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High-Risk Carotid Imaging Predicts ST-Segment Elevated Myocardial Infarction in Young Patients: A Cross-Sectional Study

Genç Hastalarda Karotis Görüntülemesinin ST-Elevasyonlu Miyokard Enfarktüsü Kestirebilirliği: Kesitsel Bir Çalışma

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ABSTRACT

Introduction: Myocardial infarction remains a major cause of morbidity and mortality in the young population. The relationship between carotid intima-media thickness (CIMT) and atherosclerosis has been shown in many studies, however, there is no study investigating the association between carotid imaging and cardiovascular events in young patients. In our study, we evaluated the carotid imaging of young patients who experienced ST-elevated myocardial infarction (STEMI) and individuals at the same age and with normal coronary arteries.

Methods: A total of 160 young patients were enrolled in the study. Of them, 115 patients were under the age of 45 years with STEMI and 45 were under the age of 45 years with normal coronary arteries shown in the coronary angiography. Carotid ultrasound was performed for all patients and they were divided into high-risk and low-risk carotid image groups according to CIMT and the presence of carotid plaque. Both groups were compared according to the traditional risk factors and the predictors of STEMI were investigated.

Results: Both CIMT (0.87±0.28, vs 0.70±0.16, $p<0.001$) and the presence of carotid plaque (14.8% vs 2.2%, $p=0.024$) were found to be significantly higher in young patients with STEMI compared to the control group. Independently from other traditional risk factors, 0.1 mm increase in CIMT was associated with a 42% increase in odds for STEMI. Similarly, being in the high-risk carotid image group had 9.2 times increased odds for STEMI than being in the low-risk carotid image group.

Conclusion: CIMT and the presence of carotid plaque have a predictive value for cardiovascular events in young age independently from traditional risk factors.

Keywords: Myocardial infarction, carotid intima-media thickness, young age, carotid plaque, subclinical atherosclerosis

ÖZ

Amaç: Miyokard enfarktüsü günümüzde en önemli mortalite ve morbidite sebebi olmaya devam etmektedir. Karotis intima media kalınlığının (KIMK) aterosklerozla ilişkisi, birçok çalışmada gösterilmiştir, fakat genç populasyonda karotis görüntüleme ile kardiyovasküler olayları araştıran bir çalışma mevcut değildir. Çalışmamızda, genç yaşta ST-elevasyonlu miyokard enfarktüsü (STEME) geçirmiş olan hastalar ile, aynı yaş grubunda normal koroner arterlere sahip olan bireylerin karotis görüntülemeleri değerlendirildi.

Yöntemler: Çalışmamıza dahil edilen 160 hasta, 45 yaş altı, STEME geçirmiş 115 hasta ve kontrol grubu olarak koroner anjiyografi ile koroner arterleri normal olarak saptanan 45 hastadan oluşuyordu. Tüm bireylere karotis ultrasonografisi yapıldı ve hastalar KIMK ve plak varlığına göre yüksek riskli ve düşük riskli karotis görüntüleme olacak şekilde 2 gruba ayrıldı. İki grup da geleneksel risk faktörleri ve STEME'nin bağımsız prediktörleri açısından incelendi.

Bulgular: STEME geçirmiş genç hastalarda hem KIMK (0,87±0,28, vs 0,70±0,16, p<0,001) hem de karotis plak varlığı (14,8% vs 2,2%, p=0,024) kontrol grubuna göre anlamlı olarak yüksek tespit edildi. Diğer geleneksel risk fak- törlerinden bağımsız olarak, KIMK'de 0.1 mm artış, STEME için %42 oranında artışla ilişkili bulundu. Benzer olarak, yüksek riskli karotis görüntüleme grubunda olmanın, düşük riskli gruba göre STEME açısından 9,2 kat artmış riskle ilişkili olduğu gösterildi.

Sonuç: Genç yaşta, geleneksel risk faktörlerinden bağımsız olarak, KIMK ve karotis plak varlığı, kardiyovasküler olaylar açısından prediktif değere sahiptir.

