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Leukocyte telomere length and lipid parameters in patients with myocardial infarction with non-obstructive coronary arteries

Nihal Inandiklioglu[1]*, Vahit Demir[2], Yunus Celik[3], Mustafa Demirtas[4]

[1]*Department of Medical Biology, Faculty of Medicine, Yozgat Bozok University, Yozgat, 66100, Turkey*
[2]*Department of Cardiology, Faculty of Medicine, Yozgat Bozok University, Yozgat, 66100, Turkey*
[3]*Department of Cardiology, Kırıkkale Yüksek Ihtisas Hospital, Kırıkkale, 71100, Turkey*
[4]*Department of Cardiology, Faculty of Medicine, Çukurova University, Adana, 01380, Turkey*

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ABSTRACT

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is defined as stenosis of less than 50% or no stenosis on coronary angiography in a patient diagnosed with myocardial infarction. Telomere length is expressed by studies that it acts as a biomarker, especially for biological aging and cardiovascular diseases. In this study, we aimed to investigate whether there is a relationship between circulating leukocyte telomere length (LTL) and serum lipid values in MINOCA patients. Forty-five newly diagnosed patients with MINOCA were included in the study, along with 45 healthy controls who matched the patients in terms of age and gender. We determined the LTL value using the RT-PCR method. As a result of the study, we found LTL ($p< 0.001$) and serum lipid values (HDL-cholesterol ($p< 0.001$), LDL-cholesterol ($p< 0.001$), triglycerides ($p< 0.05$), and total cholesterol ($p< 0.05$)) to be significantly higher in the MINOCA group than in the control group. When the correlation relationship between LTL and lipid values in the MINOCA group was evaluated, a negative correlation was determined only between LTL and HDL ($p=0.014$, $r=-0.362$). This is the first study to evaluate telomere length in MINOCA patients in Turkey. Our results support the existence of short telomere length in MINOCA patients.

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Introduction

Acute coronary syndromes (ACS) are the leading cause of death worldwide. In recent years, early coronary angiography has become the standard approach in the diagnosis and management of ACS. Studies have shown that more than 90% of ACS cases have an obstructive lesion in at least one coronary artery (1,2). On the other hand, no occlusive coronary lesion was detected in approximately 10% of the cases. In acute myocardial infarction (AMI) studies, it was determined that 1-13% of the cases were not obstructed coronary stenosis in coronary angiography. In these cases, several question marks emerged about the mechanism of myocardial damage (3-5). The European Society of Cardiology (ESC) focused on the issue and commissioned a working group for this clinical entity. The relevant group presented the results of the study as a detailed report. This consensus report calls the clinical picture "Myocardial infarction with non-obstructive coronary arteries (MINOCA)", correspondingly with the previous few literature data. MINOCA is a distinct clinical syndrome that meets the diagnostic criteria for AMI but is characterized by less than 50% stenosis on coronary angiography. Its prevalence is between 5-25% of all MIs in large AMI registries (6). In a study published in 2015 and forming the basis for the 2017 ESC guidelines, it was stated that the MINOCA patient frequency was 6%. (7). It was shown that patients with chest pain and coronary arteries without occlusive stenosis were mostly women, and contrary to what was thought, these cases couldn't have a good prognosis (8). In a retrospective study, it was reported that MINOCA patients were younger than AMI patients with obstructive coronary artery disease (MICAD) patients, had a higher frequency of women, had a better left ventricular ejection fraction (LVEF), a lower grace score, and diabetes mellitus (DM) and smoking were observed less frequently (9).

