DIABETES AND CRITICAL LIMB ISCHEMIA: THE DEADLY DUO IN PATIENTS WITH SYMPTOMATIC PERIPHERAL ARTERY DISEASE

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SUMMARY – Inflammation plays an important role in the initiation and progression of peripheral artery disease (PAD). Patients with diabetes have an increased risk of developing PAD. Data regarding the prognostic implication of diabetes and inflammation in PAD patients are scarce. The aim of the study was to investigate the impact of diabetes and inflammation on all-cause mortality in patients with symptomatic PAD and preserved left ventricular ejection fraction (LVEF >50%). The study was conducted at the Sestre milosrdnice University Hospital Center between January 2010 and January 2014 on 319 consecutive patients with symptomatic PAD and preserved LVEF (66.5% men, mean age 70±10 years, ankle brachial index 0.58±0.14). Thirty-eight (12%) patients died during median follow up period of 24 months (interquartile range, 16-34 months). On univariate analysis, C-reactive protein was significantly associated with all-cause mortality (HR 2.21, 95% CI 1.09-4.48). After multivariate regression analysis, age (HR 1.07, 95% CI 1.02-1.11), diabetes (HR 2.24, 95% CI 1.04-4.82), and critical limb ischemia (HR 2.22, 95% CI 1.03-4.80) remained the only independent predictors for all-cause mortality. Diabetes and critical limb ischemia are independently associated with an increased risk of mortality in symptomatic PAD patients with preserved LVEF.

Key words: *Diabetes mellitus; Extremities – blood supply; Ischemia; Inflammation; C-reactive protein; Mortality; Peripheral arterial disease*

Introduction

Peripheral artery disease (PAD) is a multifactorial syndrome that is associated with a very high risk of ischemic events, namely myocardial infarction, stroke, and death[1]. The probability of having polyvascular disease is greater in patients with PAD, indicating an extensive and severe degree of systemic atherosclerosis. These patients, despite more intense medical therapy, have poorer control of modifiable risk factors and higher mortality rate[2,3].

Patients with diabetes mellitus have a 2- to 4-fold higher risk of developing PAD[4,5]. Progression of atherosclerosis, as well as poor outcomes, are more often present in diabetic PAD patients, probably because of the abnormal metabolic state and increase in vascular inflammation[6]. PAD has been identified as a risk factor for glycemic dysregulation in type 2 diabetes mellitus[7]. Prospective clinical trials have shown that the occurrence of major adverse cardiovascular events (MACE) and all-cause mortality is higher in patients with both diabetes and PAD than in nondiabetic PAD patients[8-10].

C-reactive protein (CRP) has been established as a risk factor for the development of type 2 diabetes and cardiovascular disease, including PAD[11,12]. Elevated CRP levels are present in patients with impaired glucose tolerance and are associated with the stage of be-

ta-cell dysfunction and insulin resistance[13]. Results from the West of Scotland Coronary Prevention Study have shown that CRP concentration is a significant predictor of diabetes in middle-aged men, independent of the risk factors such as body mass index, fasting triglycerides and glucose levels[14]. The predictive role of CRP has been well studied in acute coronary and acute aortic syndromes[15,16]. We have recently shown that CRP independently predicted MACE in patients with symptomatic PAD and preserved left ventricular systolic function[17]. Patients with PAD have a higher prevalence of diabetes and higher levels of inflammatory biomarkers compared to patients without PAD[18].

Therefore, the aim of the study was to investigate the role of diabetes and inflammation for all-cause mortality in patients with symptomatic PAD and normal left ventricular ejection fraction (LVEF).

Patients and Methods

The study population consisted of 319 consecutive patients with symptomatic PAD and preserved LVEF admitted to the Sestre milosrdnice University Hospital Center between January 2010 and January 2014. Fifty-five patients were excluded due to LVEF <50% (n=39), malignancy (n=12) and concomitant autoimmune disorders (n=4). During hospital stay, demographic data and clinical characteristics of the patients were recorded and included general information (age, sex, weight and height), data on cardiovascular risk factors, biochemical and hematological laboratory data, comorbidities, and medications. Renal function was assessed by estimating the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula[19]. LVEF was assessed using transthoracic echocardiography (Simpson's method), and only patients with preserved LV systolic function (LVEF >50%) were included in the study. Baseline anemia was defined according to the World Health Organization criteria (hemoglobin level <13 g/dL for men and <12 g/dL for women)[20].

The diagnosis of PAD was established by clinical examination, ankle brachial index (ABI) measurement, duplex sonography and/or computed tomography or magnetic resonance angiography, and confirmed with peripheral angiography using the criteria of the European Society of Cardiology and American College of Cardiology Foundation[21,22]. According to the Fontaine

classification, among symptomatic PAD patients with preserved LVEF there were 58% of patients in stage IIB, 24% of patients in stage III and 18% of patients in stage IV. Critical limb ischemia (CLI) was defined as the presence of rest pain, ulcer or gangrene (Fontaine stages III and IV)[21].

