ORIGINAL ARTICLE

CONTENTS

Clinical correlates of lower extremity arterial calcification in peripheral artery disease patients with concomitant stable coronary artery disease

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ABSTRACT

Aim: To evaluate the associations of lower extremity arterial calcification (LEAC) with clinical profile of peripheral artery disease (PAD) patients with concomitant stable coronary artery disease (SCAD).

Materials and Methods: The cross-sectional study enrolled and analyzed clinical and instrumental data from 110 lower extremity PAD (chronic limb-threatening ischemia) patients (mean age [mean ± standard deviation] 71±8 years; 77 [70 %] males and 33 [30 %] females) with concomitant SCAD, underwent endovascular treatment during the period 2021-2025. LEAC was evaluated by CT-angiography with the assessment of Agatson calcium score (CS). The enrolled sample was subdivided into group 1 (CS <1000 units [n=60]) and group 2 (CS ≥1000 units [very extensive LEAC; n=50]).

Results: Group 2 (vs. group 1) was characterized by higher prevalence of atherosclerotic risk factors, namely smoking, overweight/obesity, and the cases of family history of cardiovascular diseases. Hypertension and diabetes mellitus tended to be more prevalent in group 2, as opposed to group 1. In addition, patients with CS ≥1000 units (vs. <1000) presented more frequently with atrial fibrillation/flutter, heart failure stage C, previous acute cerebrovascular event and the most advanced Rutherford stage 6.

Conclusions: The PAD patients with concomitant SCAD and very extensive LEAC demonstrated more severe PAD and higher comorbidity burden, as compared to their counterparts with less calcified lower extremity arteries. The obtained data substantiate the integrated approach to be implemented in the management of such polyvascular patients, particularly by the use of LEAC as a potential predictor of adverse cardiovascular events.

KEY WORDS: arteries, diabetes mellitus, calcification, endovascular treatment

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INTRODUCTION

According to the literature, the prevalence of lower extremity (LE) peripheral artery disease (PAD) varies depending on a country's level of economic development: from 28,7% in low-income countries to 13,1% in high-income countries [1, 2]. LE PAD is recognised as an independent predictor of increased cardiovascular risk and significantly affects patients' quality of life and life expectancy [3, 4].

In the presence of PAD, coronary artery involvement is detected in 62–65% of cases, cerebrovascular involvement in 32,3% of patients, and the risk of cardiovascular mortality is markedly increased. Overall cardiovascular morbidity in such patients rises sixfold [5, 6].

Mortality among patients with LE PAD is 16,1 ± 2,1%, which significantly exceeds the rate observed in patients without PAD or cardiovascular pathology, where it is 4,1 ± 0,3% [7]. According to data from the US National Health and Nutrition Examination Survey, which included over 9,000 patients with LE PAD, the prevalence of cardiovascular pathology (myocardial infarction [MI], ischemic stroke, heart failure [HF]) exceeded 33% [8].

Over the past decade, treatment strategies for chronic lower limb ischemia have shifted from traditional surgical vascular interventions towards modern endovascular techniques [9, 10]. At the same time, the clinical criteria for selecting invasive strategies have also evolved: in particular, endovascular intervention is increasingly being applied in patients with intermittent claudication, even in the absence of critical ischemia [11].

Despite the widespread adoption of endovascular technologies in clinical practice, there is no unified

Table 1. The age and sex distribution of the enrolled sample of PAD patients with concomitant SCAD

Sex	n	%	Age intervals, years							
			41 – 50		51 – 60		61 – 70		≥71	
			N	%	N	%	N	%	N	%
Males	77	70	2	2,6*	10	13,0*	26	33,8*	39	50,6*
Females	33	30	0	0**	2	6,1**	10	30,3**	21	63,6**
Total	110	100	2	1,8	12	10,9	36	32,7	60	54,6

Note: * – among males; ** – among females

interpretation of the absolute and relative contraindications to their use. Among the clinically significant limitations are the presence of advanced atherosclerosis, acute arterial thrombosis, complete arterial occlusion, eccentric stenosis, and multiple vascular lesions [12]. Meanwhile, recent studies suggest that the outcomes of endovascular procedures may vary depending on the degree of lower extremity arterial calcification (LEAC) [13].

