the morphological signs of atherosclerosis develop and is associated with many cardiovascular risk factors, including hypercholesterolaemia, diabetes, hypertension (HT), ageing and obesity[5,6].

The effects of C-reactive protein (CRP), lipoprotein-associated phospholipase A2 and various cytokines and mediators on the development of atherosclerosis have been demonstrated[7-9]. These include mitochondrial-derived peptides (MDPs) encoded in mitochondrial DNA (mtDNA). Several *in vitro* and *in vivo* studies[10,11] have shown that MDPs, such as humanin, mitochondrial open-reading-frame of the twelve S rRNA-c (MOTS-c) and small humanin-like peptides (SHLPs), protect endothelial cells from damage due to reactive oxygen radicals and contribute to the continuity of endothelial function. MOTS-c has positive effects on atherosclerosis, ageing, insulin resistance and hyperlipidaemia[12,13].

In this study, we investigated the relationship between MOTS-c level and the presence and severity of CAD in stable patients using the SYNTAX score (SS), which is an internationally accepted scoring system.

Patients and Methods

Study Population

Our single-centre prospective study included 92 consecutive stable patients who presented to the outpatient clinic with chest pain and had severe stenosis in one or more coronary arteries on invasive coronary angiography (CAG). Ninety-two patients with normal coronary arteries (NCAs) were included in the control group. Ste-

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nosis ≥ 50% in diameter in one or more major epicardial coronary arteries was considered to reflect significant CAD. Patients with acute coronary syndrome, a previous bypass operation, history of percutaneous coronary intervention, known malignancy, chronic renal failure or liver disease were not included in the study.

The medical history and laboratory values of each patient were collected. The presence of classical cardiovascular risk factors, including age, gender, diabetes mellitus (DM), HT, dyslipidaemia and smoking was determined. Patients with DM were confirmed based on prior diagnosis, currently receiving medical treatment, or a fasting glucose level > 126 mg/dL[14]. Patients with HT had a history of thereof and antihypertensive drug use, or systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg in repeated office blood pressure measurements[15]. Transthoracic echocardiography was performed on each patient before CAG. All measurements were made using a Vivid 7 machine (GE Medical Systems, Milwaukee, WI, USA) with a 3.5 MHz transducer. Patients with congestive heart failure had a left ventricular ejection fraction ≤ 40%. Patients classified as current smokers smoked one or more cigarettes/day for > 1 year. Stenosis of ≥ 50% in non-coronary arteries was defined as peripheral artery disease (PAD).

Antecubital venous blood samples were drawn from all patients into tripotassium EDTA-based anticoagulated tubes before CAG. The blood samples were taken in the morning after 20 min of rest following a 12-hour fasting period. Haemogram and all routine biochemical tests, such as glucose, serum albumin and lipid profiles, were performed using an autoanalyser (Roche Cobas6000; Mannheim, Germany). The neutrophil to lymphocyte ratio (NLR) was calculated based on the ratio of the absolute neutrophil and lymphocyte counts. The blood samples drawn before CAG were immediately centrifuged to measure the MOTS-c level, and the serum samples were stored at -80°C until the day of analysis. Serum MOTS-c levels were measured using a commercial enzyme-linked immunosorbent assay kit (sensitivity: < 10 pg/ml; assay range: 31.2-2,000 pg/ml; Boster Immunoleader, Pleasanton, CA, USA), as recommended by the manufacturer's protocol.

Coronary Angiography

CAG was indicated based on typical chest pain or non-invasive stress test results suggesting myocardial ischaemia (positive stress test and/or ischaemia on myocardial perfusion scintigraphy). CAG was performed in all patients via femoral or radial access. The coronary arteries were evaluated from at least two different views. Treatment decisions (percutaneous intervention, surgical or medical treatment) were left to the discretion of the physician performing the procedure.

The SS was developed during the SYNTAX trial to provide information regarding the complexity (coronary segment, anatomical features, tortuosity, lesion length, calcification and thrombus) of the CAD[16]. Stenosis ≥ 50% in diameter in one or more major epicardial coronary artery was considered a significant CAD. NCAs were defined as those with no visible disease or luminal irregularity (< 50%), as judged visually on CAG. The SS was calculated by two blinded, experienced interventional cardiologists using an online algorithm (www.syntaxscore.com)[17]. The final decision on disputed cases was made by consensus.

