Original article

Kardiologia Polska
2011; 69, 10: 1024–1031
ISSN 0022–9032

Relationship between carotid intima-media thickness, cytokines, atherosclerosis extent and a two-year cardiovascular risk in patients with arteriosclerosis

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Abstract

Aim: To investigate the relationship between carotid intima-media thickness (CIMT), biomarkers, atherosclerosis extent and a two-year cardiovascular (CV) event risk in patients with arteriosclerosis.

Methods: The CIMT, levels of high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), interleukin-6 (IL-6), interleukin-10 (IL-10), and NT-proBNP were measured in 279 subjects with atherosclerotic disease, mean age 64.1 ± 9.6 years. The patients were included when they had artery stenosis ≥ 50% in one, two, three or four arterial territories (coronary, supra-aortic, renal and/or lower limb arteries), and this was found in 97, 80, 69 and 33 patients, respectively. During a two-year follow-up, the incidences of CV death, myocardial infarction, ischaemic stroke and lesion progression were recorded.

Results: The identified independent predictors of ≥ 3-territorial stenoses ≥ 50% were CIMT > 1.3 mm (RR 1.72; $p < 0.001$), hs-CRP > 5 mg/dL (RR 1.28; $p = 0.005$), IL-6 > 6.5 pg/mL (RR 1.08; $p = 0.089$), IL-10 (RR 0.86; $p = 0.002$), diabetes (RR 1.11; $p = 0.027$), total-cholesterol (RR 1.21; $p < 0.001$), creatinine (RR 1.15; $p = 0.004$) and body mass index (RR 0.85; $p = 0.001$). During a two-year follow-up, CV events occurred in 52 (18.6%) patients. The CIMT > 1.3 mm ($p < 0.001$), diabetes ($p = 0.018$), TNF-α > 6 pg/mL ($p = 0.018$), LDL-cholesterol > 3.35 mmol/L ($p = 0.012$) and NT-proBNP ($p = 0.074$) were independent CV event risk factors associated with a 27%, 14%, 15%, 15% and 11% higher CV risk, respectively. However, after adjustment for a baseline location of artery stenosis ≥ 50%, CIMT became a non-significant predictor ($p = 0.245$).

Conclusions: Levels of hs-CRP, IL-6, IL-10 are independently associated with atherosclerosis extent, while TNF-α and NT-proBNP are mostly related to a two-year CV event risk. The CIMT > 1.3 mm seems to be a clinically relevant marker associated with atherosclerosis extent and CV risk, although CV event risk is primarily related to the baseline stenosis location.

Key words: polyvascular atherosclerosis, risk of cardiovascular event, carotid intima-media thickness, atherosclerosis biomarkers, hs-CRP, NT-proBNP, cytokines

Kardiol Pol 2011; 69, 10: 1024–1031

INTRODUCTION

Progressive athero-thrombotic processes resulting in cardiovascular (CV) events, predominantly myocardial infarction (MI), ischaemic stroke (IS) or renal failure are responsible for many premature deaths in developed countries [1, 2]. It has been estimated that among patients with coronary artery disease (CAD), between 28% and 33% have polyvascular extracoronary lesions exceeding at least 50% lumen reduction,

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Received: 29.12.2010 **Accepted:** 18.05.2011

including supraaortic, renal or lower limb arteries [3–5]. Patients with extracoronary arterial atherosclerotic involvements are at greater risk of unfavourable short-term as well as long-term outcomes [3, 6, 7].

Atherosclerosis is initiated by systemic mediators which play a key role in atherosclerosis progression, plaque instability and plaque rupture [8, 9]. Thus, the potential association between inflammatory biomarkers, atherosclerosis extent and dynamics of atherosclerosis-related CV events seems an important issue. The relationship between biomarkers and CV event risk needs to be elucidated, as there are some conflicting data in this field [9–11].

Parallel to atherosclerosis mediators, clinically evident atherosclerosis is preceded by preclinical changes in the arterial wall, namely intima-media complex thickening (CIMT) and plaques formation [12, 13]. The clinical value of CIMT assessment has been shown in population studies, in which risk of CV death, MI or IS was related to the CIMT value [12, 13]. Thus, vascular imaging might be another potential tool employed to assess atherosclerotic burden and risk of CV events [14–16].

