Diabetes and Peripheral Arterial Disease in Men: Trends in Prevalence, Mortality, and Effect of Concomitant Coronary Disease

Address for correspondence:
Masoor Kamalesh, MD
1481 W. 10th Street
Indianapolis, IN 46202
masoor.kamalesh@med.va.gov

Masoor Kamalesh, MD and Jianzhao Shen, MS
Krannert Institute of Cardiology and Richard L. Roudebush VA Medical Center, Indiana University (Kamalesh), Indianapolis, Indiana; Division of Biostatistics, Indiana University School of Medicine (Shen), Indianapolis, Indiana

ABSTRACT

Background: Recent data on trends in diabetes mellitus (DM) prevalence and long-term effect on mortality in peripheral arterial disease (PAD) subjects is lacking.

Methods: All subjects discharged from any VA medical center between October 1990 to September 1997 with an International Classification of Diseases (ICD)-9 code for PAD and DM in the discharge summary were retrospectively identified. Demographic data were extracted from the database. Mortality data were obtained from the Beneficiary Information and Resource Locator. Outcome measures were age specific DM prevalence over time, and short-term and long-term mortality.

Results: Of 33,629 patients with PAD, 9474 (29%) had DM. Diabetes mellitus subjects were less likely to be white and had more comorbidities. Mean length of hospital stay was greater for DM (22.3 d vs 18.7 days, $P < 0.001$). Mortality was higher for DM at 180 days (9.8% vs 8.4%, $P < 0.001$), 1 year (16.4% vs 13.7%, $P < 0.001$), and continues to increase at 8 years of follow-up. Logistic regression analysis showed no interaction between DM and coronary artery disease (CAD).

Conclusions: Diabetes mellitus increases all-cause mortality in subjects with PAD starting at 6 months post-discharge and continues to be higher even at 8 years of follow-up. There was a lack of interaction of DM and CAD on mortality in this cohort of subjects with PAD.

Introduction

Despite the well-described association of diabetes mellitus (DM) with peripheral arterial disease (PAD),[1] a recent consensus statement on this subject by the American Diabetes Association (ADA) reveals few studies done in large cohorts of patients which have looked at short-term and long-term impact of diabetes on mortality in subjects with PAD.[2] Peripheral arterial disease is under diagnosed and undertreated.[2] Although presence of PAD in DM subjects has been suggested by the ADA for some time as one of the criteria to perform stress testing to detect asymptomatic coronary disease, to date identifying DM subjects at high risk for cardiac events remains a challenge.[3,4] This is due, in part, to lack of good data on how aggressive one should be in treating coronary disease detected in this fashion so as to reduce long-term mortality.[5] Similarly, DM itself has been regarded as a coronary heart disease risk equivalent calling for aggressive risk factor modification.[6] Despite data suggesting that PAD may have an even stronger association with cardiac and cerebrovascular related mortality than prior history of myocardial infarct, subjects with PAD do not get the same proactive evaluation and treatment from physicians.[7]

We report on the impact of DM on short-term and long-term mortality in a large cohort of patients discharged with a diagnosis of PAD from any VA medical center in the United States between the time period October 1990 through September 1997. The effect of the presence of coronary artery disease (CAD), with or without DM, on mortality in PAD patients was also investigated.

Methods

Study Population

The Patient Treatment File (PTF) portion of the medical record was used to identify patients discharged from any VA medical center in the United States between October 1990 and September 1997 with a diagnosis of PAD International Classification of Diseases [(ICD)-9-CM code 440.2 through 440.24, and 440.29 through 440.32] listed as one of the discharge diagnosis. The validity of this strategy to identify patients with cardiovascular conditions has been previously established.[8,9] For veterans with more than 1 admission with an eligible ICD-9-CM code during the study period, the first admission was considered the index admission. Patients who were discharged and readmitted the same day, were assumed to have been transferred from one medical center to another (a common practice in the VA medical system) and their admissions were considered to represent a single hospitalization. We excluded from analysis patients whose length of stay exceeded 1 year. These patients had comorbid conditions causing long-term disability or were mental health care patients who have a different postinfarction

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course and health care utilization than those without these conditions. The study was approved by the institutional review board of Indiana University School of Medicine (Indianapolis, IN).

