Relationship of the angiographic extent of peripheral arterial disease with coronary artery involvement

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Abstract

Objective: To determine the co-incidence of coronary artery disease (CAD) in patients investigated for peripheral arterial disease (PAD), and to establish the relationship between the risk factors in the two groups of patients.

Methods: The prospective study, done from January 2005 and April 2009, at the Cardiology Clinic of Rize Education and Research Hospital, Rize and John F. Kennedy Hospital, Istanbul, Turkey, had a cohort of 307 patients who had been diagnosed with peripheral artery disease either clinically or by ultrasonography for the arteries of the lower extremities and had undergone coronary angiography and peripheral angiography in the same or different sessions. The patients were evaluated in terms of age, gender and atherosclerotic risk factors. Relationship of the extent of peripheral arterial disease with coronary artery involvement was investigated.

Results: Of the 307 patients, 251 (81.8%) were male, and the mean age was 62.1±9.5 years. In the study population, 178 (58.0%) patients were diagnosed as hypertensive, 84 (27.4%) patients were diabetic, 18 (5.9%) patients had a family history of coronary artery disease, 111 (36.2%) were smokers, 149 (48.5%) were hypercholesterolemic, and 20 (6.5%) had cerebrovascular/carotid disease. In 92.3% of patients with peripheral arterial disease, various levels of coronary stenosis (P=0.007) was noticed. Hypertension was a risk factor for both coronary and peripheral artery diseases (p=0.012 and 0.027, respectively). Univariate logistic regression analysis demonstrated that the presence of peripheral artery disease was related to the coronary variety (Odds ratio [OR]: 6, 95% CI: 1.4-25.5, P=0.016) and severe cases (diffused atherosclerotic stenosis and complete occlusion in all segments) significantly indicated the presence of some coronary pathology (OR: 8, 95%CI: 1.7-37.4, P=0.008). This relationship maintained its significance after adjustment for age, gender, hypercholesterolaemia, smoking, hypertension, diabetes, family history, and the presence of cerebrovascular/carotid disease (p=0.010).

Conclusions: Peripheral coronary artery diseases had similar risk factors. The extent of peripheral arterial disease observed during peripheral lower extremity angiography was significantly associated with the presence and severity of coronary artery disease. Particular attention should be focused on the possibility of coronary artery disease in patients with established and extensive peripheral arterial disease. Non-invasive, as well as invasive tests, should be performed to decrease morbidity and mortality risk of such patients.

Keywords: Peripheral arterial disease, Coronary artery disease, Peripheral angiography, Coronary angiography, Arteries of the lower extremity, Risk factors. (JPMA 62: 644; 2012)

Introduction

Atherosclerosis is a multifactorial disease, with hypertension (HT), hyperlipidaemia (HPL), diabetes mellitus (DM), smoking and other vascular risk factors. Atherosclerosis is a chronic disease which begins in childhood. It progresses asymptomatically in adulthood and finally manifests itself clinically at a certain point. The same pathological process in atherosclerosis can have a similar impact on all vessels in the body, leading to coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD).[1]

PAD is observed in 12-14% of the general population. It often co-exists with CAD and CVD, particularly in older people. Most patients with PAD ultimately die as a result of a cardiac or cerebrovascular event. Modifiable risk factors for PAD have been reported to be smoking, HPL, HT, DM, and metabolic syndrome (MS). PAD is more common in males and older people.[2] The risk factors for CAD and PAD are similar. The risk factors for CAD have been reported to be a family history of CAD, HT, decreased levels of HDL-cholesterol, elevated levels of LDL-cholesterol, DM and smoking.[3]

Despite its comparatively young population, Turkey has a high prevalence of atherosclerotic disease and associated mortality. A number of studies investigating the risk factors for CAD have reported that though total cholesterol levels were lower than those observed in Western Europe, Turkey has a huge population of smokers, that carry risk factors like DM, HT and a high incidence of metabolic syndrome. Besides, obesity, particularly in females, has also been reported.[4]

The current study was conducted to determine the coincidence of CAD in patients investigated for PAD, and to establish the relationship between the risk factors in the two groups of patients.

Patients and Methods

The patients who had been diagnosed with PAD by either clinical examination or Doppler ultrasonography for the arteries of the lower extremities and underwent coronary angiography and peripheral angiography in the same or in another session between January 2005 and April 2009 were prospectively enrolled in current study. The study was conducted in the Cardiology Clinic of the Rize Education and Research Hospital, Rize and John F. Kennedy Hospital, Istanbul, Turkey.

