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CARDIOVASCULAR RISK FACTORS - ASSOCIATION WITH LOWER EXTREMITY VERSUS CORONARY ARTERY DISEASE

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Abstract: *Atherosclerosis is the main cause of lower extremity artery disease (LEAD) and coronary artery disease (CAD). These two arterial territories share the major cardiovascular risk factors: smoking, hypertension, dyslipidaemia and diabetes. Current guidelines draw attention to other possible risk factors: homocysteine level, inflammation markers (e.g. high-sensitive C reactive-protein (CRP), interleukin 6) and chronic kidney disease (CKD.) The objective of this study was to evaluate the cardiovascular risk factors strength association with LEAD and CAD on a study population of 203 patients. Our study concluded that smoking seems to be the most powerful risk factor for LEAD, especially for significant lesion in femoral arteries, while diabetes mellitus, hypertension and CKD were significantly associated with CAD. The highest chance of association with multivessel-CAD is for diabetes mellitus compared to hypertension and CKD respectively. Moreover, in diabetic patients the percent of multivessel-CAD was significantly higher than the percent of single-CAD and non-significant CAD.*

INTRODUCTION

Lower extremity artery disease (LEAD) and coronary artery disease (CAD) are associated with considerable morbidity, diminished quality of life and mortality.(1) These two pathologies refer to different degrees of arterial stenosis subsequent to several causes: embolism, thrombosis, vasculitis disease and atherosclerotic disease.(2) Atherosclerosis is the most common cause of LEAD and CAD; thus, this two arterial territories share the major cardiovascular risk factors: smoking, hypertension, dyslipidaemia and diabetes (3). However, current guidelines also draw attention to other possible risk factors for atherosclerotic disease: homocysteine level, markers of inflammation (e.g. high-sensitive C reactive-protein (CRP), fibrinogen, interleukin 6) (4) and chronic kidney disease (CKD).

Each risk factor is associated with variable strength with each vascular territory; thus, screening of all major risk factors should be considered.(3)

Each vascular region affected by atherosclerotic disease can be considered a marker of cardiovascular risk.(3)

Atherosclerosis is a slow process, which leads to a disease slow progression. In this context, early identification and control of risk factors may contribute to a late symptomatology onset, less severe disease, better outcome and life quality improvement.

AIM

The aim of the current study is to evaluate the strength of association between cardiovascular risk factors and LEAD versus CAD.

MATERIALS AND METHODS

From January 2017 to December 2019, 203 patients with symptomatic LEAD were evaluated. The patients underwent digital subtraction angiography for LEAD evaluation and coronary angiography for CAD evaluation in Sibiu County Clinical Emergency Hospital, CVASIC research centre.

Significant LEAD and CAD were defined as at least one lesion with ≥ 50% lumen diameter stenosis. Lower extremity arteries were divided into three segments: iliac (common iliac artery, external iliac artery, internal iliac artery), femoral (common femoral artery, superficial femoral artery) and infrapopliteal (popliteal artery, tibioperonier trunk, anterior tibial artery, posterior tibial artery, fibular artery). CAD was classified as significant-CAD (any coronary artery stenosis ≥ 50% lumen diameter in left main (LM) artery or left anterior descending (LAD) artery or circumflex artery (CA) or right coronary artery (RCA)) or non-significant-CAD (without coronary artery stenosis ≥ 50% lumen) and as single-CAD (only one of LAD or CA or RCA with lesion above 50%) or multivessel-CAD (LM stenosis ≥ 50%, or any of two arteries from LAD, CA, RCA with arterial stenosis ≥ 50%).

Hypertension, dyslipidaemia and diabetes were defined according to current guidelines: hypertension as a history of antihypertensive drug use or newly diagnosed hypertension by repeated arterial blood pressure measurements (at least two) ≥ 140/90 mmHg during hospitalization, diabetes was considered present when patients were taking an hypoglycemic treatment - oral agents or insulin, and/or had a fasting glucose level ≥ 126 mg/dL or glycosylated hemoglobin ≥ 6.5%. Dyslipidemia diagnosis was considered if a patient had a history of lipid-lowering therapy (statin) use, or had a total cholesterol level ≥ 200 mg/dL or triglyceride (TG) level ≥ 150 mg/dL. The patients were considered positive for smoking if they were active smokers or former smokers - but not more than

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1 year abstinence.