Numerous studies have confirmed that LE PAD is associated with atherosclerotic involvement of other vascular territories, including the coronary artery bed in patients with coronary artery disease (CAD), leading to reduced life expectancy, significant deterioration in quality of life, and an increased risk of patient disability [13–15]. This highlights the need for comprehensive diagnostic evaluation and the implementation of a multidisciplinary approach to the management of patients with polyvascular disease, particularly through thorough investigation of predictors of adverse outcomes. In this context, the study of associations between LEAC and the clinical profile of PAD patients with concomitant CAD is of both scientific and practical interest [13, 14, 16].

AIM

The aim of the study was to evaluate the associations of LEAC with the clinical profile of PAD patients with concomitant stable CAD (SCAD).

MATERIALS AND METHODS

The cross-sectional single-center study analyzed the clinical and instrumental data from 110 LE PAD patients with concomitant SCAD, underwent endovascular treatment in the Clinical Hospital «Feofaniya» State Administrative Department (Kyiv, Ukraine) during the period 2021-2025.

The age of the enrolled patients ranged from 47 to 84 years, with a mean ± standard deviation of 71 ± 8 years. The majority of patients were male (n = 77 [70,0%]), and more than half of the participants were over 70 years of age (Table 1).

The profile of the cardiovascular risk factors among the enrolled patients was as follows: smoking – 73 (66,4 %) cases, body mass index (BMI) – 52 (47,3 %), total serum cholesterol ≥5,2 mmol/l – 97 (88,2 %), hypertension – 96 (87,3 %), family history of cardiovascular disease – 50 (45,5 %), and diabetes mellitus (DM) – 98 (89,1 %).

Verification of SCAD was performed in accordance with established guidelines [17]. Twenty-nine patients (26,4%) presented with stable angina of CCS class III–IV. A history of myocardial infarction (MI) was identified in 34 (30,9%) patients, atrial fibrillation/atrial flutter (AF/AFl) in 30 (27,3%), heart failure (HF) stage C in 35 (31,8%), and previous acute cerebrovascular event (ACVE) in 22 (20,0%). Chronic kidney disease (CKD) of stage 3–4 (according to the KDIGO guideline [18]) was diagnosed in 21 (19,1%) patients, brachiocephalic atherosclerosis in 60 (54,6%), and chronic lung disease in 31 (28,2%) cases. Baseline statin therapy was received by 76 (69,1%) patients.

LE PAD was verified according to the widely accepted guidelines [3, 4, 19]. All 110 enrolled PAD patients presented with a chronic limb-threatening ischemia (CLTI) pattern, specifically with rest pain and trophic changes of the lower extremities. According to the Rutherford classification of chronic limb ischemia [20], stage 5 was identified in 98 (87,3%) patients and stage 6 in 14 (12,7%).

All 110 patients underwent computed tomography (CT) angiography of the lower extremity arteries with the calculation of the calcium score by the Agatson method (LEAC) [13, 21].

Considering the literature on the impact of the degree of vascular calcification on the outcomes of endovascular intervention [13], the sample of patients with PAD and concomitant SCAD was divided into two groups based on the degree of LEAC (by Agatson calcium score). Group 1 (n = 60) consisted of patients with a lower extremity calcium Agatson score of <1000 units (mild calcification) according to CT angiography (mean score: 460,1 ± 215,96 units). Group 2 (n = 50) included patients with a lower extremity calcium Agatson score of ≥1000 units (extensive calcification) (mean score: 2774,3 ± 1483,21 units).

The statistical data analysis was performed using Statistica v. 14.0 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), MedCalc v. 23.1.7 (MedCalc Software Ltd., Belgium) and MedStat v. 5.2. Quantitative variables were presented as mean ± standard deviation, and qualitative variables as absolute and relative (%) frequency (with a 95% confidence interval [CI], as required). To compare continuous variables between two unrelated samples, we used the Student's t-test (if variances were equal) or Welch's t-test (if variances were unequal). To compare qualitative variables, we used the χ^2 test (with a subsequent z-test to compare specific categories [ranks] of qualitative rank variables) and Fisher's exact test (for 2 × 2 tables). A two-tailed p-value < 0.05 was considered statistically significant.