The present study aimed to assess the potential associations between CIMT, level of circulating biomarkers and atherosclerosis extent. Our secondary goal was to investigate whether CIMT, baseline levels of tumour necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), interleukin-6 (IL-6), interleukin-10 (IL-10), or N-type natriuretic peptide (NT-proBNP) are prospectively associated with CV events, over a relatively short follow-up period of 24 months.

METHODS

Study group

A total of 279 patients (178 men), mean age 64.1 ± 9.6 (range 35–82) years were admitted for angiography with symptoms of atherosclerotic occlusive disease within at least one of the following arterial territories: coronary, supra-aortic, renal or lower limb arteries. The inclusion criterion was the presence of at least one artery stenosis causing lumen reduction of at least 50%. Patients with unstable course of atherosclerotic disease such as: acute coronary syndrome, acute stroke or critical limb ischaemia were excluded from this study. Patients with acute heart failure or with congestive heart failure in NYHA classes III and IV were also excluded. The prevalence of classical risk factors: diabetes, hyperlipidaemia, arterial hypertension, and smoking (either current or previous) was recorded.

At hospital discharge, 272 (97.5%) patients were given aspirin, 194 (69.5%) tienopiridines, 208 (74.6%) ACE inhibitors, 15 (5.4%) angiotensin receptor blockers (ARBs), 202 (72.4%) β-blockers, 131 (46.9%) calcium channel blockers, 27 (9.7%) α-adrenolitics, 264 (94.6%) statins, seven (2.5%) fibrates, 131 (46.9%) diuretics, 58 (20.8%) nitrates, 16 (5.7%) warfarin and eight (2.69%) digoxin.

The study protocol was reviewed and approved by the local ethics committee and all patients gave informed consent.

Doppler ultrasound and angiography

In all 279 patients, four major arterial territories were analysed via Doppler ultrasound assessment of supra-aortic and iliac/femoral arteries, and routine angiographic evaluation of coronary and renal arteries. A given arterial territory was considered involved if at least one stenotic lesion exceeding 50% was documented in the major vessel or if the patient had undergone a revascularisation procedure in the past.

The grade of stenosis in the carotid (ICAS) and vertebral (VAS) arteries was assessed through the increase in the peak systolic and end-diastolic velocities [17]. Supraaortic artery stenosis assessed by ultrasonography as being greater than 50% was verified with angiography at the time of coronary angiography.

Coronary and renal angiography was performed by means of a Coroscop system (Siemens AG, Munich, Germany) equipped with Quantcor version 4.0 quantitative analysis software, via femoral or radial artery access. Selective angiography of supraaortic arteries (carotid or vertebral) was performed in several views that best displayed the lesion if lumen stenosis ≥ 50% was suspected on Doppler ultrasound examination.

Peripheral lower limb artery occlusive disease (PAOD) diagnosis was based mainly on the presence of intermittent claudication, ankle-brachial index < 0.9, ultrasonography, or a previous revascularisation of a lower extremity artery. Significant lesions > 50% in iliac and femoral arteries were identified with Doppler ultrasonography according to the Ramaswami criteria [18]. Angiographic verification was performed in subjects with suspected significant stenosis and symptoms referring to the revascularisation procedure.

CIMT assessment

A high resolution ultrasonography of both carotid arteries was performed using a Toshiba Aplio PowerVision ultrasound machine (Toshiba Medical Systems Co., Ltd., Tokyo, Japan) equipped with a 4–11 MHz linear-array transducer. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated by 90° to obtain and record a longitudinal image of the anterior and posterior walls. The maximum CIMT was measured at the near and far walls of the common carotid artery, the bifurcation, and the internal carotid arteries, and was expressed as a mean aggregate value (mean-CIMT). The maximum plaque diameter was assessed and included in further analysis.

Laboratory and clinical data

In all patients, a baseline total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP, mg/L) and creatinine were measured from fasting blood samples. The hs-CRP levels were measured by an enzyme-linked immunoabsorbent assay (ELISA kit, Alpha Diagnostic International, San Antonio, TX, USA). The TNF-α (pg/mL), IL-6 (pg/mL), IL-10 (pg/mL), and TGF-β (pg/mL) concentrations were measured from stored frozen serum samples using a commercially available high-sensitivity ELISA test (R&D Systems, Abingdon, UK). The NT-proBNP (pmol/L) was measured from stored frozen serum samples using an electrochemiluminescence sandwich immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany) on an Elecsys System 2010.