The patients were evaluated in terms of age, gender and atherosclerotic risk factors. Medical histories, records of physical examination and the cardiovascular risk factors of all patients were also assessed. Of the major cardiovascular risk factors, the presence of family history of premature CAD in first-degree relatives, presence of CAD or diagnosed myocardial infarction in males <55years and females <65 years), HT (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥ 90 mmHg in at least two distinct readings, or previously receiving anti-hypertensive medications), DM (fasting blood glucose ≥126 mg/dl, or previously receiving anti-diabetic medications), HPL (fasting blood total cholesterol ≥200 mg/dl, or fasting blood low-density lipoprotein levels ≥ 130 mg/dl or previously receiving anti-hyperlipidemic medications) and smoking habits were recorded. Total cholesterol and LDL levels of the morning blood samples, obtained from the patients after a 12-hour fasting a day before coronary angiography procedure, was measured with standard enzymatic colorimetric methods. LDL levels were calculated using the Friedewald formula.

Informed consent was obtained from all patients. The study was performed in accordance with the principles stated in the Helsinki Declaration and was approved by the Ethics Committee. Patients were excluded if they had renal failure, decompensated heart failure, acute coronary syndrome, heart valve disease, cardiomyopathy or Buerger disease.

Peripheral angiography of the lower extremity was performed, assisted by a radiologist, either in the same session with coronary angiography or in a separate session. Iodine-containing radiopaque media of 270-300 mOsmol was administered via the distal abdominal aorta using a pigtail catheter or via the right or left common iliac arteries selectively by using the right coronary artery catheter to examine the right-left common iliac artery, iliac externa, iliac interna, main femoral, superficial femoral, deep femoral, popliteal, tibioperoneal truncus, anterior tibial, and posterior tibial arteries, and up to the distal peroneal artery. Coronary angiography was performed by standard right-left diagnostic and pigtail ventriculography catheters via the femoral artery with a 6-French sheath. A stenosis of ≥ 50% was considered to be severe stenosis, while below that level it was regarded as non-critical (plaques not leading to significant stenosis) for coronary and peripheral arteries. Patients with cerebrovascular (CV) findings who were also observed with severe or non-critical atherosclerotic lesions on Doppler ultrasonography or carotid angiography were grouped as patients with CV/carotid artery disease.

Descriptive statistics were expressed as the mean and standard deviation for numerical variables, and frequency and percentage for categorical variables. The difference between the groups for categorical variables was evaluated by the chi-square test (χ2-test) and Student's t test for numerical variables. Relationship of the extent of PAD with coronary artery involvement was investigated by univariate and multivariate analyses. Logistic regression analyses were used to identify the relation of peripheral pathology with coronary pathology. A P value of <0.05 was regarded as statistically significant. The Statistical Program for Social Sciences (SPSS) version 15, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

In our cohort of 307 patients, 251 (81.8%) patients were male and the mean age was 62.1±9.5 years. Of the total, 178 (58.0%) were diagnosed as hypertensive, 84 (27.4%) patients were diabetic, 18 (5.9%) had a family history of CAD, 111 (36.2%) were smokers, 149 (48.5%) were hypercholesterolemic, and 20 (6.5%) patients had cerebrovascular/carotid disease.

Peripheral angiography results demonstrated that 2.9% patients had normal arteries, while 15.3% had non-critical plaques; 19.5% had proximal critical single stenosis, 12.4% had distal stenoses, and 49.8% had complete occlusion or diffused atherosclerotic stenoses in all segments. Coronary angiography revealed that 8.5% of the patients had normal coronary arteries, while 20.2% had non-critical plaques, 21.5% had single-vessel disease, 16.9% had double-vessel disease, 29.6% had multi-vessel disease, and 3.3% had left main coronary disease (Table-1).

Table-1: Patient characteristics and evaluation of coronary and peripheral arteries by angiography.