Normal values for C reactive-protein in our laboratory were 0-5 mg/dl. Chronic kidney disease was classified form grade I to V according to KDOQI classification, and creatinine clearance was calculated with Cockcroft-Gault formula.

Statistical analysis was performed using IBM SPSS Statistic software. The Shapiro-Willk test was used to analyse data normality. Normally distributed continuous variables were expressed as the mean±SD, and non-normally distributed continuous variables were expressed as the median value. Pearson Chi-Square tests, for discontinuous variables, and Kruskal Wallis test, for continuous variables, were used to evaluate the risk factors association with LEAD and CAD. Statistical significance was considered at a P value <0.05 (two-tailed).

RESULTS

Patients' characteristics

Of the 203 patients with symptomatic LEAD, 166 (81.8%) were males, 37 (18.2%) were females; the mean age was 65.31±8.616 (range 39-85years). 135 (64.5%) patients were in stage II Leriche-Fontaine, 40 (19.7%) in stage III Leriche-Fontaine, 28 (13.8%) in stage IV Leriche Fontaine. Hypertension had the higher prevalence in our study group (79.8%) followed by smoking (76.84%), CKD (58,1%), hypercholesterolemia (54.7%), hypertriglyceridemia (48.3%) and diabetes mellitus (34.5%). The majority of patients were with stage II Leriche-Fontaine LEAD with a mean claudication index of 144±24 m and a mean ankle-brachial index of 0.62±0.24.

Patient's demographic, clinical and biological characteristics are summarised in table no. 1 and table no. 2.

Table no. 1. Patients' demographic and clinical characteristics

Variable	Value		
Age, years	65.31±8.6	Min: 39	Max: 85
BMI, kg/m^2	27.44±4.48	Min: 17.72	Max: 43.21
	Underweight Normal weight Overweight Grade I obesity Grade II obesity Grade III obesity		2 (1%) 67 (33%) 82 (40.4%) 40 (19.7%) 10 (4.9%) 2 (1%)
Gender	Male Female		166(81.8%) 37 (18.2%)
Smoking	Yes No		156 (76.84%) 47 (23.16%)
Diabetes mellitus (DM)	Yes No		70 (34.5%) 133 (65.5%)
Hypertension	Yes Grade I Grade II Grade III No		162 (79.8%) 0 (0%) 76 (37.4%) 85 (41.9%) 41 (20.2%)
Hypercholesterolemia	Yes No		111 (54.7%) 92 (45.3%)
Hypertriglyceridemia	Yes No		98 (48.3%) 105 (51.7%)
CKD	Yes (Creatinine clearance <90ml/min/1.73m^2) Grade II Grade IIIa IIIb Grade IV Grade V No (Creatinine Clearence > 90 ml/min/1.73m^2)		118 (58.1%) 85 (41.9%) 28 (13.8%) 3 (1.5%) 0 (0%) 1 (1%) 85 (41.9%)
Leriche-Fontaine classification	**I** : Asymptomatic **IIa**: intermittent claudication at more than 200 m walk **IIb**: intermittent claudication in less than 200 m walk **III**: limb rest pain **IV**: ischemic lesions – necrosis, gangrene		0 (0%) 17 (8.4%) 118 (58.1%) 40 (19.7%) 28 (13.8%)
Claudication index, m	144±24	Min: 0	Max: 1000
Ankle-Brachial index	0.62±0.24	Min: 0	Max: 1

Table no. 2. Patients' biological characteristics

Parameter	Mean±SD	Minimun	Maximum
Total cholesterol, mg/dl	207.60±55.86	107	357
LDL-cholesterol, mg/dl	117.57±43.76	31	290
HDL – cholesterol, mg/dl	44.91±10.93	27	86
Triglycerides, mg/dl	185.78±148.4	44	1356
Creatinine, mg/dl	1.02±0.59	0.55	6.88
Clearance Creatinine, ml/min/1.73m^2	85.75±25.59	8.32	166.99
C reactive-protein , mg/dl	8.07±12.79	0.57	127.62

Risk factors association with LEAD

In our study population smoking was highly associated with significant arterial stenosis in iliac and femoral segments (table no. 3). 92 (59%) smoking patients had significant iliac lesions, versus 19 (40%) non-smokers patients with significant iliac lesions. The association was statistically significant (p=0.021). In femoral segment a statistically significant association is also registered (p 0.0001). The highest chance of smoking association is with significant lesions in femoral segment (likelihood ratio 20.85) compared with iliac segment (likelihood ratio 8.3) For infrapopliteal segment the association was not statistically significant (p 0.356).