Data on Hospitalization, Follow-Up, and Mortality

Data were extracted from the central VA administrative data center in Austin, Texas. Data regarding VA inpatient utilization throughout the index hospitalization was extracted from the PTF. There is a high agreement between PTF data and data extracted from patient's paper medical charts.[10] Demographic, in-hospital, and follow-up data were recorded for each patient. Each hospitalization record in the patient treatment file contains up to 10 discharge diagnoses. We used the discharge diagnoses 2 through 10 from the index admission to identify comorbid conditions. The severity of the patient's PAD and medication profile were not available in the patient treatment file.

All readmissions and readmissions due to cardiac causes to any VA medical center were assessed at 60 days and 1 year following discharge from the index hospitalization. Readmissions within 30 days of index admission were considered part of index admission and these were excluded from readmission analysis. However, these patients were included in mortality analysis.

For outpatient services, utilization data was extracted from the VA Outpatient Clinic File identifying visits to primary care, cardiology clinic, emergency units, and cardiac surgery clinics. Data regarding diagnostic tests and procedures were also extracted for cardiac catheterization, coronary bypass surgery (CABG), percutaneous coronary intervention (PCI), and pacemaker or defibrillator implantation. Time to cardiac procedures at 60 days and 1 year was also assessed

Mortality was assessed at 60 days and 1 year. To determine mortality, the Beneficiary Information and Resource Locator (BIRLS) was used.[11,12] This contains date of death but not cause of death. Hence all-cause mortality was used as an endpoint. To compare trends in mortality over time between DM and non-DM subjects, mortality at 60 days for each year from 1991 to 1998 was assessed in both groups.

Statistical Analysis

Frequency tables were produced for all categorical variables and were compared between DM and non-DM subjects via a χ^2 test. For continuous measures, the mean and standard deviation were generated and compared between groups using a 2-sample t test. Short-term mortalities such as 30 days, 60 days, 180 days, and 1 year were compared between DM and CAD using logistic regression models in which the dependent variables was mortality and the independent variables included age, gender, DM, CAD, and the interaction of DM and CAD. Long-term mortality (8 years follow-up) was compared between DM and CAD using the Kaplan-Meier method for univariate analysis and proportional hazards model for multivariate analysis. Subjects who were alive or lost follow-up after the cutoff date were censored. Survivor functions were compared using a log-rank test in univariate analysis and asymptotic Wald test in multivariate analysis.

Results

Of 33,629 patients with a diagnosis of PAD, 9474 (29%) had a diagnosis of DM. The prevalence of DM among PAD patients increased across all age groups from 1991 to 1998, but the steepest increase was among subjects over 65 years of age (Figure 1). Baseline demographics are shown in Table 1. Comorbidities were higher among DM subjects except for smoking. While 60 day mortality was no different between DM and non-DM subjects, mortality significantly increased at 6 months for DM subjects (9.8% vs 8.4%, $P < 0.001$) and continued to increase up to 8 years of follow-up (Figure 2).

Mortality among DM and non-DM subjects was stratified by presence or absence of CAD. A logistic regression model analysis in which the dependent variable was mortality and independent variables were age, sex, DM, CAD, and the interaction of DM and CAD showed that presence or absence of CAD did not affect mortality at any time in 1 year in subjects with or without DM (Table 2).

Discussion

This large, cross-sectional database study highlights the short-term and long-term impact of diabetes on mortality in subjects discharged from a medical facility with diagnosis of PAD. The principal findings are (1) the prevalence of DM among PAD subjects is increasing—especially in the elderly; (2) DM increases mortality in subjects with PAD starting at 6 months postdischarge and continues to be higher even at 8 years of follow-up; and (3) presence of PAD appears to attenuate the independent effect of CAD on mortality.

