Increased carotid intima-media thickness and low ankle brachial index in patients after acute myocardial infarction

Blaž Mlačak,[1] Tanja Mišmaš,[1] Matej Kolenc,[2] Rok Blagus,[3] Alenka Simonič[4]

[1] Community health centre Metlika, Metlika, Slovenia

[2] General hospital Novo Mesto, Novo Mesto, Slovenia

[3] Institute for Biostatistics and Medical Informatics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[4] Community health centre, Novo mesto, Novo mesto, Slovenia

Correspondence:
Blaž Mlačak, e: blaz.mlacak@siol.net

Key words:
atherosclerosis; carotid arteries; peripheral arterial disease; intima media thickness; risk factors

Received: 6. 11. 2017
Accepted: 22. 6. 2018

Abstract

Background: Increased intima-media thickness (IMT) of the carotid arteries and the ankle–brachial pressure index (ABI) are generally considered an early marker of atherosclerosis. The aim of this study was to assess the frequency of subjects with low ABI and an increased IMT as markers of atherosclerosis in a group of patients after myocardial infarction.

Methods: The test group included 50 patients after myocardial infarction (AMI), 32 males and 18 females aged between 38 and 78 years. The control group consisted of 50 subjects without ischaemic heart disease, who were comparable to the test group by age, gender and place of residence. High-resolution ultrasonography for the non-invasive measurement of IMT on the far wall at three different sites of the carotid arteries (the common carotid artery, carotid bifurcation, and internal carotid artery) has been used. Peripheral arterial disease (PAD) was diagnosed in the lower extremities by means of Doppler ultrasound (ABI ≤ 0.9).

Results: The patients after myocardial infarction (IMT = median 0.85, interquartile range 0.72–0.95) compared to the subjects in the control group (IMT = 0.74, IQR 0.67–0.86) had significantly increased IMT ($p < 0.05$). The group of patients with AMI and PAD had significantly higher IMT, 0.93(0.86–1.03) in comparison with the group of patients with AMI and without PAD, 0.73(0.65–0.84) $p < 0.001$. The difference in IMT between patients with ST-elevation AMI (STEMI), 0.84 (0.70–0.96) and patients with non-ST-elevation AMI (NSTEMI), 0.89 (0.79–0.95) was not significant. The peripheral arterial disease was diagnosed in 24 (48 %) of patients after myocardial infarction and in 10 (20 %) of the control group ($p < 0.05$).

Conclusion: Our study has demonstrated that increased carotid IMT and PAD are frequently present in patients after myocardial infarction. The subjects of the test and control group had an increased IMT and asymptomatic PAD.

Cite as: Mlačak B, Mišmaš T, Kolenc M, Blagus R, Simonič A. [Increased carotid intima-media thickness and low ankle brachial index in patients after acute myocardial infarction]. Zdrav Vestn. 2018;87(7–8):324–34.

DOI: 10.6016/ZdravVestn.2664

1 Introduction

Atherosclerosis is a chronic inflammatory degenerative disease associated with increased risk for arterial events, such as myocardial infarction and ischaemic stroke, and represents the leading cause of death in the developed world (1,2).

The Framingham score and classical risk factors for atherosclerosis have been proven to have low sensitivity and poor predictive value for major cardiovascular events and identification of high-risk persons. Increased carotid intima-media thickness (IMT) is the earliest measurable morphological change of the arterial wall in the process of atherogenesis and is generally considered as a marker for atherosclerosis (3,4,5).Given the fact that in addition to atherosclerosis increased IMT may be due to proliferation of smooth muscle cells and connective tissue in response to increased blood flow, arterial stretch or remodeling due to increase in vessel diameter, there is no agreement on the true predictive value of IMT (4,6).

Ankle-brachial index (ABI) of ≤ 0.9 with a 90 % sensitivity and 100 % specificity is a non-invasive test for assessing haemodynamically significant arterial narrowing in the lower extremities, i.e. peripheral arterial disease (PAD). It helps identify persons at increased risk for cardiovascular diseases, and is a reliable predictor of higher mortality in affected individuals (3,7,8). A great number of epidemiological studies were aimed at determining the incidence of AMI and stroke in individuals with increased IMT in order to improve prediction of cardiovascular events (9,10,11). Cross-sectional investigations reported differences in the prevalence of risk factors and preclinical morphological alterations in the carotid arteries and lower limb arteries between patients who suffered AMI and in individuals without clinically detectable ischaemic cardiac disease. Only rare studies investigated the incidence of increased IMT in patients with ST-elevation myocardial infarction (STEMI) and those with non-ST-elevation myocardial infarction (NSTEMI). The aim of our study was to determine possible differences

Table 1: Risk factors and medication in post-AMI patients and in controls.