Telomeres are specialized heterochromatin

*Corresponding author. E-mail: nihal.inandiklioglu@yobu.edu.tr

structures located at the ends of linear chromosomes of eukaryotic organisms. Human telomeres consist of a 5-15 kb long repetitive simple DNA sequence (TTAGGG) and telomere-associated protein. Telomeres play an important role in maintaining the integrity of chromosomes, stabilizing their exonucleotic disruption, and protecting them from chromosomal fusions and homologous pairings (10). Telomeres also work like a mitotic clock by determining the maximum replicative capacity for somatic cells. Telomere lengths in human somatic cells gradually decrease by 20 to 200 bp with each cell division (11). Various epidemiological studies have reported that short telomere length is a link between cardiovascular diseases and cardiovascular mortality. An American study group in 2010 stated that coronary atherosclerosis was associated with telomere length (12). As a result of radiological examinations performed in 275 coronary artery patients, a relationship was found between the stiffness and volume of large arteries such as the carotid and femoral arteries and telomere length (13).

In this study, we aimed to investigate whether leukocyte telomere length (LTL) is associated with lipid values in MINOCA patients. The researches on MINOCA patients are very limited in the literature. In fact, almost no studies are evaluating the risks of LTL and MINOCA. Therefore, this study is the first study to study telomere length in MINOCA patients in the Turkish population.

Materials and methods

Study population

Patients who applied to the emergency department between August 2018 and June 2020, diagnosed with acute myocardial infarction, underwent coronary angiography, and were then diagnosed with MINOCA were included in the study. A total of 90 people, 45 patients diagnosed with MINOCA, and 45 healthy controls of the same age and gender were included in the study. Exclusion criteria were the following: cardiogenic shock, reduced ejection fraction heart failure, ventricular arrhythmias, a history of coronary revascularization, active severe bleeding, uncontrolled hypertension, severe renal or liver failure, and chronic inflammatory disease. Body mass index (BMI) was calculated by dividing body weight by the square of the height (kg/m^2). Fasting venous blood samples were used in the morning after hospitalization for the measurement of all biochemical parameters. Complete blood count was measured with the XN‑1000 analyzer (Sysmex Ameria Inc., Lincolnshire, Illinois, the USA), and lipid profile was measured with the Architect ci4100 automated analyzer (Abbott, Abbott Park, Illinois, the USA). Ethics committee approval of the study was obtained from Yozgat Bozok University Ethics Committee (Ethics Committee No: 2017-KAEK-189_2018.12.12_02).

Cardiology analyzes

Transthoracic echocardiography was performed for each patient instantly after the admission using a commercially available machine (Philips Logic Affiniti 50G Machine; Philips, Amsterdam, Netherlands) with an ultrasound transducer. Coronary angiography was performed within one hour. Angiograms of all patients were evaluated using the coronary angiography recording system. The diagnostic criterion used for the diagnosis of occlusive coronary artery disease was accepted as the presence of 50% or more stenosis in any major epicardial coronary artery. Patients with a diagnosis of myocardial infarction and non-occlusive coronary artery were determined according to the diagnostic criteria (6, 14).

Genetic analyzes

In the study, the blood samples of the patient and control group taken to EDTA tubes were used. DNA isolation of the blood samples was done using a DNA isolation kit (PureLink™ Genomic DNA Mini Kit, Thermo Fisher Scientific, the USA). The obtained DNAs were stored at -80°C until the analyses. Leukocyte telomere length was measured by Real-Time Quantitative Polymerase Chain Reaction (RT-PCR) method according to the original study (15). DNA concentrations were equalized to 10 ng/µl in all samples (QFX Model Fluorometre, Denovix, the USA). The relative telomere length was calculated as the ratio (T/S ratio) of the telomere repeat signal (T) to the single-copy gene 36B4 (acidic ribosomal phosphoprotein P0, S). The number of telomere repeats and the amount of single-copy gene copies for each sample were defined by comparing the telomere and single-copy gene with a reference sample in quantitative PCR. The normalization of PCR products, whose relative quantification was performed with the Ct method, was performed with 36B4, which was used as a single copy gene. PCR efficiency normalization was identified with the Telomer/36B4 (T/S)= 2[Ct (Telomer) – Ct (36B4)] =2-ΔCt Method. Relative T/S ratio (R) used after normalization was calculated with R=2-(ΔCt Telomere – ΔCt 36B4) =2-ΔΔCt Method. The resulting T/S ratio was proportional to the average telomere length. T/S ratios were converted to base pairs (bp) with the formula and LTL value was calculated (15). The primers used in the study are shown in Table-1.

