Original Article

Impact of Diabetes Mellitus on Peripheral Vascular Disease Concomitant with Coronary Artery Disease

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Abstract

Background: *The aim of this study was to evaluate the impact of diabetes mellitus (DM) on peripheral vascular disease (PVD) in patients with coronary artery disease (CAD).*

Methods: *A total of 13702 consecutive patients who underwent coronary artery bypass grafting (CABG) at Tehran Heart Center between January 2002 and March 2007 were included in this study. The demographic data, PVD, and outcome of these patients were reviewed. CABG patients before surgery were detected for PVD (stenosis ≥70% in the abdominal aorta; renal, carotid, and iliac arteries; or any other peripheral vascular system) with physical examination and past medical history. The suspected cases of PVD were, thereafter, confirmed via Doppler sonography or invasive angiography.*

Results: *This study recruited 4344 diabetic patients (mean age 59.30±8.7 years) and 9358 non-diabetic patients (mean age 58.42±9.9 years). The diabetics were significantly older and had a higher incidence of PVD (2.7% vs. 1.8%), female gender, hypertension, renal failure, smoking, and dyslipidemia than the non-diabetics (P<0.05). There was no significant difference between the two groups with regard to family history and left main disease. Also, the mean ejection fraction (EF) was 48.85%±10.4 and 49.35%±10. In the patients with and without DM, respectively; and the difference was significant (P=0.008). The in-hospital mortality rate (mortality over a 30-day post-operative period) was 1.8% in the diabetics and 0.7% in the non-diabetics (P<0.001). In the multivariate analysis, PVD, left main disease, age, female gender, and EF were significant in the development of mortality amongst the diabetic patients with a respective odds ratio of 4.17, 5.54, 1.03, 2.86, and 0.95 (P≤0.050). In the multivariate logistic regression analysis, PVD was significantly higher in the diabetics than in those without DM (OR=1.283, 95% CI: 1.001- 1.644; P=0.049). In the diabetic patients, carotid (1.13% vs. 0.83%), subclavian (0.05% vs. 0.02%), femoral (0.18% vs. 0.09%), renal (0.62% vs. 0.25%), and tibialis (0.16% vs. 0.06%) arteries had a higher incidence of stenosis than those in the non-diabetics.*

Conclusion: *We conclude that in diabetic patients with concomitant CAD, special attention must be directed towards the diagnosis of PVD using physical examination, Doppler sonography; and where needed, CT-angiography or invasive angiography. Also, in risk assessment, the presence of PVD should be strongly considered for CAD patients.*

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Introduction

Atherosclerosis is a generalized disease, several manifestations of which may coexist in the same patient. Peripheral vascular disease (PVD) is characterized by a gradual reduction in the blood flow to one or more limbs secondary to atherosclerosis.[1] Patients with PVD often have coexisting cerebrovascular disease and/or coronary artery disease (CAD) and, therefore, have poor prognosis and reduced life expectancy.[2,3]

It can be hypothesized that PVD patients have a more severe impairment of endothelial function, which leads to a more frequent occurrence of acute coronary syndromes.[4] PVD may be diagnosed using non-invasive methods in 20-28% of patients with CAD as documented by coronary arteriography.[5] Amongst patients with CAD, PVD is more frequent in those with diabetes mellitus (DM).[6] Epidemiological evidence confirms the association between DM and the increased prevalence of PVD. Individuals with DM have a two to fourfold increase in the rate of PVD. DM changes the nature of PVD in that diabetic patients have
infrapopliteal arterial occlusive disease and vascular calcification more commonly than do non-diabetic cohorts.[7]

Strandness et al.[8] reported that DM patients had more infrapopliteal disease, whereas King et al.[9] found a greater involvement of the profunda femoris in diabetics. A recent study in the U.K. showed that the cost of revascularization procedures was more in diabetic patients than that in non-diabetic patients with PVD.[10] Although much is known regarding PVD in the general population, the assessment and management of PVD in those with DM is less clear and poses some special issues. At present, there are no established guidelines regarding the care of patients with both DM and PVD.[11] The aim of this study was to evaluate the impact of DM on PVD in CAD patients.