Variable	AMI (N = 50)	Control	P value
Age (years)	65,7 (10,3)	64 (11,1)	N.S.
Hypertension (N)	46 (92 %)	37 (74 %)	< 0,01
Hyperholesterolemia (N)	43 (86 %)	22 (44 %)	< 0,001
Diabetes mellitus (N)	16 (32 %)	3 (6 %)	< 0,001
Increased fibrinogen (N)	27 (54 %)	16 (32 %)	< 0,01
Family history (N)	27 (54 %)	14 (28 %)	< 0,01
Smoking (N)	8 (16 %)	12 (24 %)	N.S.
Body mass index > 25 kg/m^2 (N)	42 (84 %)	36 (72 %)	N.S.
ACE inhibitors (N)	43 (86 %)	22 (44 %)	< 0,01
ß-blockers (N)	49 (98 %)	7 (14 %)	< 0,001
Statins (N)	48 (96 %)	11 (22 %)	< 0,001
Antiplatelet drugs (N)	50 (100 %)	6 (12 %)	< 0,001

in IMT and prevalence of PAD between post-STEMI and post-NSTEMI patients (study group), and individuals without clinically noticeable heart disease (control group). Our study aimed to establish the incidence of atherosclerosis indicators in post-AMI patients, and determine the difference in IMT between post-STEMI and post-NSTEMI patients.

2 Subjects and methods

Our cross-sectional study, conducted between October 2015 and February 2016, included 50 post-AMI patients, 32 males and 18 females aged 38 to 78 years. All the patients were hospitalised at the internal medicine department of the Novo mesto General Hospital. After discharge they were taking the prescribed medication on a regular basis and were followed up by their family physician and an internist. The post-AMI group was divided into two subroups: a subgroup of 30 patients with ST-elevation (STEMI) and a subgroup of 20 patients with no ST-segment elevation (NSTEMI). The time elapsed since the measurements and hospitalisation for AMI was 1 to 12 years (mean 4.7 yrs). The method of matched pairs was used so that a control group comprised 50 subjects too. Each post-AMI patient was matched for age (± 2 yrs), gender and place of residence with the closest neighbour without clinically noticeable ischaemic heart disease or cardiovascular disorder. The groups were matched for age, gender and place of residence. The study was conducted according to the Helsinki Declaration and Medical Ethics Code of Slovenia. All the individuals included in the study were duly informed on the study design and gave a written consent to being involved in the study. The investigation was approved by the Medical Ethics Committee of the Republic of Slovenia on 29 November 2014 (No.27/12/14).

All study participants were evaluated by B-mode ultrasound with a 10 MHz-probe (Medison-EKO 7). All measurements on the far arterial wall were carried out by one sonographer in accordance with the approved standard protocol. Carotid IMT was measured on the left and right sides of the neck, at three different locations of the carotid arteries: the common carotid artery 1 cm below the bifurcation point, the carotid bulb and the internal carotid artery at 1 cm from the bifurcation (3,12). The mean value of the three measurements from the left and right carotid arteries, totaling six measurements, was used for further statistical analysis (mean IMT). The maximal IMT value measured in each subject was also used for statistical data analysis. PAD in the lower limbs was diagnosed using the Meda Sonics Doppler ultrasound, model BF 4A. Systolic blood pressure in the upper arm was measured using a Riva-Rocci sleeve and mercury pressure meter, whereas foot artery blood pressure was measured with a Doppler ultrasound flow detector. In PAD, an ABI value of ≤ 0.9 was considered abnormal (7,12).

A systolic pressure of 140 mmHg or higher and a diastolic pressure of 90 mmHg or higher were considered high blood pressure. Only patients registered as having diabetes were included in the study. All individuals who smoked, regardless of the number of cigarettes smoked per day, were defined as smokers. Persons with a body mass index (BMI) of > 24 kg/m^2 were considered overweight. Hypercholesterolaemia was present when total cholesterol levels were higher than 5.2 mmol/L. Plasma fibrinogen levels of > 3.4 g/L (13) were considered elevated. Persons taking cholesterol lowering medication whose

total cholesterol level was < 5 mmol/L at the time of the study were also assigned to the hypercholesterolaemia group. Familial risk factors included MI, stroke or limb amputation due to gangrene in an immediate family member (father, mother, grand father, grand mother, uncle, aunt) sustained before age 65.