Follow-up cardiovascular events

Over a two-year follow-up period, CV events were recorded, including CV death, fatal and non-fatal MI and/or IS, and symptomatic lesion progression. The CV death was defined as a fatal IS, fatal MI, or other CV death (i.e. any sudden or unexpected death unless proven to be non-CV at autopsy). The IS had to be sourced from a neurologist or hospital files to ensure a reliable diagnosis. Lesion progression was defined as an increase in lesion stenosis to ≥ 70% with symptom occurrence requiring revascularisation, in the location with prior stenosis < 50%.

Statistical analysis

Continuous variables are presented as mean ± one SD, categorical variables are expressed as frequencies and percentages. Means of analysed parameters across groups were tested with Analysis of Variance (ANOVA) test, and frequencies were compared by the χ^2 test for independence.

The potential factors that may be associated with atherosclerosis extent were identified first with the univariate analysis (ANOVA), then the independent predictors of CV extent were searched with the multivariate one-step backward logistic regression analysis, initially including variables for which p value < 0.1 was achieved from the univariate analysis.

The potential factors that might be associated with CV event risk were identified first with the univariate model with t-Student test. Then, the independent predictors of CV risk were searched with the multivariate one-step backward logistic regression analysis, including variables for which p value < 0.1 was achieved from the univariate analysis.

The relative risk (RR) and confidence intervals (95% CI) were calculated for factors independently associated with atherosclerosis extent and CV event risk. The cut-offs for the independent continuous CV risk factors were sought.

Statistical analyses were performed with Statistica 5.5 software. A p value of < 0.05 was considered statistically significant.

RESULTS

As a result of Doppler ultrasound and angiography, a significant CAD was found in 216 (77.4%) subjects. In 96 (34.4%) patients ICAS ≥ 50% was found, in 42 (15.1%) — ICAS and VAS, in 12 (4.3%) — VAS ≥ 50%, while renal artery stenosis and PAOD were identified in 147 (52.7%) and 82 (29.4%) patients, respectively. Patients were subdivided into four groups depending on the atherosclerosis extent, including 97 (34.8%) patients with a single arterial territory involvement, 80 (28.7%) patients with a significant stenosis in two different arterial territories, 69 (24.7%) patients with significant lesions in three territories, and 33 (11.8%) patients with four arterial territories involved (Table 1).

With more advanced atherosclerosis, a higher prevalence of diabetes, hyperlipidaemia, smoking, previous MI and IS, but lower body mass index, was observed (Table 1). The CIMT value was significantly related to the atherosclerosis extent ($r = 0.713$; $p < 0.001$) (Table 1). With more advanced atherosclerosis, higher baseline levels of IL-6, TNF-α, hs-CRP, NT-proBNP, serum creatinine and glucose were observed (Table 1), while no significant differences in IL-10 and TGF-β were found. Although all patients were given statins, TC and LDL-C tended to be higher with advancing PAOD.

The independent risk factors of artery stenosis > 50% in two or more arterial territories were: hyperlipidaemia, smoking, IL-6 level > 5.5 pg/mL and mean-CIMT > 1.25 mm (Fig. 1A). The predictors of artery stenosis > 50% in three or four arterial territories were: diabetes, mean-CIMT > 1.3 mm, TC, creatinine, hs-CRP > 5 mg/dL and low IL-10 ($p = 0.002$) (Fig. 1B).

During a two-year follow-up period, 52 (18.6%) CV events occurred. Seventeen (6.1%) patients died (nine MI, five IS, three sudden). Non-fatal MI occurred in 12 (4.3%) patients, and non-fatal IS in five (1.8%). In the remaining 18 (6.4%) patients, the ischaemic symptom occurrence was attributed to the lesion progression of internal carotid artery in five, coronary in eight, renal in one and lower limb ischaemia in four patients.