Methods

A total of 13702 consecutive patients who underwent isolated coronary artery bypass grafting (CABG) at Tehran Heart Center between January 2002 and March 2007 were included in this study. The demographic data, PVD, and outcome of these patients were reviewed. CABG patients were detected for PVD before surgery (stenosis ≥70% in the abdominal aorta; renal, carotid, and iliac arteries; or more than 15 mm Hg systolic blood pressure difference between the two arms or any other peripheral vascular system) using medical history and physical examination (pulse-less femoral arteries, intermittent claudication, and absence of both pedal and posterior tibial artery pulses). Suspected cases of PVD were confirmed via Doppler sonography. Some cases of PVD, especially those of renal artery stenosis, were found on angiography. In our center, patients with the following criteria were candidates for carotid Doppler sonography: 1) age≥65 years, 2) left main disease, 3) history of transient ischemic attack or cerebrovascular accident (CVA), and 4) carotid bruit. The patients were divided into 2 groups: a group of 4344 (31.7%) diabetic patients and a group of 9358 (68.3%) non-diabetic patients. Patient data comprised age, sex, smoking, hyperlipidemia, hypertension, PVD, left ventricular ejection fraction (LVEF), left main disease (stenosis>50%), pre- and post-operative renal failure, post-operative CVA, and in-hospital mortality (death occurring within 30 days after CABG). The study protocol was approved by the ethics committee of Tehran Heart Center.

The numerical variables were presented as mean±SD, while the categorized variables were summarized by absolute frequencies and percentages. The continuous variables were compared using Student's t-test, and the categorical variables were compared using the chi-square or Fisher's exact test.

A logistic regression model was performed as the multivariate analysis of choice to evaluate the effect of DM on PVD in the presence of confounding factors. A multivariate forward stepwise logistic regression model for the risk factors predicting mortality was constructed. The variables were included into the multivariate model if the P-value was found to be less than or equal to 0.15 in the univariate analysis. The associations between the independent predictors and mortality in the final results were expressed as odds ratios (OR) with 95% Confidence Intervals. Model discrimination was measured using the c statistics, which is equal to the area under the Receiver Operating Characteristic (ROC) curve. Model calibration was estimated using the Hosmer-Lemeshow goodness-of-fit statistics, with higher P-values implying that the model fit the observed data better. For the statistical analysis, the statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, I.L.) and the statistical package SAS version 9.1 for Windows (SAS Institute Inc., Cary, N.C., U.S.A.) were used. All the P-values were 2-tailed, with statistical significance defined by $P \leq 0.05$.

Results

This study recruited 4344 diabetic patients with a mean age of 59.30±8.7 years and 9358 non-diabetic patients with a mean age of 58.42±9.9 years. Whereas 37.6% of the DM patients were female, only 19.6% of the non-diabetics were female (P<0.001). The diabetics were significantly older (P<0.001) and had a higher incidence of PVD (2.7% vs. 1.8%; P=0.001), hypertension (64.4% vs. 47.5%; P<0.001),

renal failure (2.8% vs. 1.2%; P<0.001), smoking (28.8% vs. 44.1%; P<0.001), and dyslipidemia (73.6% vs. 63.1%; P<0.001) than those without DM (Table 1). There was no significant difference between the two groups with respect to family history and left main disease. The mean EF was 48.85±10.4 and 49.35±10.0 in the patients with and without DM, respectively; and this difference was significant (P=0.008). The incidence of post-operative renal failure (1.7% vs. 0.6%) and CVA (0.7% vs. 0.3%) in the DM patients was significantly higher than that in the non-diabetic patients. The in-hospital mortality rate (mortality occurring within 30 days after CABG) was 1.8% amongst the DM patients and 0.7% in the non-diabetics (P<0.001). After adjustment for confounding factors, in the multivariate logistic regression analysis, PVD was slightly significantly higher in the DM patients than that in those without DM (OR=1.264, 95% CI:0.989-1.617; P=0.0616). The univariate and multivariate analyses for in-hospital mortality in isolated CAGB patients are shown in Tables 2 and 3. The final model had good discrimination (area under the ROC curve, c=0.79908) and calibration (Hosmer-Lemeshow goodness-of-fit test, P=0.9388). Table 4 depicts the univariate analysis for the in-hospital mortality rate in the diabetic patients. In the multivariate analysis, PVD, left main disease, age, female gender, and EF were significant in the development of mortality in the diabetic patients with a respective odds ratio of 4.17, 5.54, 1.03, 2.86, and 0.95 (P≤0.05) (Table 5). The final model had good discrimination (area under the ROC curve, c=0.80007) and calibration (Hosmer-Lemeshow goodness-of-fit test, P=0.9390). In the patients with DM, carotid (1.13% vs. 0.83%), subclavian (0.05% vs. 0.02%), femoral (0.18% vs. 0.09%), renal (0.62% vs. 0.25%), and tibialis (0.16% vs. 0.06%) arteries had a higher incidence of stenosis than those amongst the patients without DM. The distribution of vessel stenosis in the diabetic and non-diabetic patients with PVD is illustrated in Table 6.