Table 1. Primer sequences were used in this study. Telomere FW (A), Telomere RV (B), 36B4 FW (C), and 36B4 RV (D)

A	5' GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT 3'
B	5' TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA 3'
C	5'CAGCAAGTGGGAAGGTGTAATCC 3'
D	5' CCCATTCTATCATCAACGGGTACAA 3'

Statistics

Statistical analysis was performed using the statistical package SPSS software (Version 21.0, SPSS Inc., Chicago, IL, the USA). If continuous variables were normal, they were described as the mean±standard deviation ($p>0.05$ in Kolmogorov-Smirnov Test or Shapira-Wilk Test ($n<30$)), and if the continuous variables were not normal, they were described as the median. For each continuous variable, normality was checked by the Kolmogorov Smirnov and Shapiro-Wilk Test and by histograms. The categorical variables between the groups were analyzed by using the Chi-Square Test or Fisher's Exact Test. Comparisons between groups were made using the Student T-Test for normally distributed data, and Mann Whitney U Test was used for the data that were not normally distributed. P <0.05 was considered statistically significant.

Results and discussion

The MINOCA group consisted of 45 individuals (Male: 18, Female: 27) with an average age of 59.0 ± 7.2 years, and the control group consisted of 45 healthy volunteers (Male: 19, Female: 26) with an average age of 57.0 ± 6.9 years (between the ages of 44-69), a total of 90 people (Male: 37 (41.1%), Female: 53 (58.9%)). There were no statistically significant differences between the groups in terms of age, gender, creatinine, systolic blood pressure, white blood cell (WBC), sodium (Na), and potassium (K) values ($p>0.05$). When the LTL and T/S ratios between the groups were compared in the study, a significant difference in LTL was found in the MINOCA group ($p<0.05$). The demographic, biochemical, clinical, and genetic data of the patient and control group were compared statistically (Table 2, Figure-1).

Table 2. Demographic, clinical and genetic findings are shown according to the groups

	MINOCA	Control	*p* Value
Participants (n)	45	45	-
Age (year)	59.0 ± 7.2	57.0 ± 6.9	0.158
Female gender (%)	60	57.8	0.891
BMI (kg/m^2)	26.2 ± 2.8	23.3 ± 2.2	0.000*
Systolic blood pressure (mmHg)	130.1 ± 9.4	126.9 ± 13.1	0.144
Diastolic blood pressure (mmHg)	76.0 ± 6.0	79.0 ± 6.1	0.025*
Glucose (mg/dl)	151.6 ± 37.4	103.8 ± 21.7	0.000*
Urea (mg/dL)	33.9 ± 24.9	16.8 ± 6.2	0.000*
Creatinine (mg/dL)	1.0 ± 1.0	0.8 ± 0.1	0.160
Total cholesterol (mg/dL)	219.6 ± 34.0	198.6 ± 39.6	0.008*
Triglyceride (mg/dL)	202.0 ± 64.5	161.5 ± 60.2	0.003*
HDL-cholesterol (mg/dL)	39.3 ± 6.2	48.1 ± 9.8	0.000*
LDL-cholesterol (mg/dL)	165.5 ± 24.1	114.5 ± 31.4	0.000*
WBC (10^3/mm^3)	7.9 ± 2.9	8.1 ± 2.3	0.394
Hemoglobin (g/dL)	13.3 ± 1.6	14.4 ± 1.6	0.002*
Platelet (10^3/mm^3)	232.8 ± 61.2	265.6 ± 54.6	0.009*
Na (mEq/L)	138.5 ± 4.6	137.9 ± 3.5	0.310
K (mEq/L)	4.1 ± 0.6	3.9 ± 0.4	0.152
LVEF (%)	52.6 ± 5.4	55.0 ± 4.7	0.034*
LTL (kbp)	4.416 ± 0.232	4.615 ± 0.248	0.000*
T/S ratio	0.47 ± 0.1	0.56 ± 0.1	0.000*

* P <0.05 was considered statistically significant. Values presented as mean ± standard deviation. LVEF: Left ventricular ejection fraction; LTL: Leukocyte telomere length; K: Potassium; Na: Sodium, WBC: White blood cell.