Statistical Analysis

Statistical analyses were conducted SPSS (version 26.0, SPSS Inc., IBM, Armonk, NY, USA) and MedCalc statistical software (version 12.7.8; MedCalc Software, Mariakerke, Belgium). Continuous variables are presented as mean ± standard deviation and/or medians (range). Categorical variables are summarised as percentages and were compared using the chi-square test or Fisher's exact test. The Kolmogorov-Smirnov test was used to evaluate the normality of the continuous variables. To estimate CAD, age, female sex, DM, MOTS-c, NLR, WBC and MPV were included in the univariate analysis. Parameters with a p-value ≤ 0.05 (age, female sex, DM, MOTS-c, NLR, WBC and MPV) were included in the multiple logistic analysis. Receiver operating characteristic (ROC) curves were used to determine the best cut-off value for MOTS-c value in the prediction of CAD. A two-tailed p-value < 0.05 was considered significant.

Results

The analyses included 184 patients seen from August 2021 through September 2021. The mean age was 58.1±9.6 and the mean SS was 17.1±6.8. Table I summarizes the clinical and demographic characteristics. Age (p=0.021), female sex (p=0.018), diabetes mellitus (p<0.015), WBC (p<0.001), MPV (p=0.010), neutrophil (p<0.001), lymphocyte (p<0.001), neutrophil/lymphocyte ratio (p<0.001) differed significantly

Table I. Clinical and demographic characteristics of groups.

	CAD (+) (n=92)	CAD (-) (n=92)	*p*
Age, years,	60.0 ± 7.3	56.7 ± 11.5	0.021
Female sex, n (%)	36 (39.1)	52 (56.5)	0.018
Diabetes mellitus, n (%)	42 (45.7)	26 (28.3)	0.015
Hypertension, n (%)	44 (47.8)	38 (41.3)	0.374
Heart failure, n (%)	8 (8.7)	14 (15.2)	0.173
Smoking, n (%)	22 (47.8)	19 (41.3)	0.529
PAD, n (%)	10 (10.8)	8 (8.6)	0.863
Systolic BP (mmHg)	133.1 ± 18.0	131.8 ± 20	0.760
Diastolic BP (mmHg)	80.6 ± 8.9	81.0 ± 9.5	0.830
Glucose (mg/dL)	136 ± 59	116 ± 42	0.055
CRP (mg/dL)	0.78 ± 0.2	0.64 ± 0.1	0.165
Serum creatinine (mg/dL)	0.89 ± 0.1	0.82 ± 0.2	0.117
Hemoglobin, g/dl	13.6 ± 1.0	13.4 ± 2.0	0.429
WBC, 10^3/mL	8.8 ± 1.4	7.2 ± 1.7	<0.001
Mean platelet volume, fL	10.2 ± 0.8	9.9 ± 0.7	0.010
Neutrophil, 10^3/mL	5.0 ± 1.5	4.0 ± 1.4	<0.001
Lymphocyte, 10^3/mL	2.2 ± 0.5	2.5 ± 0.7	<0.001
NLR	2.4 ± 0.9	1.6 ± 0.6	<0.001
Total cholesterol (mg/dL)	204 ± 42	202 ± 37	0.293
Low density lipoprotein cholesterol (mg/dL)	129 ± 26	124 ± 26	0.247
High density lipoprotein cholesterol (mg/dL)	44 ± 12	48 ± 17	0.207
Triglyceride (mg/dL)	211 ± 33	176 ± 38	0.164
MOTS-c	111 ± 13	161 ± 23	<0.001
Aspirin use, n (%)	36 (39.1)	34 (37.0)	0.763
ACE-inhibitor/ARB use, n (%)	38 (41.3)	34 (37.0)	0.546
Statin use, n (%)	16 (17.4)	16 (17.8)	0.945
CCB use, n (%)	18 (19.6)	24 (26.1)	0.292
Beta-Blocker use, n (%)	24 (26.1)	22 (24.4)	0.799
Diuretic use, n (%)	6 (6.5)	18 (19.6)	0.119
Ejection Fraction, (%)	55.8 ± 5.0	55.9 ± 7.3	0.908