Table 1. Baseline characteristics*

Variables	Diabetic (n=4344)(31.7%)	Non-diabetic (n=9358)(68.3%)	P value
Age (y)	59.30±8.77	58.42±9.99	<0.001
Female	37.6	19.6	<0.001
Hypertension	64.4	47.5	<0.001
Peripheral vascular disease	2.7	1.8	0.001
Smoking	28.8	44.1	<0.001
Left ventricular ejection fraction (mean±SD)	48.85±10.46	49.35±10	0.008
Renal failure	2.8	1.2	<0.001
Left main disease	9.3	9.9	0.238
Family history	35.6	35.8	0.886
Hyperlipidemia	73.6	63.1	<0.001

* Number are presented as mean±SD or percentage

Table 2. Univariate analysis of pre-operative variables for mortality in isolated CABG patients

Variables	Non-surviving (n=148)	Surviving (n=13554)	P value
Age (y)	64.18±9.10	58.64±9.61	<0.001
Female	43.9	25.1	<0.001
Hypertension	74.3	52.6	<0.001
Peripheral vascular disease	14.2	2	<0.001
Smoking	31.1	39.3	0.041
Left ventricular ejection fraction	45.24±11.51	49.23±10.13	<0.001
Renal failure	6.8	1.7	<0.001
Left main disease	33.1	9.4	<0.001
Family history	35.6	35.7	0.976
Hyperlipidemia	77	66.3	0.006
Diabetes	52.7	31.5	<0.001

* Number are presented as mean±SD or percentage

Table 3. Results of multivariate analysis for mortality in isolated CABG patients

Variables	Odds ratio	95% CI	P value
Peripheral vascular disease	4.157	2.465-7.008	<0.0001
Hypertension	1.842	1.253-2.707	0.0012
Female	2.031	1.428-2.887	<0.0001
Left main disease	4.251	2.966-6.094	<0.0001
Age	1.052	1.031-1.073	<0.0001
Diabetes	1.855	1.317-2.613	<0.0001
Renal failure	2.378	1.161-4.871	0.0149
Ejection fraction	0.961	0.946-0.976	<0.0001

Table 4. Univariate analysis of pre-operative variables for mortality in diabetic patients

Variables	Non-surviving (n=78)	Surviving (n=4266)	P value
Age (y)	62.72±8.46	59.24±8.77	0.001
Female	59	37.2	<0.001
Hypertension	71.8	64.3	0.169
Peripheral vascular disease	12.8	2.5	<0.001
Smoking	21.8	29	0.166
Left ventricular ejection fraction	44.36±12.49	48.93±10.40	0.002
Renal failure	6.4	2.7	0.063
Left main disease	35.9	8.8	<0.001
Family history	38.2	35.6	0.645
Dyslipidemia	79.5	73.5	0.235

* Number are presented as mean±SD or percentage

Table 5. Results of multivariate analysis for mortality in diabetic patients

Variables	Odds ratio	95% CI	P value
Peripheral vascular disease	4.174	2.026-8.600	<0.0001
Ejection fraction	0.956	0.937-0.976	<0.0001
Female	2.863	1.788-4.585	<0.0001
Left main disease	5.549	3.409-9.034	<0.0001
Age	1.037	1.009-1.067	0.0103