Patients in whom a CV event occurred were older and they had more arterial territories with atherosclerotic stenosis > 50% at baseline, compared to those without a CV event. Diabetes, LDL-C > 3.35 mmol/L, claudication and a history of prior IS were more frequent in patients with a CV event (Table 2). Mean-CIMT, as well as baseline levels of TNF-α, NT-proBNP and hs-CRP were significantly higher in patients with a CV event *vs* those without (Table 2).

The mean-CIMT value was found to be independently associated with CV event risk, similarly to diabetes, TNF-α > 6 pg/mL and LDL-C > 3.35 mmol/L (Fig. 2A). However, when stenosis location was included in the logistic regression model, a baseline location of atherosclerotic stenosis was identified as the most important risk factor of a CV event (Fig. 2B). Internal carotid artery, lower limb artery or coronary artery

Table 1. Baseline clinical risk factors, levels of circulating cytokines, hs-CRP, NT-proBNP, lipid profile, serum creatinine and mean-CIMT by the number of territories with lumen stenosis ≥ 50%

	One territory (n = 97)	Two territories (n = 80)	Three territories (n = 69)	Four territories (n = 33)	P value
Age [years]	62.8 ± 10.5	63.5 ± 9.5	65.1 ± 8.5	66.8 ± 8.8	0.077
Male gender [%]	55.7	67.5	75.4	54.5	0.355
Hypertension [%]	83.5	93.7	94.2	93.9	0.353
Diabetes [%]	28.9	32.5	33.3	48.8	0.018
Hyperlipidaemia [%]	77.3	87.5	94.2	90.1	0.013
Smoking [%]	50.5	67.1	79.7	72.7	0.001
Prior MI [%]	28.9	35.0	33.3	72.7	0.000
Prior IS [%]	5.1	13.7	24.6	24.2	0.002
Claudication [%]	0	5.0	37.7	81.8	< 0.001
BMI [kg/m^2]	28.2 ± 4.5	27.6 ± 3.9	26.5 ± 3.7	26.1 ± 3.6	0.013
IL-6 [pg/mL]	4.34 ± 2.8	5.38 ± 3.8	5.72 ± 5.7	6.32 ± 3.6	0.045
IL-10 [pg/mL]	12.9 ± 16.5	14.2 ± 18.3	10.4 ± 11.4	7.7 ± 6.0	0.149
TNF-α [pg/mL]	3.50 ± 2.4	3.99 ± 3.65	4.65 ± 5.2	7.08 ± 8.3	0.001
TGF-β [pg/mL]	18.9 ± 37.1	12.8 ± 14.0	14.0 ± 15.8	18.1 ± 19.4	0.443
NT-proBNP [pmol/L]	24.7 ± 32.8	27.7 ± 42.7	46.5 ± 69.2	66.3 ± 85.9	0.022
hs-CRP [mg/L]	3.34 ± 3.22	4.26 ± 3.8	4.67 ± 3.82	5.14 ± 6.40	0.070
Creatinine [μmol/L]	94.4 ± 36	100.8 ± 35	125.4 ±101	113.0 ± 47	0.009
Triglycerides [mmol/L]	1.51 ± 0.9	1.55 ± 0.7	1.73 ± 1.0	1.87 ± 1.0	0.147
TC [mmol/L]	4.86 ± 1.1	5.06 ± 1.3	5.28 ± 1.2	5.34 ± 1.19	0.080
LDL-C [mmol/L]	2.90 ± 1.0	3.07 ± 1.0	3.25 ± 0.99	3.27 ± 1.21	0.091
HDL-C [mmol/L]	1.27 ± 0.33	1.22 ± 0.37	1.21 ± 0.3	1.17 ± 0.28	0.456
Glucose [mmol/L]	5.69 ± 1.5	6.07 ± 2.0	5.96 ± 1.6	6.23 ± 1.6	0.004
Mean-CIMT [mm]	1.10 ± 0.25	1.37 ± 0.34	1.80 ± 0.38	1.91 ± 0.4	< 0.001

MI — myocardial infarction; IS — ischaemic stroke; BMI — body mass index; IL — interleukin; TNF — tumour necrosis factor; TGF — transforming growth factor; NT-proBNP — N-terminal brain natriuretic peptide; hs-CRP — high-sensitivity C-reactive protein; TC — total cholesterol; LDL-C — low density lipoprotein cholesterol; HDL-C — high density lipoprotein cholesterol; CIMT — carotid intima-media thickness