Anahtar Kelimeler: Miyokard enfarktüs, karotis intima-media kalınlığı, genç yaş, karotis plak, subklinik ateroskleroz

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Introduction

Coronary heart disease (CHD) remains one of the most important causes of mortality despite advances in diagnosis and treatment (1). Although CHD generally occurs in patients over the age of 45 years, it can also cause serious morbidity and mortality in younger individuals.

The Framingham risk score system, which is used mostly, is composed of traditional risk factors and has a modest predictive level at best (2). In addition, it has been reported that most of the patients having cardiovascular problems are classified as low- or moderate risk groups by conventional score systems (3,4). Regarding this, non-invasive tests are needed to be used to establish high-risk groups for subclinical atherosclerosis, which are classified as moderate risk group by traditional risk score systems.

Many studies have shown that carotid doppler ultrasonography (USG), ankle-brachial index, and coronary calcium score are all useful in predicting cardiovascular risk beside traditional risk factors (5-7). Those methods, especially carotid intima-media thickness (CIMT) and the presence of carotid plaque, can be widely used to determine early atherosclerotic lesions.

CIMT may be a predictor of cardiac related ischemic events (8). In addition, previous studies have shown that carotid imaging and CIMT are related to the severity of atherosclerosis and the increase in CIMT correlates with the prevalence of cardiovascular diseases (9,10).

To the best of our knowledge, there are a few studies which review the relation between young myocardial infarction (MI) patients and CIMT. Besides, in these studies, control group has not been selected from patients who have completely normal coronary arteries proven by conventional coronary angiography and none of them has been evaluated in terms of the presence of carotid plaque (11-14). For this reason, the clear separation of patient and control groups and the detailed examination of the carotid image make our study unique and valuable. Consequently, we aimed to compare the CIMT and the presence of carotid plaques in young patients who experienced ST-elevated myocardial infarction (STEMI) and in the same aged patients whose coronary angiography results were totally normal. In order to reach this study design, 115 patients that had STEMI and 45 patients with normal coronary angiography were compared considering their carotid scans.

Methods

Study Groups

Totally 160 patients under the age of 45 years, who were admitted to the hospital between the dates of January 1, 2012 and January 1, 2015, were included in the study. One hundred and fifteen patients, who were performed primary percutaneous coronary intervention because of STEMI (mean age: 39.4±4.3 years), and 45 control group patients, who were performed coronary angiography with the suspect of the acute coronary syndrome but resulted with normal coronary angiography (mean age: 39.3±4.2 years), were the subgroups of the study. The decision of angiography for the control group was made according to the patients' symptoms and risk factors. Stress tests (effort test and scintigraphy) were not performed because of suspected unstable angina pectoris. Routine provocation test is not performed in our catheter laboratory. Two of the patients that were clinically suspected of having vasospasm in the control group underwent a provocation test. No coronary vasospasm was detected in these patients. Although the limit values for young age MI vary in various studies, most studies have used an age cut-off of 40 to 45 years to identify young patients with MI. In our study, we used the upper limit to achieve an adequate number of patients and patients below the age of 45 years were accepted to be at young age. Framingham risk score was calculated for all patients. Patients' demographic properties, past medical histories, and cholesterol-hemogram levels were collected. The evaluation of blood lipid levels and other measurements were performed as the standard procedures. Risk factors were categorized as those having or not having the illness. Smoking habits were recorded according to the patients' statements. Hypertension was defined as a systolic blood pressure above 140 and diastolic blood pressure above 90 mmHg, daytime ABP of 135/85 mmHg or use of antihypertensive medications for longer than 2 weeks. Low density lipoprotein level above 130 or using antilipidemic medications was called hypercholesterolemia. A fasting glucose level above 126 or receiving insulin therapy or oral antidiabetic therapy for more than 2 weeks was evaluated as diabetes mellitus (DM). Ambulatory blood pressure monitorization and carotid USG were performed after the coronary angiography. This study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital under the (decision no: 03.07.2014/6). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Ambulatory Blood Pressure Monitorization