Abbreviations: ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, BP: blood pressure, CCB: calcium channel blocker, CRP: c-reactive protein, MOTS-c: mitochondrial open-reading-frame of the twelve S rRNA-c, NLR: neutrophil/lymphocyte ratio, PAD: peripheral artery disease, WBC: white blood cell.

between the two groups. Patients with CAD had a significantly lower value of MOTS-c (111±13 *vs.* 161±23, $p<0.001$). A significant negative correlation was also observed between the MOTS-c values and the SS (r=-0.635, $p<0.001$) (Figure 1).

The receiver operating characteristic (ROC) curve was applied to determine the best MOTS-c cut-off value to predict CAD. The optimal threshold for the prediction of CAD was ≥ 130.9. This threshold had a 80.3% sensitivity and 73.2% specificity (area under curve [AUC]: 0.858, 95% CI: 0.895-0.999, $p<0.001$) (Figure 2).

Univariate and multivariate logistic regression analysis results are given in Table II. In univariate analysis, age, female sex, DM, MOTS-c, NLR, WBC and MPV were significant predictors of CAD. In multivariate analyses, MOTS-c (β=0.886; CI 0.850–0.923, $p<0.001$) and NLR (β=3.883; CI 1.338–11.269, $p=0.013$) were independent predictors of CAD.

Discussion

Serum MOTS-c levels were lower in our CAD patients than in the NCA patients. In addition, CAD patients with a high SS had lower serum MOTS-c levels than CAD patients with a low SS. Furthermore, the MOTS-c level was negatively correlated with the SS, and a low MOTS-c level was an independent risk factor for CAD with a high SS.

CVD is a leading cause of death and disability worldwide[1]. CAD accounts for approximately half of all CVD cases[18]. Multiple factors contribute to the pathogenesis of atherosclerosis, including dyslipidaemia, inflammation, plaque rupture and smoking. Endothelial dysfunction also contributes to the development of atherosclerosis and coronary plaque[19,20]. The endothelium has many functions in the circulatory system, such as providing haemostasis, preventing inflammation, enhancing cell migration and promoting vascular