Table no. 3. Smoking association with LEAD

Arterial stenosis>50 %	Smoking		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Iliac segment	92 (59%)	19(40%)	7.7	2	**0.021**	**8.30**
Femoral segment	132 (84.7%)	47 (100%)	17.4	2	**0.0001**	**20.85**
Infrapopliteal segment	130 (83.3%)	43 (91.5%)	2.06	2	0.356	2.26

The others risk factors evaluated, diabetes mellitus, hypertension, CKD, hypercholesterolemia, hypertriglyceridemia, C reactive protein were not associated with significant arterial stenosis in any of the iliac, femoral and infrapopliteal arterial segments (p>0.05) as shown in table no.4.

Table no. 4. Diabetes mellitus, hypertension, CKD, hypercholesterolemia, hypertriglyceridemia, C reactive protein association with LEAD.

Arterial stenosis>50 %	DM	Hyper-tension	CKD	Hyper-cholesterolemia	Hyper-triglyceridemia	CRP
	p two-tailed Chi – Square Test					
Iliac segment	0.241	0.891	0.986	0.890	0.349	0.058
Femoral segment	0.116	0.096	0.445	0.144	0.349	0.337
Infrapoplitea l segment	0.158	0.708	0.249	0.819	0.174	0.058

Similar with the value of total cholesterol, LDL-cholesterol value was not significantly associated with significant LEAD, in none of the three arterial segments: iliac (p=0.786), femoral (p=0.461), infrapopliteal (p=0.342).

Risk factors association with CAD

In our study population smoking, hypercholesterolemia, hypertriglyceridemia was not

significantly associated with significant CAD or multivessel-CAD as shown in table no. 5.

Table no. 5. Smoking, hypercholesterolemia, hypertriglyceridemia association with CAD

CAD	Smoking		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Significant CAD	111(71.2 %)	38(80.9%)	1.74	1	0.187	1.82
Multivessel CAD	73(46.8 %)	28(56.9%)	2.74	2	0.254	2.81
	Hypercholesterolemia		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Multivessel CAD	56(50.5%)	45(48.9%)	0.19	2	0.908	0.193
	hypertriglyceridemia		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Multivessel CAD	50(51%)	51(48.6%)	2.07	2	0.354	2.09

The other risk factors – diabetes mellitus, hypertension and CKD were significantly associated with significant CAD and multivessel-CAD ($p<0.05$). The highest chance of association with multivessel-CAD is for diabetes mellitus (likelihood ratio 28.73), compared to hypertension (likelihood ratio 12.14) and CKD (likelihood ratio 6.23), respectively (table no. 6).

Table no. 6. Diabetes mellitus, hypertension and CKD association with CAD

CAD	Diabetes mellitus		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Significant CAD	61(87.1%)	88(66.2%)	10.3	1	**0.001**	**11.24**
Multivessel CAD	52(74.3%)	49(36.8%)	27.1	2	**0.0001**	**28.73**
	Hypertension		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Significant CAD	126(77.8 %)	23(56.1%)	7.87	1	**0.005**	**7.32**
Multivessel CAD	90(55.6%)	11(26.8%)	12.08	2	**0.002**	**12.14**
	CKD		Chi Square test			
	Yes	No	χ^2	df	p	Like-lihood ratio
Significant CAD	94(79.7%)	55(64.7%)	5.66	1	**0.017**	**5.60**
Multivessel CAD	66(55.9%)	35(41.2%)	6.26	2	**0.044**	**6.23**

Also, in diabetic patients the percent of multivessel-CAD was significantly higher (74.3%) than the percent of single-CAD (17.1%) and non-significant CAD (8.6%).

DISCUSSIONS

The predominance of male gender in our study group is concordant with literature data, both LEAD and CAD affecting more frequently males than females.(5,6) The mean age in the studied group correspond to literature information; it is well known that the risk of developing CAD and LEAD increases with age, and includes age greater than 45 years in men and greater than 55 years in women.(5,6)

The increased incidence of smoking, hypertension and hypercholesterolemia among studied patients coincides with literature data.(4,5)

Smoking was found to be a particularly strong risk factor for lower extremity artery disease. In a paper published in 2012 by Joosten et al it was pointed out that smoking has a population attributable fraction for LEAD of approximately 44%.(9) In our study group smoking was highly associated with significant arterial stenosis in iliac and femoral segments, but the association was not statistically significant for infrapopliteal segments.