In the statistical analysis numerical variables were presented as a mean (standard deviation) or median (interquartile range), as appropriate. The difference in the numerical variables between the study group and controls was determined using the independent-samples t-test or the Mann-Whitney test, as appropriate. The Shapiro-Wilk test was employed to test for normality. Descriptive data were presented as absolute frequencies (%). The difference between the study group and controls was determined with the chi-square test with Yates correction, and differences between the four groups (patients grouped by AMI or PAD) with the Kruskal-Wallis test. Planned subsequent comparisons (a total of 4) for group pairs were tested with the Mann-Whitney test. P-values were adjusted according to the Bonferroni-Holm procedure. A p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using the R-statistical computing package (R version 3.0.3) (14).

3 Results

Table 1 shows risk factors for atherosclerosis and farmacological treatment in post-AMI patients in the study and the control group. In comparison with the control group individuals in the study group had a significantly greater number of the following risk factors: hypertension (92 % vs.74 %; $p < 0.01$); increased cholesterol levels (86 % vs.44 %); $p < 0.001$), elevated fibrinogen (54 % vs. 32 %; $p < 0.01$), positive familial history, heredity (54 % vs.28 %; $p < 0.01$).

The mean IMT was significantly higher for the study group compared to the controls (0.85; 0.72–0.95 vs. 0.74; 0.67–0.86), ($p < 0.05$). There was no difference, however, in the maximal IMT values between the study group (0.95; 0.84–1.18) and the control group (0.83; 0.78–0.98) (Table 2). A maximal IMT of > 0.9 mm was found in 32 (64 %) individuals from the study group, and in 16 (32 %) controls ($p < 0.01$). Differences in mean IMT between the groups were as follows: Group I AMI = yes, PAD = yes; Group II AMI = yes, PAD = no; Group III AMI = no; PAD = yes; Group IV AMI = no; PAD = no (Table 3). Statistically significant differences in mean IMT were found between the groups ($p < 0.05$). Further testing of these differences showed a statistically significant difference in mean IMT between Group

Table 2: Mean and maximal IMT values in post-AMI subjects (N=50) and in controls (N=50).

Intima and media thickness (median and interquartile ranges), mm	All subjects	AMI	Control group	P-value
Mean value	0.80 (0.69–0.90)	0.85* (0.72–0.95)	0.74* (0.67–0.86)	0.035
Maximal value	0.92 (0.79–1.06)	0.95* (0.84–1.18)	0.83* (0.78–0.98)	0.052

I (AMI = yes; PAD = yes) and Group II (AMI = yes, PAD = no), ($p < 0.001$), and between Group I (AMI = yes; PAD = yes) and Group IV (AMI = no; PAD = no), ($p < 0.001$).STEMI group and NSTEMI group did not differ singificantly as concerns their mean and maximum IMT values (Table 4). Decreased ABI/PAD was found in 24 (48 %) post-AMI patients and in 10 (20 %) control subjects ($p < 0.05$).In the study group, nine (18 %) patients had Fontaine Stage I PAD, 13 (26 %) Stage II PAD and two (4 %) Stage III PAD. Fontaine Stage I PAD was found in eight (16 %), and Stage II PAD in two (4 %) subjects in the control group.

4 Discussion

This cross sectional study was undertaken to determine the incidence of atherosclerosis indicators/ the number of persons with decreased ABI and increased carotid IMT in the study and control groups. A significantly higher mean IMT and more subjects with decreased ABI were found in the post-AMI group in comparison with the group without clinically detectable ischaemic heart disease.Post-STEMI and post-NSTEMI subjects, however, did not differ in their mean and maximal IMT values. There was no statistically significant difference between the study group and controls regarding their maximal IMT values. After assigning the study subjects and the controls to four subgroups on the basis of the presence of haemodynamically significant coronary and peripheral arterial stenosis, we found that individuals with both AMI and PAD had the highest mean IMT value, which exceeded significantly the values determined in other groups (Table 3). This result can be explained by the fact that AMI and PAD represent two independent risk factors for atherosclerosis-related complications.The presence of both factors increases the risk of recurrent cardiovascular events (3,7). The lowest IMT was expected in subjects who suffered no AMI and had no PAD, i.e. in subjects without noticeable atherosclerotic complications, yet numerous risk factors for atherogenesis and carotid intima-media thickening were found in this group too.