Peripheral arterial disease is under diagnosed and undertreated.[2] Our findings confirm and expand prior

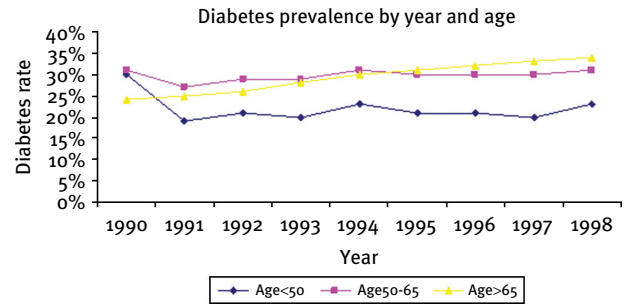

Figure 1. Prevalence of diabetes among PAD subjects over time, stratified by age. Abbreviation: PAD, peripheral arterial disease.

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Table 1. Baseline Demographics and Clinical Characteristics

	No Diabetes	Diabetes	Total	*P* Value
n	22 949 (71%)	9474 (29%)	32 423	
Mean (SD) age	66.7(9.7)	67(8.6)	66.8(9.4)	0.005
Gender (% male)	98.8	99	98.9	0.132
Ethnicity (% White)	82.5	77.1	80.9	< 0.001
Chronic conditions (%)				
Hypertension	40.7	51	43.7	< 0 .001
Coronary artery disease	29.4	34.7	30.9	< 0 .001
Congestive heart failure	8.5	12.6	9.7	< 0 .001
Hyperlipidemia	6.4	7.6	6.8	< 0 .001
Atrial fibrillation	6.7	6.7	6.7	0.977
Mean (SD) number of discharge diagnoses	6.0 (2.7)	7.2 (2.4)	6.3 (2.7)	< 0 .001
Mean (SD) Length of stay	18.7 (30.9)	22.3 (35.4)	19.8 (32.4)	< 0.001
Charlson Index >2 (%)	13.8	35.1	20	< 0.001
Postdischarge mortality				
30-day mortality (%)	1.2	1.1	1.2	0.557
60-day mortality (%)	3.1	3	3.1	0.723
180-day mortality (%)	8.4	9.8	8.8	< 0 .001
1-year mortality (%)	13.7	16.4	14.5	< 0 .001
Mean (SD) number of readmissions				
Readmission within 1 year	1.26 (1.52)	1.5 (1.72)	1.33 (1.58)	< 0.001
CV readmission within 1 year	0.02 (0.14)	0.02 (0.16)	0.02 (0.15)	< 0.001
Readmission ever	2.75 (3.34)	3.13 (3.69)	2.86 (3.45)	< 0 .001
CV readmission ever	0.05 (0.25)	0.06 (0.27)	0.05 (0.26)	0.013

Abbreviations: CV, cardiovascular ; SD, standard deviation.

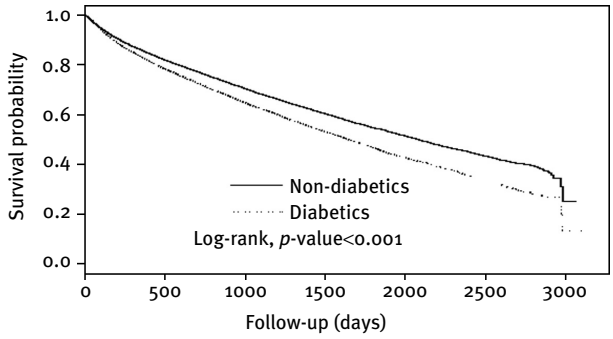

Figure 2. Kaplan-Meier survival curves for diabetics and nondiabetics in PAD patients. Abbreviation: PAD, peripheral arterial disease.

reports on PAD prevalence and mortality. Most of all, they clearly show the profound impact of DM on mortality in subjects with PAD. Information from this study can be used by clinicians in several ways. The increasing prevalence of DM in subjects with PAD is hardly surprising given the fact that DM prevalence is rising worldwide[13] and the known close association of DM with PAD.[1] The underlying message appears to be the importance of screening patients with PAD for glucose intolerance to detect DM early and treat it aggressively. To maximize dollar cost value, the priority target group should be the elderly, where the increase in DM prevalence is highest. Peripheral arterial disease prevalence is strongly age dependent[7] and our data