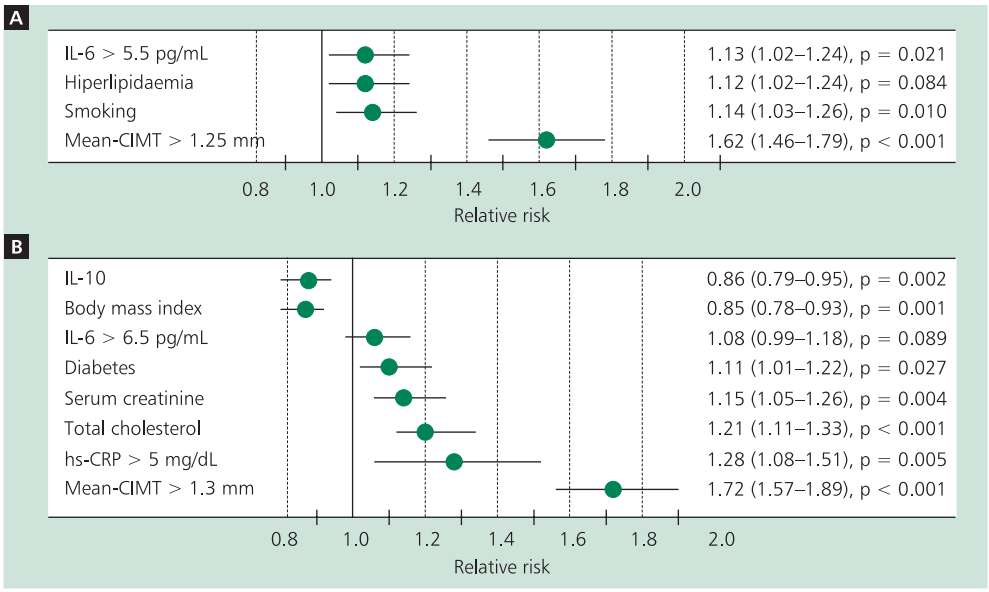

Figure 1. A. Independent risk factors of atherosclerotic occlusive disease (artery lumen reduction ≥ 50%) at two and more arterial territories. The multivariate one-step backward logistic regression analysis; **B.** Independent risk factors of atherosclerotic occlusive disease (artery lumen reduction ≥ 50%) in three or four arterial territories. The multivariate one-step backward logistic regression analysis; abbreviations as in Table 1

Table 2. Comparison of baseline clinical risk factors, levels of circulating cytokines, hs-CRP, NT-proBNP, lipid profile, serum creatinine, mean-CIMT, atherosclerosis extent and lesion location in patients who had a CV event with those who did not during the follow-up period of 24 months

Biomarker	No CV event (n = 227)	CV event (n = 52)	P value
Age [years]	63.5 ± 9.5	66.6 ± 9.8	0.036
Male gender [%]	71.1	62.1	0.223
Hypertension [%]	89.9	92.3	0.593
Diabetes [%]	29.5	50.0	0.005
Hyperlipidaemia [%]	85.0	90.4	0.316
Smoking [%]	62.8	75.0	0.098
Prior MI [%]	34.4	48.1	0.065
Prior IS [%]	11.9	26.9	0.006
Claudication [%]	13.2	51.9	< 0.001
BMI [kg/m^2]	27.4 ± 4.1	26.8 ± 3.95	0.320
IL-6 [pg/mL]	5.02 ± 4.2	6.07 ± 3.58	0.097
IL-10 [pg/mL]	11.5 ± 13.4	14.3 ± 20.9	0.219
TNF-α [pg/mL]	3.92 ± 3.8	6.23 ± 6.96	0.001
TGF-β [pg/m]	18.9 ± 37.1	12.8 ± 14.0	0.443
NT-proBNP [pmol/L]	31.8 ± 51.3	63.2 ± 79.6	0.007
hs-CRP [mg/L]	3.34 ± 3.22	4.26 ± 3.8	0.045
Creatinine [μmol/L]	104.9 ± 64.6	111.1 ± 42.5	0.513
Triglycerides [mmol/L]	1.57 ± 0.9	1.83 ± 0.99	0.065
TC [mmol/L]	5.04 ± 1.21	5.23 ± 1.17	0.320
LDL-C [mmol/L]	3.05 ± 0.97	3.20 ± 1.05	0.021
HDL-C [mmol/L]	1.24 ± 0.34	1.18 ± 0.30	0.280
Glucose [mmol/L]	5.7 ± 1.5	7.3 ± 2.59	< 0.001
Mean-CIMT [mm]	1.377 ± 0.44	1.707 ± 0.39	< 0.001
Atherosclerosis extent and stenosis location:			
Number of territories with a stenosis ≥ 50% [%]	1.96 ± 0.97	2.90 ± 0.91	< 0.001
Significant coronary artery stenosis ≥ 50% [%]	74.8	90.4	0.015
Internal carotid or vertebral artery stenosis ≥ 50%	46.7	84.6	< 0.001
Renal artery stenosis ≥ 50% [%]	50.7	61.5	0.158
Lower limb artery stenosis ≥ 50% [%]	23.3	55.8	< 0.001