Regarding smoking and CAD, there is a strong association with ischemic heart disease.(5) Heavy smokers - more than 20 cigarettes per day - have a 2- to 3-fold increase in total heart disease. Moreover, continued smoking is a very important risk factor for recurrent myocardial infarction.(5,10) In our study population smoking was not significantly associated with CAD.

In the Framingham Heart Study, even high-normal blood pressure (defined as a systolic blood pressure of 130-139 mm Hg, diastolic blood pressure of 85-89 mm Hg, or both) increased the risk of cardiovascular disease 2-fold, as compared with healthy individuals.(7) Studies have also shown that a 20 mmHg increase of systolic blood pressure was associated with a 63% higher risk for LEAD.(8) In our study group hypertension was significantly associated with CAD, but there was no significant association with LEAD.

Dyslipidemia is a major cardiovascular risk factor. The risk of CAD increases proportional with the cholesterol level, as shown in Framingham Heart Study.(5,7) Hypercholesterolemia is a significant contributor to peripheral artery disease, being independently associated with incident clinical LEAD.(9) Several studies have shown that high LDL-cholesterol and low HDL-cholesterol are associated with an increased risk for atherosclerotic disease.(4) Moreover, in large epidemiological studies, high levels of HDL-cholesterol ware found to be protective for CAD and LEAD.(4,11) In univariate analysis hypertriglyceridemia is associated with LEAD, but in multivariate analysis it usually drops out as an independent risk factor.(4,12,13) In our study group hypercholesterolemia and hypertriglyceridemia were not associated with significant arterial stenosis in any of the iliac, femoral and infrapopliteal arterial segments and with significant CAD. The small number of patients enrolled in this study among with lipid-lowering therapy can explain this discordant result compared to literature data.

Diabetes mellitus is an important risk factor for CAD and LEAD. Diabetic patients are more likely to experience future cardiovascular events compared with healthy population.(5,14) Strong diabetes – LEAD association was proved in populations studies, with ORs ranging from 1.9 to 4.(4,12) For our study group diabetes mellitus was significantly associated with significant CAD and multivessel-CAD. Moreover, the percent of diabetic patients with multivessel-CAD was significantly higher than the percent of diabetic patients with single-CAD and non-significant CAD. On the other hand, diabetes was not associated with LEAD in our study group, probably due to the small cohort and small percent of diabetic patients evaluated.

Classic cardiovascular risk factors are common findings in CKD patients, but CKD brings additional specific risk factors that promote atherosclerotic process (e.g. pro-calcific state, chronic inflammation and hypoalbuminemia.(16) CKD is also an independent risk factor for CAD, being associated with both development and severity of CAD.(15) In this study, CKD was significantly associated with significant CAD and multivessel CAD, but there was no association with LEAD.

A large number of studies have shown that inflammation plays an important role in atherosclerosis pathophysiology (4). High-sensitivity C-reactive protein is an inflammation marker and is associated with an increased risk of

LEAD presence, progression and complication.(17) In our study group, the C-reactive protein was determined and not the High-sensitivity C-reactive protein and no significant association with LEAD was detected.

The main limitation of this study is the small numbers of patients enrolled. This is a possible explanation for discordant study result with literature data.

CONCLUSIONS

LEAD and CAD share the same cardiovascular risk factors. The strength of associations between each conventional or non-conventional cardiovascular risk factor with LEAD and CAD was an important topic in large epidemiological studies.

Among risk factors evaluated in this study, smoking and hypertension had the higher prevalence followed by CKD and hypercholesterolemia.

In our study group, only smoking was strongly associated with LEAD. The other risks factors – diabetes mellitus, hypertension, dyslipidaemia, CKD and C-reactive protein – did not have statistically significant association with LEAD, probably due to the small number of patients evaluated.

In contrast, for CAD, diabetes mellitus, hypertension, dyslipidaemia and CKD were associated with the presence and severity of coronary lesions; instead smoking was not significantly associated with coronary stenosis ≥ 50% of lumen diameter.

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