Patient characteristics	
Mean Age (years)	62.1±9.5
Gender, n (%)	
Female	56 (18.2)
Male	251 (81.8)
Hypertension, n (%)	178 (58.0)
Diabetes mellitus, n (%)	84 (27.4)
Family history of CAD, n (%)	18 (5.9)
Smoking, n (%)	111 (36.2)
Hypercholesterolemia, n (%)	149 (48.5)
CV/Carotid disease, n (%)	20 (6.5)
Coronary and peripheral angiography	
Coronary angiography, n (%)	
C0: Normal coronary artery	26 (8.5)
C1: Non-critical plaque	62 (20.2)
C2: Single-vessel disease	66 (21.5)
C3: Double-vessel disease	52 (16.9)
C4: Multiple-vessel disease	91 (29.6)
C5: Left main coronary disease	10 (3.3)
Peripheral Angiography, n (%)	
P0: Normal arteries	9 (2.9)
P1: Non-critical plaques	47 (15.3)
P2: Proximal critical single stenosis	60 (19.5)
P3: Distal stenoses (popliteal artery distal)	38 (12.4)
P4: Multiple severe stenoses in all segments (graft restenosis, diffuse stenosis, complete occlusion)	153 (49.8)

CAD: Coronary artery disease, CV: Cerebrovascular.

The patient characteristics and risk factors with respect to CAD and PAD were noted (Table-2). Hypertension was a risk factor for both CAD and PAD (p=0.012 and p=0.027, respectively). Differences with respect to gender, smoking, cholesterol, DM, familial history, and the presence of CV/carotid disease were not found to be significant.

Patients were also assessed for the severity of disease as established on peripheral and coronary angiography (Table-3). In 92.3% of the patients with PAD, there was an established presence of CAD at various levels (p=0.007). Over 50% of the patients with multiple-vessel disease or left main coronary disease on coronary angiography were in the group having diffused atherosclerotic stenosis and complete occlusion in all segments according to the peripheral angiography.

Univariate logistic regression analysis demonstrated that the presence of PAD was related to CAD (Odds ratio [OR]: 6, 95%CI: 1.4-25.5, p=0.016) and the severe PAD (diffused atherosclerotic stenosis and complete occlusion in all segments) significantly indicates the presence of some coronary pathology (OR: 8, 95%CI: 1.7-37.4, p=0.008) (Table-4). This relationship maintained its significance after adjustment for age, gender, hypercholesterolaemia, smoking, hypertension, DM, family history of CAD, and the presence of CV/carotid disease (p=0.010) (Table-5).

Table-2: The relationship of the presence of coronary and peripheral pathology with risk factors.

	Coronary pathology			Peripheral pathology		
	(-) n (%)	(+) n (%)	P value	(-) n (%)	(+) n (%)	P value
Mean Age (years)	58.4±10.2	62.4±9.4	0.041	57.9±7.1	62.2±9.6	0.182
Gender (Male)	18 (69.2)	233 (82.9)	0.084	6 (66.6)	245 (82.2)	0.234
Smoking	7 (26.9)	104 (37.0)	0.306	6 (33.3)	152 (36.2)	0.858
Hypertension	9 (34.6)	169 (60.1)	0.012	2 (22.2)	190 (59.1)	0.027
Hypercholesterolaemia	12 (46.2)	137 (48.8)	0.800	3 (33.3)	146 (48.9)	0.354
Diabetes mellitus	4 (15.4)	80 (28.5)	0.152	4 (44.4)	80 (26.9)	0.243
Family history of CAD	0 (0.0)	18 (6.4)	0.183	1 (11.1)	17 (5.7)	0.496
CV/carotid disease	0 (0.0)	20 (7.1)	0.159	0 (0.0)	20 (6.7)	0.422

Coronary pathology (-): Normal coronary artery (C0). Coronary pathology (+): Other coronary angiographic findings (C1, C2, C3, C4 and C5). Peripheral pathology (-): Normal peripheral arteries (P0). Peripheral pathology (+): Other Peripheral angiographic findings (P1, P2, P3 and P4). CAD, Coronary artery disease; CV, Cerebrovascular.

Table-3: Reciprocal relationship of peripheral and coronary angiographic findings.