All patients underwent ABPM to rule out the effect of blood pressure on CIMT. A portable compact digital recorder (Tonoport V, Milwaukee, GE Healthcare) was used to perform 24-h ABMP measurement. This device was programmed to measure daytime and nighttime blood pressures. Daytime was defined as the time from 07.00 to 23.00 and the device measured blood pressure at 30-min intervals. Nighttime was defined as the time from 23.00 to 07.00 and the device measured blood pressure at 60-min intervals. The patients were told to do their daily activities, but only to remain stable during the device measurement. If more than 80% of the measurements were valid, the test was considered appropriate.

Evaluation of Carotid Images

Carotid USG was performed on all patients for CIMT measurement and carotid plaque evaluation after the coronary angiography. The recommendation of the American Society of Echocardiography and The Society of Vascular Medicine for the calculation was considered (15). Carotid USG was performed by a vascular radiologist who was certificated for the procedures of duplex scan. The LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) was used to measure the carotid arteries. All calculations were made from the common carotid arteries on both sides, approximately 15 mm proximal of the carotid bifurcation. CIMT was calculated between the medial-adventitial surface and luminal-intimal surface. Three different places of the thickest ones were measured, and the maximum values were taken to reach valid CIMT without including the plaques. The mean values of the right and left carotid arteries were accepted as the ultimate CIMT. Carotid plaque was accepted and described as the increase of intima- media thickness focally for more than 50% or CIMT >1.5mm. Finally, the study population was divided into two groups as the high-risk carotid profile group and the low-risk carotid profile group. Having plaques or CIMT >0.9 mm was defined as the high-risk carotid profile and not having plaques or CIMT ≤0.9 mm was defined as the low risk carotid profile considering the previous studies (16,17).

Statistical Analysis

Continuous variables are presented as means and standard deviations. The categorical variables are expressed as numbers and percentages. Study groups were compared using the unpaired Student's t-test for continuous variables that displayed normal distribution and using the Mann-Whitney U test for continuous variables that did not display normal distribution. Categorical data were compared with the chi-square test. For predicting potential risk factors for MI, logistic regression analysis was used. A p value below than 0.10 was employed for potential variable selection in multivariate analysis. The Nagelkerke r-squared values for logistic regression were recorded. Receiver operating characteristics (ROC) curves for potential risk factors were drawn to distinguish MI. The Youden's index was used to derive the best cut-offs. The area under the ROC curves (AUC) was recorded. P values under 0.05 were considered to be statistically significant. Statistical analyses were performed using the SPSS software version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

There was no statistically significant difference between the groups in terms of traditional risk factors and Framingham risk score. As expected, only white blood cell level was significantly higher in the MI group (Table 1).

Carotid USG scans and ambulatory blood pressure monitorization results of the patients having MI and the patients with normal coronary arteries can be seen in Table 2. There was no difference between the two groups in terms of daytime, nighttime, and mean systolic and diastolic blood pressures. Thus, blood pressure effect, which is one of the most important determinants of CIMT, was ruled out. There was a statistically significant difference in CIMT (p<0.001) and carotid plaque presence (p=0.024) between the groups. In addition, high-risk carotid profile was significantly higher in the MI group. (40.0% vs 6.7%, p<0.001).

In logistic regression analysis, it was determined that Framingham risk score and traditional risk factors were not independent predictors of MI. Only high density lipoprotein was detected as a predictor (p=0.019). Nevertheless, independent from traditional risk factors and Framingham risk score, 0.1 mm increase in CIMT was associated with a 42% increase in odds for STEMI. Similarly, independent from traditional risk factors and Framingham risk score, being in the high-risk carotid image group had 9.2 times higher odds for MI than being in the low-risk carotid image group (Table 3). A CIMT cut-off >0.8 mm had AUC of 0.686 for distinguishing MI patients from patients with normal coronary angiography, with a 48.7% sensitivity and 80.0% specificity (Figure 1).