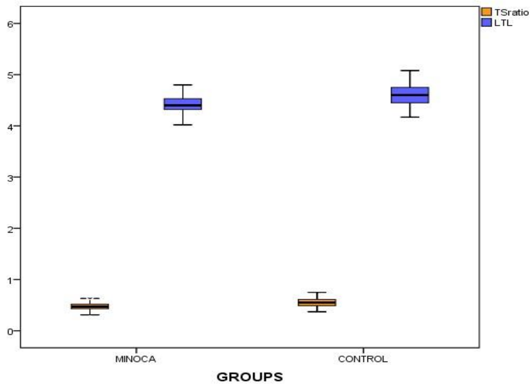

Figure1. LTL and T/S ratio are shown between groups

When the correlation results of LTL and T/S ratio in the MINOCA group were evaluated, the data in Table-3 were obtained. As a result of the correlation analysis, LTL (p=0.014, r=-0.362) and T/S ratio (p=0.018, r=-0.352) were only negatively correlated with high-density lipoprotein-cholesterol (HDL-C). When we evaluated the data according to gender in the MINOCA group, age (p=0.544), BMI (p=0.089), platelet (p=0.779), glucose (p=0.683), urea (p=0.491), creatinine (p=0.321), K (p=0.770), triglyceride (p=0.147), HDL-C (p=0.066), LDL-C (p=0.111), and LTL (p=0.842) were insignificant (Figure-2). On the other hand, hemoglobin (p=0.000), WBC (p=0.003), Na (p=0.007), total cholesterol (p=0.003), systole (p=0.030) and LVEF (p=0.014) values were significant according to gender.

Table 3. Correlation of patient group data with LTL and T/S ratio

		LTL	T/S oranı
BMI	r	-0.008	-0.006
	p	0.958	0.970
Diastolic blood pressure (mmHg)	r	0.109	0.099
	p	0.475	0.517
Glucose	r	0.101	0.106
	p	0.508	0.489
Urea	r	0.217	0.224
	p	0.151	0.138
Total cholesterol	r	-0.177	-0.177
	p	0.246	0.245
Triglyceride	r	-0.204	-0.211
	p	0.179	0.165
LDL-cholesterol	r	-0.075	-0.075
	p	0.623	0.623
HDL-cholesterol	r	-0.362*	-0.352*
	p	0.014	0.018
Hemoglobin	r	-0.138	-0.132
	p	0.386	0.386
Platelet	r	-0.029	-0.030
	p	0.848	0.846
LVEF	r	0.017	0.017
	p	0.911	0.911
LTL	r	-	0.997**
	p	-	0.000
T/S ratio	r	0.997**	-
	p	0.000	-

*. Correlation is significant at the 0.05 level. **. Correlation is significant at the 0.01 level

In this study, it was found that the changes in LTL and T/S ratio decreased in the MINOCA Group compared to the control group and were statistically significant. It was also observed that lipid values were significant in the MINOCA Group, but only a negative significant correlation was detected between HDL-C and LTL. We could not prove a significant difference in LTL and T/S ratio according to gender in the MINOCA group.

The data highlighted that MINOCA patients were younger and more likely to be female than MICAD patients. It was also found that patients were less likely to have hyperlipidemia (9). This indicates that one of the underlying factors of MINOCA may be gender and/or hormonal effects. Supporting this opinion, it was revealed that the decrease in estrogen levels was associated with a 7-fold increased risk for coronary artery disease (16). It was also found that exogenous estrogen exposure was associated with telomere length and preservation (17). There have been studies based on this idea, but some of them could not fully establish a relationship (18, 19). Although we found a higher female patient population in our study, we could not establish a relationship between LTL and gender.