CV — cardiovascular; other abbreviations as in Table 1

stenosis ≥ 50% were associated with a 24%, 16%, and 15% RR increase in CV event, respectively (Fig. 2B). After adjustment for a baseline location of artery stenosis ≥ 50%, CIMT became a non-significant prognostic factor.

DISCUSSION

The most important finding of our study is that a baseline lesion location is one of the most important prognostic risk factors of future CV events associated with RR increase by 15–24%, irrespective of the performed revascularisation procedure. In the REACH study, the one-year CV event rate (CV death/MI/IS/hospital admission for CV reasons) was 26.3% in patients with three symptomatic arterial disease locations, compared to 12.6% in patients with single territory stenoses [7]. In our previous study, the two-year thromboembolic CV event rates were 9%, 17%, 26% and 51% in patients with one-, two-, three- and four-territories stenoses ≥ 50%, respectively [15]. In the present study, patients experiencing a CV event had more advanced atherosclerotic occlusive disease (2.9 territories), compared to those who did not (1.9 territories). Thus, information on atherosclerosis extent is very useful in clinical practice.

Extracoronary occlusive lesions are common, occurring in approximately one third of patients with symptomatic CAD [4–6]. Drohomirecka et al. [19] observed that a previous IS, claudication and unstable CAD were related to 3.3-fold, 2.3--fold and 1.6-fold higher RR of internal carotid artery stenosis ≥ 50%, respectively. Lanzer [4] found that diabetes was independently associated with a 1.5-fold higher probability of multi-territorial stenoses. In present study, hyperlipidaemia and smoking (current or former) turned out to be independent risk factors of artery stenosis > 50% in two-territories, while diabetes was an independent risk factor for three- and four-territorial occlusive disease.

As angiography should be performed only in selected patients, the role of numerous clinical biomarkers in predic-