Table 1. Baseline characteristics of study population, mean ± standard deviation, or n (%)

Variable	MI patients, (n=115)	Control group, (n=45)	p
Age, years	39.4±4.3	39.3±4.2	0.856
Male, n (%)	103 (89.6%)	38 (84.4%)	0.368
BMI (kg/m²)	29.1±3.9	29.1±4.1	0.949
Smoking, n (%)	58 (50.4%)	16 (35.6%)	0.090
DM, n (%)	16 (13.9%)	5 (11.1%)	0.637
HT, n (%)	33 (28.7%)	8 (17.8%)	0.155
HL, n (%)	48 (41.7%)	14 (31.1%)	0.215
Family H, n (%)	37 (32.2%)	9 (20.0%)	0.126
Framingham risk score, %	7.3±5.6	5.8±7.1	0.159
Creatinine (mg/dL)	0.81±0.17	0.78±0.14	0.165
Total cholesterol (mg/dL)	200.8±42.6	213.3±59.1	0.138
LDL (mg/dL)	132.7±34.1	129.3±42.5	0.601
HDL (mg/dL)	36.9±10.2	39.9±10.4	0.102
Triglycerides (mg/dL)	190.7±157.5	213.8±123.4	0.376
Glucose (mg/dL)	132.2±57.2	142.2±91.4	0.420
WBC count (10^3/L)	11.8±3.3	8.0±2.7	<0.001
Platelet (10^3/L)	270.1±61.4	266.2±69.2	0.727
Hematocrit (g/dL)	42.9±4.4	41.7±2.6	0.080

MI: myocardial Infarction, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, HL: hyperlipidemia, H: history, LDL: low density lipoprotein, HDL: high density lipoprotein, WBC: white blood cell

Table 2. Ambulatory blood pressure monitorization and carotid imaging results of study population mean ± standard deviation, or n (%)

	MI patients, (n=115)	Control group, (n=45)	p
Mean SBP, mmHg	125.3±16.4	126.5±10.9	0.651
Mean DBP, mmHg	80.7±12.9	79.4±13.8	0.584
Daytime SBP, mmHg	128.2±17.0	128.6±11.1	0.870
Daytime DBP, mmHg	83.6±13.3	83.1±9.0	0.816
Nighttime SBP, mmHg	116.8±18.1	117.2±20.2	0.911
Nighttime DBP, mmHg	72.3±13.5	74.6±10.8	0.311
CIMT, mm	0.87±0.28	0.70±0.16	<0.001
Carotid plaque presence, n (%)	17 (14.8%)	1 (2.2%)	0.024
High-Risk Carotid Profile, n (%)**	46 (40.0%)	3 (6.7%)	<0.001

**High risk carotid profiled defined as having plaques or CIMT >0.9 mm.

SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness

Table 3. Multivariate logistic regression analysis for potential predictors of myocardial infarction

	Univariate analysis		Multivariate analysis¶	
	OR (CI 95%)	p	OR (CI 95%)	p
Age, years	1.015 (0.935-1.103)	0.716	-	-
Male, yes	0.606 (0.215-1.708)	0.343	-	-
BMI, kg/m^2	0.997 (0.914-1.057)	0.940	-	-
Hyperlipidemia, yes	1.678 (0.796-3.677)	0.173	-	-
DM, yes	1.363 (0.454-4.090)	0.581	-	-
Smoking, yes	1.844 (0.907-3.757)	0.092	1.634 (0.759-3.520)	0.210
Hypertension, yes	1.861 (1.084-4.418)	0.159	-	-
Family history, yes	1.897 (0.829-4.345)	0.130	-	-
Framingham score	1.037 (0.970-1.105)	0.254	-	-
HDL, mg/dL	0.963 (0.931-0.997)	0.032	0.958 (0.923-0.993)	0.019
LDL, mg/dL	1.003 (0.993-1.012)	0.598	-	-
Mean SBP, mmHg	0.967 (0.924-1.012)	0.150	-	-
Mean DBP, mmHg	1.041 (0.984-1.100)	0.161	-	-
CIMT, mm x 10	27.162 (4.151-177.744)	0.001	1.420 (1.168-1.725)	0.001
Carotid plaque presence	7.633 (0.985-59.166)	0.052	5.138 (0.642-41.117)	0.123
High risk carotid image†	9.333 (2.730-31.909)	<0.001	9.241 (2.682-31.841)	<0.001