Table 3: Carotid intima-media thickness in four study groups : Group I (AMI = yes, PAD = yes), Group II (AMI = yes, PAD = no), Group III (AMI = no, PAD = yes), Group IV (AMI = no, PAD = no).

	AMI		Controls	
Number	24	26	10	40
Intima and media thickness (mediane and interquartile ranges), mm	PAD = YES 0,93 (0,86–1,03)	PAD = NO 0,73 (0,65–0,84)	PAD = YES 0,75 (0,66–0,82)	PAD = NO 0,74 (0,68–0,86)
	p < 0,001		p = 1,00	
	p = 1,00			
	p < 0,001			

AMI =acute myocardial infarction; PAD = peripheral artery disease

So patients with PAD and patients with ABI of > 0.9 were found in the group of patients who suffered no AMI. Cycle ergometer test and coronorography would have to be performed for a more accurate determination of the extent of coronary involvement in this group. Our assumption is supported by the the fact that total blockage of a coronary artery due to atherosclerotic plaque progression and increase in collateral blood flow, may easily go unnoticed when it is atypical or asymptomatic (1,2). Yet, increased IMT due to media hypertrophy associated with atherosclerosis or age/ hypertension does not necessarily predict unstable plaque disruption and the resulting atherothrombosis (4,6). STEMI is caused by erosion and disruption of a coronary plaque and formation of a blood clot, which, as a rule, causes total occlusion of the coronary artery in the absence of adequate collateral blood flow from patent arteries to the affected vessel territory. These patients would have been expected to have lower IMT values than the NSTEMI subjects. In the latter, ischaemia of the target coronary artery territory develops as a result of a combination of several underlying mechanisms, such as increment of a stable atherosclerotic plaque, thrombosis, plaque inflammation and coronary artery spasms. This study showed that NSTEMI patients had higher IMT values, yet the difference was not statistically significant. In order to confirm or refute our assumption, further studies with a higher degree of probability will have to be conducted on age- and gender-matched groups comprising a greater number of STEMI and NSTEMI patients.

The results of this study demonstrated a significantly higher incidence of PAD and ABI of < 0.9 in post-AMI patients than in controls. This is in accordance with the results of other authors, who reported higher PAD prevalence in post-AMI and post-stroke patients, in whom numerous risk factors accumulate and cause damage to arteries in the entire organism (15,16). This study revealed increased carotid IMT values in patients with PAD and in post-AMI patients, which indirectly identifies decreased ABI as a significant indicator of atherosclerosis. National and international investigations have confirmed a close association between increased IMT and decreased ABI values, and the presence of risk factors for atherosclerosis, their number and duration. A strong relationship has been found between total cardiovascular disease risk and the level of preclinical functional and morphological changes of the arterial wall. There is no agreement, however, on the predictive value of IMT for cardiovascular events, such as MI and stroke (15,16).

According to »The Atherosclerosis Risk in Communities Study«, increased IMT is associated with a two- to fou-

Table 4: Mean and maximal carotid intima-media thickness in post-STEMI (N = 30) and post-NSTEMI patients (N = 20).

Intima and media thickness (mediane and interquartile ranges), mm	NSTEMI	STEMI	P-Value
Mean value	0,89 (0,77–0,95)	0,84 (0,70–0,96)	0,579
Maximal value	1,00 (0,90–1,23)	0,92 (0,85–1,15)	0,501

r-fold increase in the risk of coronary events (17). Meta-analyses of cross-sectional and prospective studies showed, however, that the value of increased IMT values to predict cardiovascular events is not significantly higher than that of Framingham risk scores. Additional predictive value for future cardiovascular events was found to be low, clinically atypical (9,18,19). ABI of < 0.9 is a marker for generalised atherosclerosis and a risk factor for atherothrombosis-related complications, such as MI, ischaemic stroke and cardiac death. By determining ABI in asymptomatic Fontaine Stage I persons, we can identify individuals with atherosclerosis and haemodynamically significant vascular narrowing of > 70 % i.e. those with a very high long-term risk (20,21). The studies conducted hitherto have identified an ABI of < 0.9 as one of the most important independent predictors of cardiovascular events (21,22). A 5-year Slovene interventional study of PID-PAD has confirmed that reducing risk factors for atherosclerosis decreases the incidence of cardiovascular events. In subjects with decreased ABI, MI and stroke were not the leading causes of death (23). Prospective studies carried out so far showed that individuals with low ABI had lower 5-, 10- and 15-year survival rates.