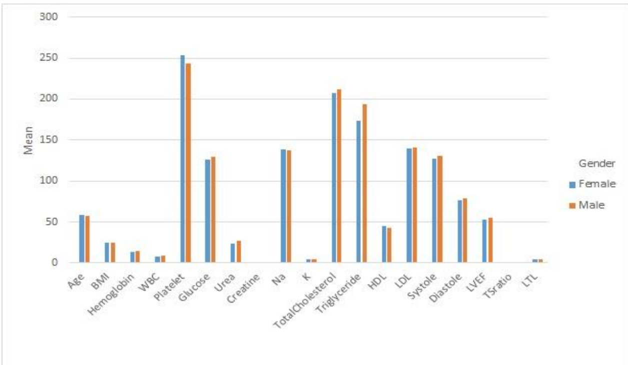

Figure 2. Distribution of values by gender in the MINOCA group. BMI: body mass index; WBC: white blood cell; Na: sodium; K: potassium; HDL: high density lipoprotein; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; LTL: Leukocyte telomere length

In the literature, we found only one study on telomere length in MINOCA patients. In the study that included 126 coronary artery disease (CAD) patients, telomerase activity was higher and LTL length was shorter in 7 MINOCA patients compared to the control group (20). Similar to this study, we found the LTL value to be shorter in the MINOCA Group compared to the control group. There are many studies in the literature showing the relationship between telomere shortness and CAD. Shorter telomeres were detected in CAD patients (21), and subsequent studies reported a relationship between short telomeres and cardiovascular mortality (22). On the contrary, as a result of the examinations performed in juvenile AMI cases, it was emphasized that telomere lengths were not statistically significant in terms of AMI and it was not a significant predictive finding (23). When the relationship between left ventricular function levels and telomere length after AMI was evaluated, no relationship could be shown between left ventricular function levels and telomere length in post-operated cases (24).

As is known, serum lipid levels are among the risk factors for the development of cardiovascular diseases (CVD). In many studies, a negative correlation was reported in terms of coronary artery disease and atherosclerosis development in cases as a result of reduced low-density lipoproteins (14). While shortening of telomere length was observed in CAD patients with a family history of coronary artery disease, it was detected that the telomere length was higher in the vegetarian-fed control group compared to the CAD group (25). As a result of another study in England in which lipid levels were evaluated with left ventricular parameters, it was determined that high LDL-C and high triglyceride were associated with lower LVEDV, lower LV mass, and higher LVEF levels. High HDL-C was associated with higher LVEDV and higher LV mass, but it could not be associated with LVEF (26). Research data evaluating 17 biomarkers of cardiovascular disease risk with LTL indicate only HDL-C and triglycerides from lipoproteins (27). On the other hand, there was a positive correlation between HDL-C and LTL, but not for LDL-C and triglycerides (28). It was determined that short telomere length is associated with coronary artery disease in men with hypertension in left ventricular hypertrophy, whereas it is correlated with short ischemic attacks in women (29). As a result of this study, it was found that LVEF, LDL-C, and triglyceride values were not associated with LTL. However, we also observed a negative correlation between LTL and HDL-C. When we evaluated both the literature findings and our findings, studies in different populations are needed to determine the relationship between CVD risk factors and LTL.

In summary, there is very little research and data about MINOCA in the literature, since MINOCA is a difficult CVD to detect. Therefore, we generally evaluated our data in relation to the findings of previous studies on CVD. In this context, our study will be a source for future studies as it is one of the first telomere studies conducted in MINOCA patients. Moreover, our findings have original values, as it is one of the first studies to evaluate LTL and MINOCA risk factors. The significance of our findings will be supported by future studies on telomere length.

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Authorship Contribution Statement

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Ethics Approval

Ethics committee approval of this study was approved by Yozgat Bozok University Ethics Committee (Ethics committee no: 2017-KAEK-189_2018.12.12_02).

Conflict of Interest

The authors declared no conflict of interest.

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