†These groups were included in a second model instead of carotid intima-media thickness and carotid plaque presence

¶Nagelkerke R square of the full model was 23.6%.

OR: odds ratio, CI: confidence interval, BMI: body mass index, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness

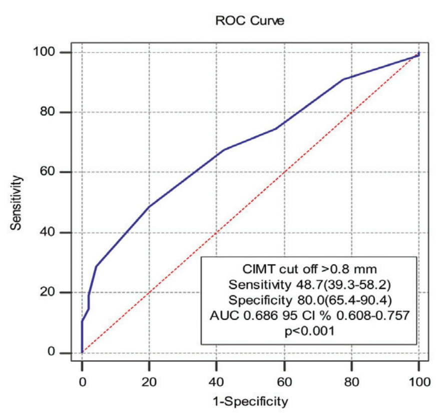

Figure 1. Receiver operating characteristics curve showing the distinguishing ability of Carotid Intima-Media Thickness for ST Segment Elevated Myocardial Infarction.

ROC: receiver operating characteristics, CIMT: carotid intima-media thickness, AUC: area under the ROC curve, CI: confidence interval

Discussion

In this study, we found an effect of CIMT on cardiovascular events in young patients. Besides, high-risk carotid image that was defined as CIMT >0.9 mm or the presence of carotid plaque was related with increased risk of cardiovascular events. Our findings have suggested that beyond traditional risk factors, the carotid imaging plays an important role in determining the risk of MI in young patients. The demonstration of the usefulness of carotid imaging as a predictor of MI in young age-matchedindividuals with similar Framingham scores makes our study unique and valuable.

It has been shown that more than half of the cardiovascular heart diseases are seen in low- and moderate-risk groups when patients are assembled into groups according to the traditional risk scores (3,4). Furthermore, there are insufficient data on the predictability of the Framingham risk score, which is used most commonly, in younger patients. Therefore, alternative scanning tests, which can be used to evaluate subclinical atherosclerosis in those patients, may become more important in revising the risk score systems.

CIMT measurement by carotid USG and plaque definition can be found in the guidelines. CIMT >0.9 mm or having a carotid plaque is defined as the target organ damage for hypertension according to the Europe Society of Cardiology (18). The American Heart Association (AHA) recommends CIMT measurement for cardiovascular risk evaluation but not in the form of population screening (19,20). Furthermore, under the guidance of a meta-analysis, which shows that detecting plaques in carotid arteries is more important than CIMT measurement, AHA also recommends carotid scan for plaques (21). Considering these guidelines, we arranged the risk groups according to both CIMT measurement and presence of carotid plaques in our study.