ETHICS

The study was conducted in accordance with the principles of bioethics outlined in the Helsinki Declaration "Ethical Principles for Medical Research Involving Human Subjects," the "Declaration on Universal Norms on Bioethics" (UNESCO), and in compliance with current legislation of Ukraine. The study protocol was approved by the local ethics committee. All patients signed informed consent.

RESULTS

The data presented in Table 1 indicate an increase in the proportion of female patients among the older age groups, which is due to gender-specific features of CAD progression [6, 17]. The mean age of the female participants in this study was higher than that of the male participants (74 ± 8 vs. 69 ± 8 years, respectively; p < 0,001). In the oldest age group (≥81 years), women were six times more frequent than men: 39,4% (13/33) vs. 6,5% (5/77), respectively (p < 0,001). According to existing data, men suffer from CAD twice as often as women, but in patients with DM and aged >70 years, the incidence of CAD is similar in both sexes [6, 17, 22].

The distribution of patients in the study groups with varying degrees of lower extremity arterial calcification by age and sex is presented in Table 2.

Although patients aged 51-60 years were more frequent in group 1, and those aged 61-70 years were more frequent in group 2, no statistically significant differences in mean age were found between the study groups. At the same time, the comparison groups were comparable in terms of sex (Table 1). This provides grounds to suggest that the differences identified later are not related to the gender distribution of patients in each of the study groups.

Table 3 summarizes the data on the frequency of detection of individual risk factors for atherosclerosis in the study groups.

In the course of the study, we found that a higher percentage of smokers, individuals with overweight and/or obesity, hypertension (at the trend level), a family history of cardiovascular diseases, and DM (at the trend level) were observed in patients of group 2 compared to their percentage in patients of group 1 (Table 2). These findings align with general beliefs regarding the contribution of traditional atherosclerosis risk factors to the development of vascular calcification [23]. At the same time, the data regarding the frequency of a family history of cardiovascular diseases in the study groups may indirectly indicate the role of genetic factors in the development of vascular calcification [24].

When analyzing the risk factors for atherosclerosis among patients of the mentioned groups, attention is also drawn to the high frequency of patients with elevated serum cholesterol levels, which may be related to individual characteristics of lipid-lowering drug use. In group 1, 40 patients (66,7%) were receiving lipid-lowering therapy, while in group 2, 36 patients (72,0%) were receiving it (p=0,679). This fact may be associated with both insufficient statin therapy intensity and suboptimal patient adherence to treatment in both study groups. At the same time, assessing the effectiveness of hypolipidemic therapy is not advisable, as statin treatment leads to increased calcification of plaques, which can be considered part of their stabilization. Thus, the increase in the calcium index against the background of hypolipidemic therapy is more likely to be associated with the stabilization of atherosclerotic plaques rather than indicating the ineffectiveness of therapeutic treatment [25, 26].

At the next stage, we deemed it appropriate to examine the clinical picture of the study groups of patients with different degrees of lower extremity arterial calcification (Table 4).

Analysis of the data in Table 4 indicates a higher frequency of stage 5 according to Rutherford among patients of group 2 compared to those in group 1, which may clinically reflect differences in the prevalence of atherosclerotic processes in the studied groups.