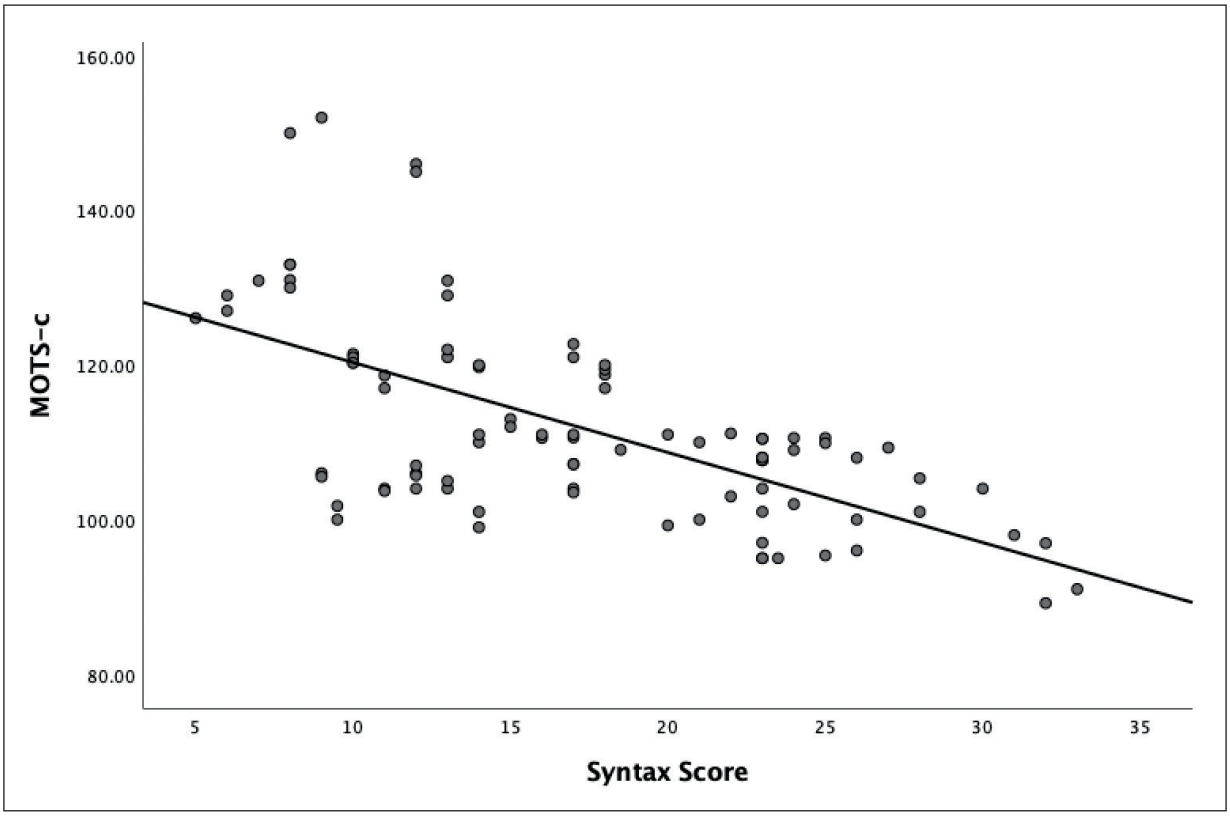

Figure 1. A significant negative correlation observed between the MOTS-c values and the SS (r=-0.635, $p<0.001$). MOTS-c, mitochondrial open-reading-frame of the twelve S rRNA-c; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial.

tone. Endothelial vasodilator dysfunction is the first step in atherosclerosis and is thought to result from loss of endothelial-derived nitric oxide[21].

MDPs are a series of peptides encoded by mtDNA with similar functions to mitochondria. Three types of MDPs have been identified: MOTS-c, SHLP and humanin. They are all metabolic regulators in the body that play a cytoprotective role in mitochondrial function and cell viability. The effects of MDPs on ageing, atherosclerosis, insulin resistance, hyperlipidaemia and inflammation have been determined.

It has been observed that MOTS-c, a novel peptide derived from mitochondria, has positive effects on endothelial function, where administering MOTS-c to mice improves endothelial function[22]. *In vitro* studies by Kim et al[13] showed that MOTS-c reduces vascular inflammation by inhibiting inflammatory gene expression, and improves acetylcholine-mediated vasodilation. Other *in vivo* and *in vitro* studies have shown that MDPs protect against the harmful effects of reactive oxygen radicals and thus have positive effects on endothelial function. MOTS-c improves muscle metabolism, weight regulation, bone fracture healing and osteoporosis[13,23,24]. MOTS-c also reduces insulin resistance and the development of DM by preventing diet-induced obesity[13]. DM is associated with an increased prevalence and severity of CAD, increased incidence of acute coronary syndrome and poor outcomes compared to patients without DM[25]. In our study, the incidence of DM was significantly higher than in the control group. Some studies have shown that MOTS-c plays a cytoprotective role in age-related diseases by modulating mitochondrial energy metabolism[26,27]. Wei et al[28] reported that MOTS-c reduces vascular calcification and myocardial remodelling through the adenosine monophosphate-activated protein kinase signalling pathway. Studies[29-31] have shown that MDPs exert cytoprotective effects *in vivo* through anti-apoptosis, anti-oxidative stress, endoplasmic reticulum stress and anti-inflammatory responses. Muzumdar et al[32] revealed that MDPs play a protective role in myocardial ischaemia reperfusion injury.