Many epidemiologic studies such as the atherosclerosis risk in communities (9) and the cardiovascular health study (10) detected a direct relationship between MI and CIMT even in the absence of cardiac illness. The study of Paroi Arterielle et Risque Cardiovasculare in Asia Africa/Middle East and Latin America (parc-aala) is another study that found a relationship between CIMT and carotid plaques with Framingham risk score, free from geographic differences (22). In the Rotterdam study, Bots et al. followed 7893 patients and found 194 MI cases during that period. At the end of the study, MI group had higher CIMT values than the other group (23). The Kuppio ischemic heart disease study found that if the CIMT value had increased 0.1 mm, 11% increase of MI cases could happen regarding this (24). In another study, Salonen and Salonen (25) showed that plaque formation was related to increased MI risk by 4.15 times and accordingly, they speculated that early carotid USG and risk classification could have advantages to decrease acute coronary syndromes. Irie et al. (26) had shown that maximum CIMT measurement in addition to traditional risk factors could improve risk classification. Baldassare found that CIMT measurement in addition to Framingham risk score was a rational approach to prevent cardiovascular diseases (27). In our study, unlike above-mentioned studies, we focused only on young patients and we combined CIMT and plaque formation. Consequently, we investigated that being in the high-risk carotid image group had 9.2 times increased odds for MI. These results indicate the additional effect of CIMT and plaque presence. Besides, MI patients and the patients with normal coronary arteries had no statistically significant difference in terms of traditional risk factors and Framingham risk score, however, there were significant differences in terms of CIMT and carotid plaque, which means that carotid scanning is a valuable test apart from traditional risk scores to determine the risk of coronary artery disease in the young population.

We established our study on young population. When choosing this population, our goal was to determine the function of the carotid imaging to determine the risk group in this population. Since both traditional risk scoring and scoring such as coronary calcium are not high predictive values, a primary precaution cannot be taken in young age groups. CIMT measurement is a reliable marker for the plaque formation for the atherosclerotic process in young patients (28). Similarly, studies showed that carotid USG was more confidential than coronary calcium score to detect atherosclerosis in young adults since the calcification period could take years (29,30). Carotid scanning becomes more valuable to detect subclinical atherosclerosis in young MI patients as Fournier et al. (31) have shown that atherosclerosis can be seen relatively less in young MI. Also, Linhart et al. (11) revealed that young MI patients had an increased CIMT thickness, which is consistent with our study data ($p=0.001$). So, we can speculate that atherosclerosis is a diffuse disease and may affect many vascular beds at the same time in young population.

Especially in patients with a moderate risk according to traditional risk factors for cardiovascular disease, carotid imaging appears to be valuable for detecting increased latent cardiovascular risk. However, there are not enough data to prescribe acetylsalicylic acid or statin in patients who have high-risk carotid images. Regarding this, more prospective randomized trials should be carried out.

There was no difference between the MI group and the control group in terms of traditional risk factors. Since risk factors were taken into account in the process of angiographic decision-making in the control group, it is not surprising that this group had as many risk factors as MI patients. Moreover, the scores on gender, DM, hyperlipidemia, smoking, family history, and hypertension were higher in the MI group, but the difference was not statistically significant. The statistically significant difference of carotid imaging between the groups may be considered to be additional effects of these risk factors. In addition, increased CIMT and the presence of carotid plaque may occur as a result of indirect mechanisms independently of traditional risk factors.

This study provided novel evidence enlightening the importance of carotid imaging in young patients. However, it has some limitations. First, this was a single-center study which may result in selection bias. Second, the cross-sectional design of the study suggests an association but does not establish a cause and effect relationship. Third, carotid scanning was evaluated by only one researcher. Nonetheless, the test was performed by standard protocols and specialists in the field. Finally, this is not a prospective study so the absence of long-term results has prevented us from obtaining future results of high-risk carotid imaging.

Conclusion

In summary, we found a relationship between MI and high-risk carotid profile defined as increased CIMT and the presence of carotid plaque in young patients. Our findings suggest that beyond having established risk factors, high-risk carotid imaging provides additional information to detect subclinical atherosclerosis in young patients. In light of this study, clinicians need to focus on carotid imaging apart from traditional risk factors when screening young patients for atherosclerosis. Furthermore, we should consider closer and more frequent follow-up of individuals with high-risk carotid imaging to prevent fatal and non-fatal cardiovascular events in young population.

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Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital under the (decision no: 03.07.2014/6).

Informed Consent: Informed consent was obtained from all participants included in the study.

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