Coronary angiography, n (%)	Peripheral Angiography, n (%)				
	P0	P1	P2	P3	P4
C0	3 (11.5)	5 (19.2)	6 (23.1)	3 (11.5)	9 (34.6)
C1	1 (1.6)	9 (14.5)	19 (30.6)	7 (11.3)	26 (41.9)
C2	2 (3.0)	14 (21.2)	13 (19.7)	8 (12.1)	29 (43.9)
C3	1 (1.9)	4 (7.7)	10 (19.2)	9 (17.3)	28 (53.8)
C4	2 (2.2)	14 (15.4)	9 (9.9)	11 (12.1)	55 (60.4)
C5	0 (0.0)	1 (10.0)	3 (30.0)	0 (0.0)	6 (60.0)

C0: Normal coronary artery, C1: Non-critical plaque, C2: Single-vessel disease, C3: Double-vessel disease, C4: Multiple-vessel disease, C5: Left main coronary disease; P0: Normal peripheral arteries, P1: Non-critical plaques, P2: Proximal critical single stenosis, P3: Distal stenoses, P4: Stenoses or complete occlusion in all segments.

Table-4: Univariate relationship of the angiographic extent of PAD with the presence of CAD.

Variables	OR	95%CI	P value
Mean Age (years)	1.047	1.001-1.094	0.044
Gender (Male)	2.157	0.887-5.248	0.09
Smoking,+	1.595	0.649-3.922	0.309
Hypertension,+	2.85	1.227-6.619	0.015
Hypercholesterolemia, +	1.11	0.496-2.484	0.8
Diabetes mellitus, +	2.189	0.731-6.553	0.161
PAD, +	5.978	1.403-25.479	0.016
P0	Reference	-	0.12
P1	4.2	0.793-22.255	0.092
P2	4.5	0.888-22.793	0.069
P3	5.833	0.946-35.988	0.057
P4	8	1.714-37.349	0.008

CAD: Coronary artery disease; PAD, Peripheral arterial disease.

Table-5: Multivariate relationship between the extent of PAD and CAD.

Variables	Beta	Standard Error	P value*
Hypertension,+	0.597	0.158	<0.001
Extent of PAD (0-4)	0.161	0.062	0.010

*Linear regression analysis with stepwise method was used for multivariate analysis of independent variables including age, gender, HT, DM, smoking, hypercholesterolemia and family history of CAD.
After exclusion of irrelevant variables from model, linear analyses with enter method were performed with remaining significant variables.
Dependen variable: extent of coronary artery disease
CAD, coronary artery disease; PAD, Peripheral arterial disease.

Discussion

Our study results demonstrated that PAD and CAD had similar risk factors. The extent of PAD observed during peripheral lower extremity angiography was significantly associated with the presence and severity of CAD.

Peripheral arterial disease had a prevalence of >10% in males >60 years of age. As the disease progresses, the true prevalence of PAD may be even higher than the registered prevalence, but for the fact that it can remain asymptomatic or with atypical symptoms.

The ankle brachial blood pressure index (ABI), defined as the systolic blood pressure measured at the ankle divided by the systolic blood pressure measured in the arm during supine rest, is the most widely used quantitative measure to determine the presence and severity of PAD. An abnormal ABI value of ≤ 0.90 is generally considered to be the best reference standard of identifying PAD, whereas normal values range between 0.9 to 1.3.[5] A study analysing 6172 participants who were randomly selected from the general population and in whom procedures had been carried out earlier, reported the prevalence of subjects with an ABI score of <0.9 to be 4.5%. The same study established age, current smoking status, CAD, uncontrolled HT, as well as intermittent claudication in males and DM in women to be associated with low ABI.[6]

Peripheral arterial disease and CAD are different clinical manifestations of atherosclerosis and have common risk factors. PAD risk factors are similar to those for CAD and CVD. However, PAD is strongly correlated with DM and smoking. Other risk factors have been reported to be age (≥ 45 years in males, ≥ 55 years in females), HT and HPL.[7] Other risk factors that have to be carefully observed were reported to be Lp(a), elevated lipoprotein, homocysteine, LDL-cholesterol, and acute phase protein (CRP and amyloid A protein) levels, as well as coagulation and fibrinolytic factors (tissue plasminogen activator, plasminogen activator inhibitor 1 and fibrinogen).[8]

A study conducted in 952 patients at high risk for CVD established that 86.2% of the patients had symptomatic atherosclerosis, and reported that at least 2 risk factors were present in the asymptomatic patients. Of the patients with CAD, 42% had PAD. No significant differences were observed between CAD and PAD patients with respect to risk profiles.[9] A previous study in which 33629 patients with PAD were evaluated, established that 29% (9474) of the patients had DM.[10] Similarly, in our study, 27.4% of the patients with PAD had DM.