Diabetes was defined according to the criteria of the American Diabetes Association and was considered to be present in all patients taking antidiabetic medication[23].

Hypertension was diagnosed in accordance with the European Society of Cardiology/European Society of Hypertension 2013 guidelines[24].

Cardiovascular disease, in addition to confirmed PAD, was defined as history of angina, myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), history of stroke, transient ischemic attack, or carotid revascularization.

High sensitivity CRP was determined on admission by immunoturbidimetric method (Olympus, Dublin, Ireland).

Study endpoint was the all-cause mortality. Mortality was documented by death certificates or by reviewing hospital records. The median follow up was 24 months (interquartile range 16-34 months). Outcome was assessed by independent observers blinded to patient laboratory and clinical data. The investigation was performed in accordance with the Declaration of Helsinki and was approved by the University Hospital Center Ethics Committee.

Continuous normally distributed variables were expressed as mean (± standard deviation) and non-normally distributed variables as medians (interquartile range). Differences between the groups were analyzed with t-test and Mann-Whitney test for continuous variables and with χ^2-test for categorical variables. Normality of distribution was tested with Kolmogorov-Smirnov test. The ability of CRP to predict mortality was tested by the receiver-operating characteristic (ROC) analysis and optimal cut-off point of CRP was dichotomized to > or <4.5 mg/L. Kaplan-Meier analyses with log-rank test were performed and comparisons were based on the presence of diabetes and CLI. Cox proportional-hazards regression analysis was performed to determine the independent predictors of all-cause mortality and results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Covariate selection included known correlates of poor cardiovascu-

lar outcome and those that were found to be significant on univariate analysis, i.e. age, gender, CLI, anemia, renal function, CRP and diabetes. The value of p<0.05 was considered statistically significant. Statistical analysis was performed using the MedCalc® Version 11.3.1.0 (MedCalc, Ostend, Belgium).

Results

Baseline characteristics of the study population are shown in Table 1. Of 319 symptomatic PAD patients with preserved LVEF, 172 (54%) had type 2 diabetes.

Table 1. Baseline characteristics of 319 patients with symptomatic peripheral artery disease and preserved left ventricular systolic function

Characteristic	
Age (years)*	71 (63-78)
Male sex, n (%)	212 (66.5)
Ankle brachial index †	0.58±0.14
Systolic blood pressure (mm Hg)*	140 (130-154)
Diastolic blood pressure (mm Hg)*	80 (80-90)
Heart rate (beat/min)*	75 (67-80)
Body mass index (kg/m²)*	27 (25-30)
Hypertension, n (%)	277 (87)
Diabetes mellitus, n (%)	172 (54)
Smoking, n (%)	173 (54)
Dyslipidemia, n (%)	242 (76)
Polyvascular disease, n (%)	132 (41)
Critical limb ischemia, n (%)	134 (42)
Anemia, n (%)	67 (21)
High sensitivity C-reactive protein (mg/L)*	4.5 (2.2-10.0)
Estimated glomerular filtration rate (mL/min)†	63.4±18.3
Left ventricular ejection fraction (%) †	57.0±5.5
Statin therapy, n (%)	194 (61)
Antiplatelet therapy, n (%)	299 (94)