At the same time, it is noteworthy that in group 2, patients with AF/AFl and HF stage C were more frequent compared to group 1 (Table 4). Additionally, the frequency of past myocardial infarction (MI) cases was quantitatively, though not significantly, higher in group 2. These findings may indirectly suggest more significant changes in myocardial functional state and hemodynamics in patients with extreme degrees of lower extremity arterial calcification. The latter creates

Table 2. Baseline demographic characteristics of PAD patients with concomitant SCAD in the studied groups

Parameters		Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Age, years		70 ± 9*	72 ± 6**	0,168
Age intervals, years, n (%)	41-50	2 (3,3)	0	0,012
	51-60^z	10 (16,7)	2 (4,0)	
	61-70^z	13 (21,7)	23 (46,0)	
	≥71	35 (58,3)	25 (50,0)	
Sex, n (%)	Males	42 (70,0)	35 (70,0)	1,000
	Females	18 (30,0)	15 (30,0)	

Note: * – age range: 47-84 years; ** – age range: 57-81 years; z – statistically significant difference by z-test (at p<0,05)

Table 3. The specific risk factors for atherosclerosis in PAD patients with concomitant SCAD in the studied groups

Parameters	Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Smoking, n (%)	32 (53,3)	41 (82,0)	0,002
BMI ≥25,0 kg/m^2, n (%)	18 (30,0)	37 (74,0)	<0,001
Total cholesterol ≥5,2 mmol/l, n (%)	51 (85,0)	46 (92,0)	0,375
Hypertension, n (%)	49 (81,7)	47 (94,0)	0,083
Family history, n (%)	21 (35,0)	29 (58,0)	0,021
DM, n (%)	50 (83,3)	48 (96,0)	0,062

Table 4. Baseline clinical presentation of PAD patients with concomitant SCAD in the studied groups

Parameters		Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Stable angina CCS class III-IV, n (%)		18 (30,0)	11 (22,0)	0,390
AF/AFl, n (%)		10 (16,7)	20 (40,0)	0,009
Previous MI, n (%)		15 (25,0)	19 (38,0)	0,153
HF stage C, n (%)		14 (23,3)	21 (42,0)	0,042
Rutherford stage, n (%)	5	60 (100)	36 (72,0)	<0,001
	6	0*	14 (18,0)**	

Note: * – 95 % CI [0-3,2 %]; ** – 95 % CI [16,3-41,5 %]

Table 5. Certain baseline comorbidities in PAD patients with concomitant SCAD in the studied groups

Parameters	Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
CKD of stage 3-4, n (%)	9 (15,0)	12 (24,0)	0,330
Previous ACVE, n (%)	7 (11,7)	15 (30,0)	0,030
Brachiocephalic atherosclerosis, n (%)	30 (50,0)	30 (60,0)	0,339
Lung diseases, n (%)	13 (21,7)	18 (36,0)	0,136

a basis for a comprehensive approach to diagnosing (determining natriuretic peptide levels in blood serum, performing transthoracic echocardiography, and coronary angiography) and treating such patients [3, 4, 17]. At the same time, the high frequency of past MI in both study groups may indicate that the calcium score is a powerful predictor of cardiovascular events, particularly MI, in patients with multifocal atherosclerosis [13, 14, 21].

Data on other comorbid conditions among the patients in the studied groups are presented in Table 5.

When analyzing the comorbidities in the studied groups, the slightly higher, though not statistically

significant, frequency of CKD stage 3-4 in patients of group 2 (Table 5) stands out. As is known, CKD can be an aggravating factor that complicates the disease course, affects the outcomes of endovascular treatment, and increases mortality in patients with PAD [27].

At the same time, previous ACVE cases were more frequently observed in group 2 compared to group 1. Additionally, the high frequency of brachiocephalic artery atherosclerosis in both groups may indicate the systemic nature of the damage and also supports the previously suggested hypothesis regarding the role of the genetic factor in the formation of vascular calcification [24]. Finally, the more frequent detection of lung pathology in patients of group 2 (quantitatively, though not significantly) may be positioned as an additional marker of their more pronounced comorbid burden (Table 5).

DISCUSSION

The results obtained indicate a significant association between the degree of LEAC and the severity of the clinical course of atherosclerotic damage in PAD patients with concomitant SCAD. It was found that an extreme degree of calcification (Agatston index >1000 units) is associated with a more frequent detection of higher stages of chronic lower limb ischemia according to the Rutherford classification (stage 6), as well as a higher prevalence of conditions such as AF/AFl, previous MI (numerically, but non-significantly), HF stage C, and previous ACVE. These data are consistent with literature reports emphasizing the role of vascular calcification as a predictor of more severe clinical course and unfavorable intervention outcomes [13, 14, 21]. Vascular calcification is considered an active, regulated process similar to osteogenesis, involving cells of the vascular wall, mediators of inflammation, oxidative stress, and factors regulating calcium-phosphate metabolism [28]. The presence of pronounced calcification impairs the biomechanical properties of the vessel wall, reduces arterial elasticity, complicates endovascular intervention, reduces the effectiveness of angioplasty, and is associated with a higher risk of restenosis and stent thrombosis [13, 21, 29].