Inflammation plays a central role in the pathogenesis of atherosclerosis, and elevated inflammatory markers indicate vascular damage[33]. The NLR is an indicator of the inflammation associated with many clinical events, such as atherosclerosis, acute coronary syndrome and

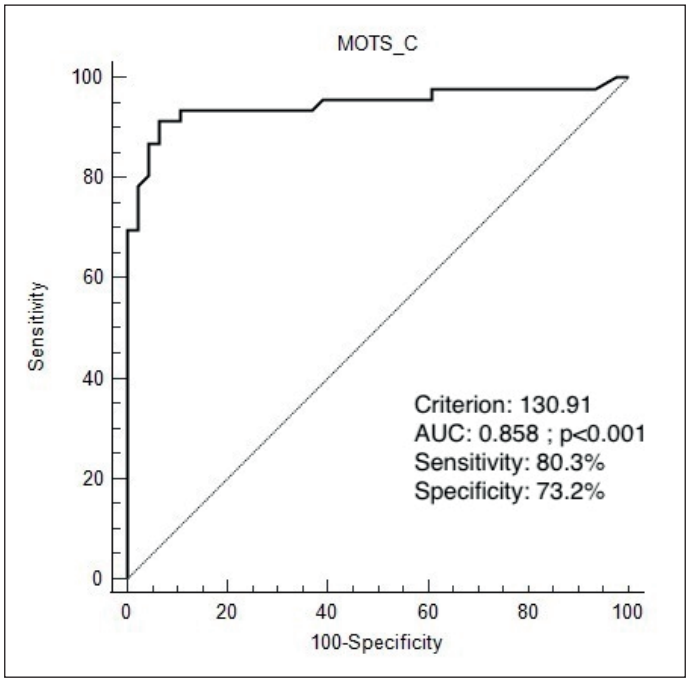

Figure 2. ROC curve graphics to detect the best cut-of value for the MOTS-c in predicting CAD. AUC indicates area under the curve; MOTS-c, mitochondrial open-reading-frame of the twelve S rRNA-c.

adverse clinical events[34]. Verdoia et al[35] detected a relationship between the NLR and CAD. MPV indicates platelet size, and larger platelets have been shown to be more reactive and associated with inflammatory status. Studies have shown that high MPV values are associated with coronary artery disease[36]. Consistently, in our study, the NLR and MPV were significantly higher in the CAD than control group and NLR was an independent predictor for CAD.

In addition, there may be a close relationship between SS and inflammation[37]. The SS is an angiographic tool used to grade the complexity of CAD by considering the number of lesions and their functional and anatomic characteristics, including location, presence of bifurcations, tortuosity, total occlusions, thrombus and calcification. The SS helps physicians determine the optimal revascularisation strategy, particularly among patients with complex CAD. A high SS indicates a more complex disease and therapeutic challenge. Patients with a high SS have more major adverse cardiac or cerebrovascular events[38].

Conclusions

In the present study, the MOTS-c level was lower in patients with stable CAD than in the control group without CAD, and the MOTS-c level was inversely correlated with the severity and complexity

Table II. Univariate and multivariate analysis for prediction of stable coronary artery disease.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.031 (1.000-1.063)	0.050	1.072 (0.989-1.162)	0.089
Female Sex	2.022 (1.124-3.639)	0.019	0.951 (0.222-4.069)	0.946
Diabetes mellitus	2.132 (1.157-3.931)	0.015	1.041 (0.255-4.260)	0.955
MOTS-c	0.899 (0.873-0.925)	<0.001	0.886 (0.850-0.923)	<0.001
NLR	2.907 (1.869-4.522)	<0.001	3.883 (1.338-11.269)	0.013
WBC	1.798 (1.454-2.224)	<0.001	1.424 (0.935-2.167)	0.099
MPV	1.609 (1.115-2.323)	0.011	2.200 (0.859-5.638)	0.100

CI: confidence interval, MOTS-c: mitochondrial open-reading-frame of the twelve S rRNA-c, MPV: mean platelet volüme, NLR: neutrophil to lymphocyte ratio, OR: odds ratio, WBC: white blood cell.

of CAD, as assessed by the SS. Therefore, MOTS-c may help identify patients with CAD, thus allowing for early preventive treatment.

The limitations of this study included the small number of patients and single-centre design. Endothelial dysfunction may have been undetectable by conventional CAG in the control group. Studies with larger populations are required to clarify the relationships among MOTS-c, CAD and the SS.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Committee

All the procedures used in the study were approved by Inonu University Malatya Clinical Research Ethics Committee (No. 2021/76) and informed consent was obtained from all participants.

Authors' Contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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