*Median (interquartile range); †mean ± standard deviation

Fig. 1. Cumulative survival according to the presence of: (A) critical limb ischemia (CLI); (B) diabetes mellitus (DM); and (C) combined effect of diabetes and CLI in 319 patients with symptomatic peripheral artery disease and preserved left ventricular systolic function. ➤
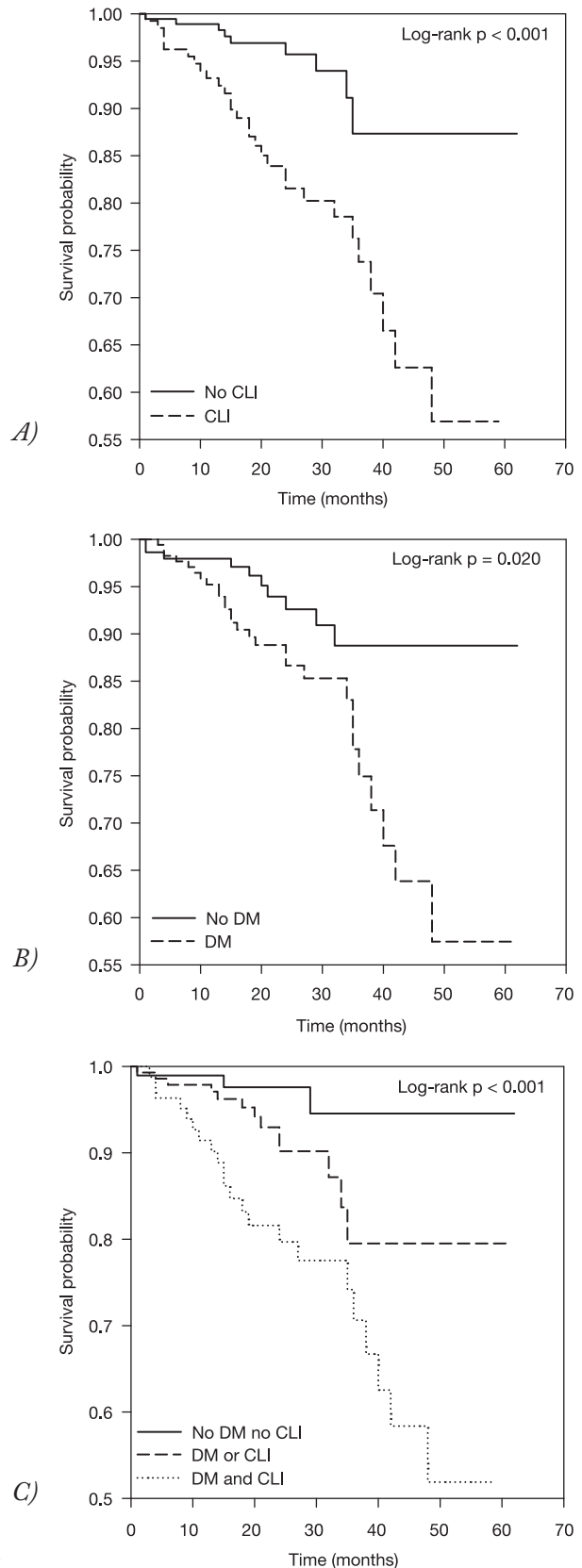
Table 2. Univariate and multivariate Cox proportional–hazards regression analysis for all-cause mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.081 (1.038-1.125)	<0.001	1.066 (1.021-1.113)	0.004
Female sex	1.404 (0.738-2.671)	0.304	-	
Hypertension	2.685 (0.650-11.081)	0.174	-	
Diabetes mellitus	2.295 (1.116-4.718)	0.025	2.241 (1.041-4.824)	0.040
Critical limb ischemia	3.592 (1.695-7.611)	<0.001	2.220 (1.026-4.803)	0.044
Polyvascular disease	1.667 (0.884-3.142)	0.116	-	
hsCRP (>4.5 mg/L)	2.206 (1.088-4.475)	0.029	-	
eGFR (<60 mL/min)	1.806 (0.951-3.430)	0.073	-	
Anemia	3.724 (1.976-7.016)	<0.001	1.897 (0.952-3.780)	0.070

HR = hazard ratio; CI = confidence interval; hsCRP = high sensitivity C-reactive protein; eGFR = estimated glomerular filtration rate

Among diabetics, 149 (87%) were on oral hypoglycemic therapy or insulin, and 23 (13%) were on diet. Thirty-eight (12%) patients died during median follow up period of 24 months (interquartile range 16 to 34 months). On univariate analysis, age (p<0.001), CLI (p<0.001), diabetes (p=0.025), anemia (p<0.001), renal impairment (p=0.073) and CRP (p=0.029) were significantly associated with all-cause mortality (Table 2). CLI and diabetes predicted freedom from all-cause mortality, and patients having both CLI and diabetes were 6.6 times (95% CI 2.89-14.99) more likely to die than those with claudication but without diabetes (Fig. 1A, 1B, and 1C). After multivariable analysis, age, diabetes and CLI remained the only independent predictors of mortality (Table 2).

Discussion

The present study investigated the prognostic role of diabetes and inflammation for all-cause mortality in patients with symptomatic PAD and preserved LVEF. Age, diabetes, and CLI were found to be the only independent predictors of all-cause mortality in the study population.

Previous epidemiological studies showed a higher incidence of PAD in diabetic patients. Furthermore, patients with both PAD and diabetes have more often CLI, a higher prevalence of amputation and greater risk of mortality[25]. Our study showed the patients with symptomatic PAD and diabetes to be at more than twofold greater risk of death compared with non-diabetic PAD patients. This is in line with Leibson *et al.*[26],

who showed that the adjusted risk of all-cause mortality in patients with both PAD and diabetes was 2.2 times higher than for patients with PAD alone. Golledge *et al.*[27] investigated patients with occlusive or aneurysmal disease of peripheral arteries and showed 1.6- to 1.7-fold and 2.0- to 2.9-fold higher mortality risk in patients with non-medicated diabetes and patients with diabetes receiving insulin, respectively, as compared with non-diabetics.