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Table 2. Interaction Between CAD and Diabetes with Respect to Cumulative Mortality

	No Diabetes		Diabetes		
	No CAD Dead(%)	CAD Dead (%)	No CAD Dead (%)	CAD Dead (%)	*P* Value[a]
30-day mortality (%)	1.20%	1.14%	1.13%	1.07%	0.8919
60-day mortality (%)	3.08%	3.05%	2.83%	3.32%	0.1556
180-day mortality (%)	8.23%	8.73%	9.39%	10.50%	0.2985
1-year mortality (%)	13.50%	14.10%	16.00%	17.00%	0.464
Median survival (year)	5.82%	5.36%	4.62%	4.24%	0.5917

[a]The *P* values resulted from an interaction of diabetes and coronary artery disease in the logistic regression models for 30-day, 60-day, 180-day, and 1-year mortalities and proportional hazards model for long-term survival. Abbreviations: CAD, coronary artery disease.

shows the prevalence of DM is also highest among the oldest cohort.

The effect of PAD on overall mortality has recently been summarized.[7] Our finding of lack of interaction of diabetes and CAD on mortality suggests that PAD overwhelms the independent effect of CAD on mortality in diabetic subjects. Although presence of diabetes is considered equivalent to presence of CAD by the National Cholesterol Education Program (NCEP) guidelines,[6] as shown in the East-West study, even in that study the mortality in subjects had both CAD and diabetes was 45% compared to 20% in diabetics without CAD.[14] Given this profound increase in mortality in subjects with CAD and diabetes, compared to diabetes alone, the lack of interaction of diabetes and CAD on mortality in our PAD cohort raises the significance of implications of PAD alone on mortality. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study only 9% of the subjects at baseline had PAD and presence of PAD did not identify patients with a positive test.[15] However, our data clearly shows that long-term mortality in PAD subjects with diabetes is worse than subjects without diabetes and lends credence to the ADA recommendation of using presence of PAD as an indicator for screening for asymptomatic CAD. Our data are also useful in supporting recommendations by the American Heart Association for aggressive screening for PAD in high risk subjects[16]—especially the elderly.[17]

Our study has several strengths. It is one of the largest studies to date to investigate mortality in PAD. The data were collected all over the country, as opposed to certain regions or medical centers, thus giving a homogeneous and unbiased population. Hospitals treating the patients included both community hospitals and tertiary care referral centers. There is a good mix of Caucasian and African American population, with 17% of nondiabetic subjects and 23% of diabetic subjects being African American. We used all-cause mortality as an endpoint, which has been used and accepted in such investigations previously.[18]

Several study limitations need to be mentioned. First, this study relied on retrospectively collected administrative data and hence is subject to general limitations of such reports.[19] However, it must be emphasized that we are comparing 2 groups within the same dataset and hence these limitations will be equally applicable to both groups—diabetics and nondiabetics. Our ability to control for differences between certain variables for which data were not available—such as the fact some veterans may have been followed at non-VA hospitals for follow-up is also limited. However, it needs to be pointed out that since we are comparing 2 groups (DM and non-DM subjects) from the same data source, these limitations apply to both groups. The diagnosis of DM and myocardial infarction was based on ICD-9-CM codes, and validation of the diagnosis in a random sample was not done. Data on duration of diabetes, medications, glycosylated hemoglobin (HbA1c) levels, severity of PAD, and classification of DM as type I or type II were not available. We used the index admission to classify patients as with or without diabetes; patients who were diagnosed subsequent to their index admission may be misclassified. Our study population consisted of predominantly male veterans.

In conclusion, our study extends prior reports on the profound effect DM has on mortality in subjects with PAD. In PAD subjects, DM increases mortality by 6 months after discharge from hospital. A combination of DM and PAD thus represents a very high risk group that needs to be targeted for preventive intervention aggressively.

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