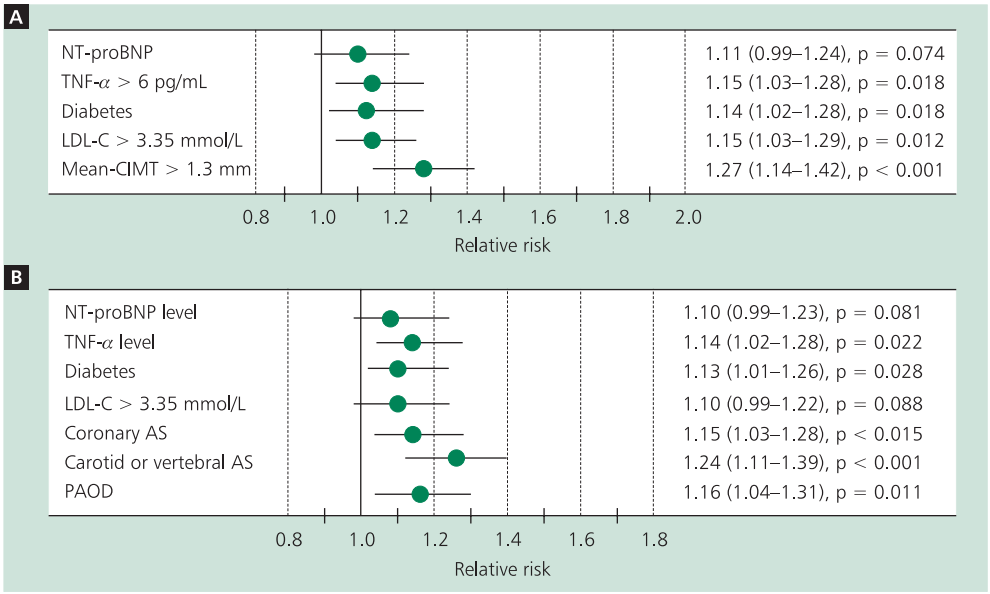

Figure 2. A. Independent risk factors of a two-year cardiovascular (CV) event risk (CV death/MI/IS/lesion progression) in the multivariate one-step backward logistic regression analysis with inclusion of the mean carotid intima-media thickness value; **B.** Independent risk factors of a two-year CV event risk (CV death/MI/IS/lesion progression) in the multivariate one-step backward logistic regression analysis with inclusion of stenosis location; AS — artery stenosis; PAOD — peripheral lower limb artery occlusive disease; rest abbreviations as in Table 1

ting atherosclerosis extent should be investigated in depth. The assessment of carotid atherosclerosis as a surrogate marker for occlusive atherosclerotic coronary or renal disease has been validated in various clinical studies [8, 12, 14, 16, 17, 20–22]. In the present study, we found that mean-CIMT value exceeding 1.3 mm was associated with a 1.7-fold RR increase of the artery stenosis > 50% in three and more arterial territories. Also, the inflammatory status was taken into consideration.

The results concerning associations between cytokines and atherosclerosis extent are often not conclusive [11, 23, 24]. In the VADT study, a positive association was found between IL-6 level and coronary atherosclerosis extent [23]. In the present study, IL-6 level > 5.5 pg/mL was associated with a 13% RR increase, while hs-CRP > 5 mg/L was associated with a 28% RR increase of atherosclerotic occlusive disease in at least two, and three or four territories. On the other hand, a higher IL-10 level was associated with a 16% lower risk of multi-territorial stenoses. In the study by Krecki et al. [24], increased levels of hs-CRP and NT-proBNP were associated with CAD severity, while no such associations were noted for levels of TNF-α or IL-8.

The pro-inflammatory cytokines studied in the present study, IL-6, TNF-α and hs-CRP, take part in the process of plaque destabilisation and plaque rupture [16]. The adverse predictive value of high TNF-α and IL-6 has been demonstrated in acute coronary syndromes as well as in healthy individuals [8, 9, 25–28]. In patients with unstable angina, high serum IL-6 level has been associated with increased in-hospital morbidity and mortality; while in stable post-MI patients, high levels of TNF-α correlated with increased risk of recurrent events [28].

In the present study, a baseline level of TNF-α > 6 pg/mL was associated with a CV event risk increase of 14%, while no associations for IL-6 or hs-CRP levels were found. One explanation of this finding might be that all patients were given statins. The IL-6 expression and thus hs-CRP level are inhibited by statins, and this finding suggests the existence of additional mechanisms, other than those mediated by CRP synthesis. It is worth noting that the mean baseline NT-proBNP level was twice as high in patients who suffered a CV event compared to those who did not, although there was only a trend to association with CV event risk.

The CIMT use relies on its ability to predict future clinical CV end-points [12, 13, 15, 20, 24, 29]. The RR per CIMT difference, in the meta-analysis performed by Lorenz et al. [29], was higher for IS than for MI. In the present study, CIMT > 1.3 mm was found to be an independent risk factor associated with a 27% RR increase of CV event only when stenosis location was not included in the multivariate model. In the logistic regression model, including location of atherosclerotic stenosis, internal carotid or vertebral artery stenosis > 50%, PAOD and CAD were the most important risk factors of a future CV event.

CONCLUSIONS

The mean-CIMT value, as well as circulating levels of IL-6, IL-10, and hs-CRP, are independently associated with the number of arterial territories with a significant lumen stenosis (≥ 50%). The presence of diabetes, high LDL-C and TNF-α > 6 pg/mL were found to be independent risk factors of a CV event. The CIMT > 1.3 mm seems to be a clinically relevant marker associated with a future CV event risk. However, baseline lesion location was better than CIMT assessment in the context of future CV events.