Critical limb ischemia is the most severe form of PAD with poor overall survival. The annual mortality rate in patients with CLI is approximately 25% and between 50% and 70% at 5 years[28]. Lower ABI values and diabetes are the most important risk factors for the development of CLI[29]. Vogt *et al.*[30] have reported that patients with ABI <0.5 have a higher relative risk of all-cause mortality compared to patients with higher ABI values. In our study, patients with CLI had two times increased risk of all-cause mortality compared to patients without CLI.

C-reactive protein is a regularly used biomarker in daily clinical practice, and of note, patients with diabetes have increased levels of inflammatory biomarkers, such as CRP[8]. Data on the prognostic role of CRP for all-cause mortality in PAD patients are controversial. It has been shown that in patients with symptomatic PAD, increased CRP values are independently associated with all-cause mortality within 2 years, but at longer follow up period, the biomarker lost its prognostic significance[31]. CRP is associated with the development and severity of PAD, as well as of impaired glucose regulation[12]. Moreover, in patients with PAD, elevated

CRP levels correlate with the risk of cardiovascular mortality[32]. Recently, Mueller *et al.*[33] have reported that CRP and CLI were independent predictors of death among patients with symptomatic PAD. Our study clearly revealed that CRP was significantly associated with all-cause mortality on the univariate but not after multivariate analysis.

Although anemia was found to be an independent predictor of composite outcome (death and limb amputation) in patients hospitalized for PAD, it was not included in the earlier outcome studies[34].

We have to bear in mind that patients with chronic kidney disease have an increased risk of developing PAD, and renal impairment was found to predict all-cause mortality in patients with symptomatic PAD[35,36]. Left ventricular systolic dysfunction is quite prevalent in PAD patients and is associated with all-cause mortality[37].

So, we believe this is the first report that showed the independent prognostic role of diabetes and CLI for mortality in symptomatic PAD patients with preserved left ventricular systolic function, regardless of renal function, anemia and inflammation.

Patients with PAD are at an increased risk of MACE and all-cause mortality compared to general population. Additionally, lower ABI values correlated with reduced survival and increased rate of concomitant coronary and cerebrovascular disease[38]. Despite a very high incidence of MACE and mortality rate, PAD is still underdiagnosed and undertreated. Therefore, screening for PAD, early management, together with modification of cardiovascular risk factors and timely assessment of prognosticators for unfavorable outcome are of utmost importance.

In conclusion, our data confirm that diabetes and CLI are independent predictors for all-cause mortality in patients with symptomatic PAD and preserved LVEF. Additionally, the coexistence of CLI and diabetes significantly increased the risk of worse clinical outcome.

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Sažetak

ŠEĆERNA BOLEST I KRITIČNA ISHEMIJA EKSTREMITETA: SMRTONOSNI DVOJAC U BOLESNIKA SA SIMPTOMATSKOM PERIFERNOM ARTERIJSKOM BOLEŠĆU

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Upala igra važnu ulogu u nastanku i napredovanju periferne arterijske bolesti (PAB). Bolesnici sa šećernom bolešću imaju povišen rizik za razvoj PAB. Podatci o utjecaju šećerne bolesti i upale na prognozu PAB su oskudni. Cilj studije bio je istražiti utjecaj šećerne bolesti i upale na ukupnu smrtnost u bolesnika sa simptomatskom PAB i očuvanom sistoličkom funkcijom lijeve klijetke (istisna frakcija lijeve klijetke >50%). Studija je provedena u razdoblju od siječnja 2010. do siječnja 2014. godine na 319 bolesnika sa simptomatskom PAB i očuvanom sistoličkom funkcijom lijeve klijetke (66,5% muškaraca, prosječna dob 70±10 godina, pedobrahijalni indeks 0,58±0,14). Tijekom razdoblja praćenja od 24 mjeseca (interkvartilni raspon 16-34 mjeseca) 38 (12%) bolesnika je umrlo. C-reaktivni protein bio je statistički značajno povezan s ukupnom smrtnošću u univarijatnoj analizi (HR 2,21; 95% CI 1,09-4,48). Nakon multivarijatne regresijske analize, dob (HR 1,07; 95% CI 1,02-1,11), šećerna bolest (HR 2,24; 95% CI 1,04-4,82) i kritična ishemija ekstremiteta (HR 2,22; 95% CI 1,03-4,80) bile su jedini značajni nezavisni predskazatelji ukupne smrtnosti. Šećerna bolest i kritična ishemija ekstremiteta nezavisno su povezani s povišenim rizikom smrtnosti u bolesnika sa simptomatskom PAB i očuvanom sistoličkom funkcijom lijeve klijetke.

Ključne riječi: *Dijabetes melitus; Ekstremiteti – prokrvljenost; Ishemija; Upala; C-reaktivni protein; Smrtnost; Periferna arterijska bolest*