Decreased ABI indicates asymptomatic PAD and is not only a marker for raised cardiovascular risk, but also a good predictor of future cardiovascular events (16,24). Ordinary measurements of systolic blood pressure in the arms and legs using ultrasound Doppler detector provide relevant information on a general cardiovascular risk in an individual (22,23). In a Slovene study which investigated early markers of atherosclerosis in post-AMI patients younger than 50 years, ABI was not found to be a reliable indicator of generalised atherosclerosis. This was explained by the fact that an ABI of < 0.9 indicates a > 75 %-vascular stenosis, i.e. advanced atherosclerosis, and is therefore not sensible enough to predict early morphological intimal alterations (25). As indicated by the results of some other investigations, increased IMT is a marker of atherosclerosis, which agrees with our findings of the presence of high IMT in post-AMI patients with PAD (26,27). In these cases, increased IMT levels may be related to the earliest stage of atherosclerosis and later atherosclerotic plaque build-up. Frequently, intima-media thickening and plaque are two phenotypic variants under different biological and genetic control; a plaque, as a rule, forms de novo and is not related to intimal thickening (5,10,27). Intima-media thickening is the first structural change affecting the arterial wall in the process of artherogenesis and can be diagnosed with a non-invasive ultrasound examination. In addition to atherosclerosis, the cause of increased carotid IMT may be proliferation of smooth muscle cells and connective tissue in response to increased blood flow, arterial stretch associated with hypertension or vascular remodeling due to increase in the artery lumen diameter (4,28,29). Today, non-invasive diagnostic procedures cannot discriminate atherosclerosis-associated intima-media thickening from increased IMT due to other causes. During the observation period, patients with increased IMT due to atherosclerosis and concomitant risk factors for atherosclerosis were expected to suffer a higher rate of atherosclerosis-related cardiovascular events as compared to subjects with unaffected arteries. It is difficult to follow the incidence of cardiovascular events associated with increased carotid IMT because pharmacological and nonpharmacological treatments are

used to inhibit natural progression of atherogenesis in persons with increased coronary risk and early-stage atherosclerosis (29). A majority of investigators believe that atherosclerotic plaques, especially unstable plaques covered by a thin fibrous cap and vulnerable lipid--rich plaques, have a strong predictive value for cardiovascular events (27,28). On the basis of our findings and the results of numerous prospective epidemiological studies it can be concluded that increased carotid IMT and decreased ABI in the presence of atherosclerotic plaques are indicators of atherosclerosis and have additional predictive value for cardiovascular events (30,31,32). Although the 2013 Guidelines on the Assessment of Cardiovascular Risk of the American College of Cardiology do not recommend using routine IMT measurements in clinical practice (33), Polak et al. (34) reported that prognostic value of IMT for future cardiovascular events can be improved by taking into account normative data for age-, gender- and race/ethnicity -specific IMT of the common carotid artery and the internal carotid artery. To confirm these results we need further longitudinal epidemiological studies on geographically and ethnically diverse cohorts, conducted in accordance with uniform guidelines for assessment of IMT and other morphological alterations of internal carotid arteries.

This study has several limitations: it is a cross-sectional study and does not allow for determining the incidence of atherosclerotic events in individual study groups showing different levels of coronary risk; a small sample was used and the differences determined for a small sample may become statistically significant when measured in a larger cohort; high values of the measured variables may have significant effects on the means/values of statistical parameters. All post-AMI subjects were taking statins, antihypertensives and antiplatelet drugs, which may have affected atherogenesis and measurements of some variables. All study participants and controls came from a narrow geographical area with similar socioeconomic characteristics and lifestyles, therefore the ethnic factor had no impact on IMT values and atherosclerotic complications. The results refer to the population aged 50 years and older, coming from a narrow geographical area.

5 Conclusions

Increased carotic intima-media thickness and decreased ankle-brachial index are markers for atherosclerosis and are more frequently present in patients who suffered myocardial infarction. The association between increased intima--media thickness and no ST-elevation myocardial infarction will have to be investigated in a larger cohort of patients.

6 Acknowledgement

We express our thanks to Professor M.Šabovič from the Department of Cardiovascular Diseases for his expert assistance and advice. His expertise and the constructive comments and suggestions from the reviewers have influenced significantly the final version of this paper.