Conflict of interest: *none declared*

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Zależność między zaawansowaniem zmian miażdżycowych, cytokinami zapalnymi oraz grubością kompleksu intima-media tętnic szyjnych i ich znaczenie prognostyczne u chorych z miażdżycą tętnic

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Streszczenie

Wstęp i cel: Celem pracy była ocena zależności między zaawansowaniem zmian miażdżycowych, cytokinami zapalnymi i grubością kompleksu intima-media tętnic szyjnych (CIMT) oraz ich znaczenie w przewidywaniu zdarzeń sercowo-naczyniowych w 2-letniej obserwacji.

Metody: Ocenę grubości CIMT, stężenia białka C-reaktywnego o wysokiej czułości (hs-CRP), interleukiny 6 i 10 (IL-6, IL-10), czynnika martwicy nowotworów α (TNFα), czynnika transformującego wzrostu β (TGFβ), oraz N-końcowego peptydu natriuretycznego typu B (NT-proBNP) wykonano u 279 chorych w wieku średnio 64,1 ± 9,6 roku, ze zwężeniem miażdżycowym ≥ 50% w przynajmniej 1 obszarze tętniczym spośród tętnic wieńcowych, nerkowych, dogłowowych i kończyn dolnych. U 97 chorych stwierdzono zmiany miażdżycowe w 1 obszarze, u 80 — w 2, u 69 — w 3, a u 33 — w 4 obszarach tętniczych. Podczas 2-letniej obserwacji analizowano częstość zdarzeń sercowo-naczyniowych (zgon, zawał serca, udar mózgu, progresja zwężenia).

Wyniki: Stwierdzono, że niezależnymi czynnikami związanymi z ryzykiem obecności zwężeń ≥ 50% w 3 i więcej obszarach tętniczych są: grubość CIMT > 1,3 mm (RR = 1,72; p < 0,001) oraz stężenia hs-CRP > 5 mg/dl (RR = 1,28; p = 0,005), IL-6 > 6,5 pg/ml (RR = 1,08; p = 0,089), IL-10 (RR = 0,86; p = 0,002), cholesterolu całkowitego (RR = 1,21; p < 0,001), kreatyniny (RR = 1,15; p = 0,004), a także cukrzyca (RR = 1,11; p = 0,027) i wskaźnik masy ciała (RR = 0,85; p = 0,001). Zdarzenia sercowo-naczyniowe wystąpiły u 52 (18,6%) chorych. W analizie wieloczynnikowej wykazano, że niezależnymi czynnikami ryzyka zdarzeń sercowo-naczyniowych są: grubość CIMT > 1,3 mm (p < 0,001), cukrzyca (p = 0,018), stężenia TNFα > 6 pg/ml (p = 0,018), cholesterolu frakcji LDL > 3,35 mmol/l (p = 0,012) i NT-proBNP (p = 0,074), które wiązały się z ryzykiem zdarzeń sercowo-naczyniowych wyższym o odpowiednio: 27%, 14%, 15%, 15% i 11%. Jednak po standaryzacji wyników do lokalizacji zwężeń tętnic grubość CIMT okazała się nieistotnym statystycznie czynnikiem ryzyka zdarzeń sercowo-naczyniowych (p = 0,245).

Wnioski: Stwierdzono, że stężenia hs-CRP, IL-6, IL-10 są niezależnie związane z zaawansowaniem miażdżycy, podczas gdy stężenia TNFα i NT-proBNP były przede wszystkim związane z ryzykiem zdarzeń sercowo-naczyniowych w 2-letniej obserwacji. Średnia grubość CIMT > 1,3 mm okazała się zarówno wskaźnikiem stopnia zaawansowania miażdżycy, jak i zdarzeń sercowo-naczyniowych, jednak ryzyko tych zdarzeń zależało przede wszystkim od lokalizacji zmian miażdżycowych.

Słowa kluczowe: wieloobszarowa miażdżyca, zdarzenia sercowo-naczyniowe, kompleks intima-media tętnic szyjnych, wskaźniki miażdżycy, hs-CRP, NT-proBNP, cytokiny

Kardiol Pol 2011; 69, 10: 1024–1031

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Praca wpłynęła: 29.12.2010 r. **Zaakceptowana do druku:** 18.05.2011 r.