A recent research conducted in 3047 hypertensive patients has shown that older age, female gender, elevated triglycerides levels, low HDL level, DM, and a history of smoking is associated with a low ABI. Survival rates were noted to be significantly lower in the low ABI group compared with those of the normal ABI group. Low ABI was established to be an independent risk factor for all-cause and CVD mortality.[11]

Of the patients in our study, 58% had hypertension, which was established as a risk factor for both CAD and PAD. Therefore, patients with hypertension should carefully be monitored for PAD, and be scanned by ABI measurement to ensure an early diagnosis.

A previous study was conducted in patients undergoing intracoronary stent implantation (n=7696).[12] Two subgroups were formed of patients with or without PAD (n=1397, n=6299, respectively). The subgroup with PAD had older age and higher rate of HT, DM, HPL and a history of smoking compared with patients without PAD. The presence of PAD was also shown to be a major risk factor in terms of poor procedural success and high rate of in-hospital complications. The group was also observed with a higher rate of adverse cardiovascular events on follow-up. Of the patients with concomitant PAD, 79% had HT, 33% DM, 76% HPL, and 70% had a history of smoking. In a manner consistent with the findings of this study, of all the patients in our study, 58% had HT, 27.4% DM, 48.5% HPL and 36.2%

had a history of smoking.

In another study, the prognosis of patients with PAD concomitant with or without CAD was investigated.[13] It consisted of 483 patients with PAD without CAD, and 479 patients with both PAD and CAD. The mean was 67.3±8.9 years for both groups of which 72.3% was male. Of the patients, 80.18% were either current smokers or had a history of smoking, and 49.6% had abdominal obesity. The PAD+CAD group was compared with PAD-only group over a 2-year follow-up period and no significant differences were observed in terms of total mortality (4.6% vs. 5.5%), cardiovascular mortality (3.7% vs. 3.9%), or non-fatal myocardial infarction (1.9% vs. 2.7%). However, difference between the two groups for non-fatal stroke (4.4% vs. 2.0%, $p<0.05$) was significant.[13]

A number of studies have been conducted to investigate the comorbidity of PAD and CAD. These studies suggest that all patients with PAD should be regarded as having CAD until proven otherwise.[5] The results of our study also support the assertion, as 92.3% of the patients with PAD had an established presence of CAD at various levels.

Different studies have reported CAD as a comorbid condition in 10-30% of all PAD patients.[14-16] In a previous study conducted in patients hospitalised by CAD, PAD prevalence was reported to be 40%. It was established that one-half of those patients had not been diagnosed with PAD previously. It was recommended that patients presenting with CAD should be examined for PAD as well.[17]

When proper care is not provided, PAD patients may experience ischaemia leading to amputation, which has a significant effect on morbidity and mortality. A study conducted in patients with CAD without known PAD who underwent coronary angiography and/or an intervention established an incidence of 15% for PAD.[18] The study compared the patients with and without PAD in terms of risk factors. The patients with PAD were older and it was more common in females. Hypertension, DM and CV event prevalence were also established to be higher. Of the 745 patients whose CAD diagnosis was confirmed by coronary angiography, the ones with PAD had higher prevalence for left main and multi-vessel CAD, as well as a history of coronary artery bypass surgery.

In our study, the extent and severity of PAD was significantly correlated with the presence and severity of CAD. It was also demonstrated that diffused atherosclerotic stenosis and complete occlusion in all segments in the peripheral arteries were significant risk factors for coronary pathology. Therefore, close monitoring for CAD in patients with severe PAD is of critical importance to decrease vascular morbidity and mortality. A better understanding of the risk factors will make it possible to take precautions against the modifiable risk factors, and will facilitate early diagnosis and implementation of effective therapy.

Conclusion

PAD and CAD have similar risk factors. The extent and severity of PAD was significantly associated with the presence and severity of CAD. Screening for PAD and CAD in patients with relevant risk factors must ensure early diagnosis for an improved prognosis. Particular attention should be focused on the possibility of CAD in patients with established and extensive PAD. CAD should be investigated in patients with PAD even when cardiac symptoms, such as chest pain, are not present, and non-invasive tests, as well as invasive tests, when deemed necessary, should be performed to decrease morbidity and mortality risk.

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