Table 6. Distribution of vessel stenosis in diabetic and non-diabetic patients*

Vessel stenosis	Diabetic	Non-diabetic
Carotid	1.13	0.83
Iliac	0.12	0.21
Subclavian	0.05	0.02
Femoral	0.18	0.09
Renal	0.62	0.25
Pedis dorsalis	0.12	0.16
Tibialis	0.16	0.06
Abdominalaorta aorta	0	0.04
Proneal	0	0
Popliteal	0	0.01
Axillary	0	0.01
Renal + Iliac	0.05	0
Carotid + Iliac	0.02	0
Femoral + Popliteal	0.02	0.01
Tibialis + Renal	0.02	0
Pedis dorsalis + Tibialis	0.07	0.02
Carotid + Renal	0.07	0.04
Femoral + Iliac	0.02	0.02
Tibialis + Carotid	0.05	0
Subclavian + Renal	0	0.01
Tibialis + Proneal	0	0.01
Tibialis + Femoral	0	0.01
Subclavian + Abdominalaorta	0	0.01
Tibialis + Proneal + Femoral	0.02	0
Carotid + Iliacl + Femoral	0	0.01
Sum	2.72	1.82

*Data are presented as percentage

Discussion

PVD is a clinical manifestation of the atherosclerotic process, which is associated with cardiovascular disease and the increased risk thereof. A major chronic disease, DM is able to accelerate atherosclerosis and numerous studies have identified it as a key risk factor for PVD.[12] Coronary arteriography shows that amongst patients with documented CAD, PVD is more frequent in patients with DM.[6]

Classic major risk factors for CAD (smoking, hypertension, DM, and hypercholesterolemia) are associated with the presence of PVD and the prevalence of cerebrovascular disease. PVD in patients with CAD is particularly enhanced by the concomitant occurrence of two or more of these risk factors.[4] Gianluca Rigatelli showed that age>65 years, multiple risk factors, and three- to four-vessel CAD appeared to be the independent predictors of PVD.[13]

In our study, DM was more prevalent amongst the women (P<0.001). Our DM patients were significantly older and had a higher incidence of PVD (P=0.001), hypertension, renal failure, smoking, and dyslipidemia (P<0.001). Premature CAD was more prevalent in our series than that in reports from Western countries, which may explain the older age of ordinary CAD patients with known risk factors such as non insulin dependent DM. Minakata et al.[14] showed that patients with PVD were significantly older and had a higher incidence of DM, hypertension, pre-operative cerebral infarction, and chronic renal dysfunction. These data suggest that patients with PVD have more severe systemic atherosclerosis.

On the other hand, the in-hospital mortality rate was significantly higher (P<0.001) in our diabetic patients than that amongst our non-diabetic subjects. Several large studies have demonstrated that the presence of PVD is an important, independent predictor of in-hospital mortality rates.[14]

Our findings indicated that the carotid and renal arteries had the highest prevalence of stenosis amongst vessels, and this explains the higher incidence of CVA and post-operative renal dysfunction in our series.

It is important to diagnose PVD in patients with DM to elicit symptoms, prevent disability and limb loss, and identify a patient at high risk of death. The method of the pre-operative diagnosis of PVD in candidates for CABG is still a matter of debate. Each non-invasive technique such as duplex ultrasonography has drawbacks in precisely depicting the extracranial region, renal arteries, subclavian vessels, and aortoiliac artery due to poor sonographic window, severe calcification of the vessel wall, obesity, and being highly operator dependent. As a result, the interventional or surgical treatment of PVD is often planned using invasive angiographic studies.

Conclusion

We conclude that in DM patients with concomitant CAD, special attention must be directed towards the diagnosis of PVD by means of physical examination, Doppler sonography, and where needed, CT- angiography or invasive angiography. On the other hand, due to the high impact of PVD on the outcome in these patients, it should be strongly considered in the risk assessment and the choice of proper surgical techniques to minimize mortality and major complications such as CVA or post-operative renal impairment.

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