The detected differences in the higher prevalence of traditional atherosclerosis risk factors, such as smoking, excess body weight/obesity, family history, hypertension, and DM, among patients with a high calcium index, suggest their potential cumulative role in the development and progression of vascular calcification. These observations are supported by the works of other authors who indicate the multifactorial nature of vascular calcification, particularly in patients with systemic atherosclerosis and CKD [29-31].

Special attention is drawn to the high level of calcification despite the use of lipid-lowering therapy. According to the literature, statins may contribute to an increase in the density and degree of calcification of atherosclerotic plaques, which is interpreted as a mechanism of their stabilization rather than an indication of treatment inefficacy [25, 26, 32]. This is consistent with our observations regarding the absence of a statistically significant relationship between the frequency of baseline statin therapy and the degree of LEAC.

The high frequency of brachiocephalic artery involvement in the studied patients, as well as frequent cases of a positive family history, suggest a genetic predisposition to systemic calcification. The role of hereditary factors, particularly mutations in genes encoding mineralization inhibitors (e.g., MGP, ENPP1, etc.), is actively being studied and warrants further attention [24, 33].

Thus, the results of our study are consistent with the data from the global literature regarding the clinical significance of vascular calcification in patients with multifocal atherosclerotic lesions, particularly in those with concomitant PAD and SCAD, while also confirming the need for comprehensive diagnostics that encompass not only the anatomical characteristics of the lesions but also comorbidities, myocardial functional status, renal function, and genetic predisposition.

FUTURE RESEARCH PERSPECTIVES

Further studies should focus on assessing the impact of the intensity and duration of lipid-lowering therapy on the dynamics of the calcium index and the stability of atherosclerotic plaques, incorporating biomarkers of inflammation, vascular wall remodeling, and plaque stabilization. It is also important to investigate the role of genetic factors and calcification markers (such as osteoprotegerin, matrix Gla-proteins, etc.) in predicting the risk of vascular calcification and cardiovascular events in this patient category [24, 33, 34].

An important direction is the development of risk stratification models that take into account the degree of vascular calcification along with traditional risk factors, for a personalized approach to planning endovascular treatment and secondary prevention in patients with systemic atherosclerosis.

CONSLUSIONS

The conducted analysis allowed us to establish that PAD (CLTI) patients with concomitant SCAD and an extreme degree of LEAC (Agatston index ≥1000 units) are characterized by worse clinical features compared to patients with pronounced but less significant calcification (Agatston index <1000 units). Specifically, they more frequently experienced arrhythmias (AF/AFl), HF

stage C, previous ACVE, and the most advanced Rutherford stage 6, indicating a more severe course of LE PAD and a greater burden of comorbidities in patients with an exceptionally high degree of LEAC.

In patients with an extreme degree of LEAC, traditional risk factors for atherosclerosis, in particular smoking, overweight/obesity, and a family history of cardiovascular diseases, were more commonly observed. This confirms the key role of these factors in the progression of vascular calcification. Despite the comparable frequency of baseline statin therapy in both studied groups, the frequency of elevated total serum cholesterol remained high in a significant proportion of patients, which may indicate insufficient intensity or low adherence to treatment. At the same time, the increase in the calcium index during lipid-lowering therapy may reflect the stabilization of atherosclerotic plaques rather than their ineffectiveness.

The results obtained highlight the importance of considering the degree of LEAC when planning endovascular interventions in PAD patients with concomitant SCAD, as a high calcium index is associated with worse clinical status, a greater burden of comorbidities, and the presence of multiple risk factors.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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