Impact of Diabetes Mellitus on Long-Term Mortality in Patients Presenting for Coronary Angiography

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To understand the current impact of diabetes mellitus (DM) on long-term outcomes among patients referred for coronary angiography, we studied 14,337 consecutive patients (5,279 diabetic patients [37%]) referred to coronary angiography for assessment or treatment of coronary artery disease. We investigated long-term all-cause mortality and its interaction with hypoglycemic therapy and presenting coronary status. At baseline, patients with DM had more hypertension, hyperlipidemia, and renal failure; more were women, overweight, and more had previous coronary interventions. Mortality was higher in those with DM and was related to treatment status: multivariate adjusted hazard ratio during a median follow-up period of 78 months was 1.41 (95% CI 1.11 to 1.80, p = 0.006) for diet only−treated DM, 1.63 (95% CI 1.51 to 1.77, p <0.001) for DM treated with oral hypoglycemics, and 2.50 (95% CI 2.20 to 2.85, p <0.001) for DM requiring insulin therapy. The earlier findings were similar in magnitude in patients presenting with acute or stable coronary syndromes. In addition, long-term mortality of medically treated DM presenting with a stable coronary syndrome was even higher than that of nondiabetic patients presenting with an acute coronary syndrome (hazard ratio 1.21, 95% CI 1.08 to 1.35, p = 0.001). In conclusion, in patients referred for coronary angiography in the current era, DM remained an independent predictor of long-term mortality regardless of the coronary presentation and mortality increased in direct relation to intensity of hypoglycemic therapy at presentation. **(Am J Cardiol 2017;119:1141−1145)**

The prevalence of type 2 diabetes mellitus (DM) is rising because of the aging of the population and an adverse lifestyle reflected by unhealthy diet, increasing obesity, and physical inactivity.[1] Excess mortality in DM is multifactorial, but the major cause of death remains cardiovascular disease.[2] Despite this, the role of invasive coronary arterial assessment and revascularization in DM continues to be debated.[3] Most previous studies evaluating the impact of DM on mortality in patients with cardiovascular disease reported data from historical cohorts and generally evaluated outcomes after acute myocardial infarction.[4−7] Further understanding of the current impact of DM on long-term outcomes is important. In the present study, we aimed to determine the impact of both the presence and treatment status of DM on long-term mortality in a consecutive cohort of patients who underwent coronary angiography in the contemporary post-2000 era for evaluation or treatment of acute coronary syndromes (ACS) or stable complaints.

Methods

A retrospective analysis of the cardiac catheterization laboratory database at Carmel Medical Center, Haifa, Israel, between the years 2000 and mid-2015 was performed. Cardiac catheterization was carried out in 19,550 patients excluding recurrent procedures. Patients with missing data (n = 896) and those referred for catheterization for reasons other than the primary assessment of coronary artery disease (CAD) (n = 4,317) were excluded. The final study population comprised 14,337 patients referred for coronary angiography for primary evaluation and/or treatment of CAD. Patients were classified into 3 groups of angiographic indications: (a) stable clinical presentation, 6,911 patients, (b) unstable angina pectoris or acute non−ST-segment elevation myocardial infarction (UAP/NSTEMI), 5,730 patients, and (c) acute ST-segment elevation myocardial infarction (STEMI), 1,696 patients. Presence of DM and its treatment status (diet therapy, oral hypoglycemic medications or insulin therapy) at presentation to cardiac catheterization were prospectively documented as well as gender, age, risk factors, comorbidities, and previous coronary interventions. Data regarding all-cause mortality were identified through the national registry of death. The study was approved by Carmel Medical Center Ethics Committee with waiving of the need for individual patient consent.

Continuous data are presented as means ± SD and categorical variables as numbers and percentages. The ANOVA test was used to compare continuous variables and the Kruskal-Wallis tests for skewed data. The chi-square test was used to compare categorical variables. Fisher's exact test was used in cases of small sample sizes. Short- and long-term survival rates of diabetic patients compared with those without diabetes were calculated using the Kaplan-Meier method, and the statistical comparison performed using the log-rank test. Multivariate analysis of the association of DM status with long-term mortality was performed

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See page 1144 for disclosure information.

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Table 1
Patient characteristics and mortality

Variable	Diabetes mellitus					
	Total (n=14,337)	No (n=9,058)	Diet Tx. (n=304)	Oral Tx. (n=4,002)	Insulin Tx. (n=973)	P value
Age (years)	64.1±11.6	63.7±12.2	64.6±10.9	65.5±10.3	62.6±10.3	<0.001
Men	10421 (73%)	6770 (75%)	219 (72%)	2790 (70%)	642 (66%)	<0.001
Body mass index (kg/m^2)	28.3±4.6	27.7±4.3	29.2±5.0	29.1±4.8	29.6±4.9	<0.001
Body surface area (m^2)	1.90±0.19	1.89±0.19	1.93±0.19	1.91±0.19	1.93±0.20	<0.001
Hemoglobin (g/dl) (n=13,687)	13.6±1.6	13.9±1.5	13.8±1.7	13.2±1.6	12.9±1.7	<0.001
Creatinine (mg/dl) (n=13,671)	1.06±0.71	1.03±0.58	1.09±0.83	1.08±0.76	1.29±1.24	<0.001
Estimated glomerular filtration rate* < 60 (mL/min/1.73 m^2)	3119 (23%)	1797 (21%)	72 (25%)	948 (24.5%)	302 (32%)	<0.001
Family history of coronary artery disease†	2607 (18%)	1787 (20%)	63 (21%)	573 (14%)	184 (19%)	<0.001
Hypertension†	10029 (70%)	5467 (60%)	240 (79%)	3469 (87%)	853 (88%)	<0.001
Hyperlipidemia†	9925 (69%)	5582 (62%)	228 (75%)	3255 (81%)	861 (89%)	<0.001
High-density lipoprotein cholesterol (mg/dl) (n=8,623)	43±12	44±12	43±11	42±11	42±12	<0.001
Triglycerides (mg/dl) (n=8,779)	171±116	156±91	182±131	192±134	207±190	<0.001
Low-density lipoprotein cholesterol (mg/dl) (n=8,290)	106±36	111±36	105±34	97±34	98±39	<0.001
Smoker	3267 (23%)	2222 (25%)	67 (22%)	782 (20%)	196 (20%)	<0.001
Previous coronary revascularizations	1917 (13%)	1022 (11%)	42 (14%)	660 (17%)	193 (20%)	<0.001
Death during follow-up	3225 (23%)	1786 (20%)	68 (22%)	1080 (27%)	291 (30%)	<0.001

* Estimated glomerular filtration rate was calculated according to Modification of Diet in Renal Disease formula [MDRD = 175 × (creatinine)-1.154 × (Age)-0.203 × (0.742 if female)].

† Data were collected from electronic medical records. Diagnosis was given by primary care physicians according to clinical judgment and customary definitions.

using the Cox proportional hazards model with forward stepwise selection of covariates, calculating hazard ratios (HR) and 95% confidence intervals. Included in the model were variables that were statistically significant in a univariate analysis. In addition, a propensity score−matched analysis for insulin and non−insulin-treated DM was performed (methods detailed in Supplementary Material). The results were considered statistically significant when the 2-sided p value was <0.05. SPSS statistical software, version 20.0, and MEDCALC, version 16.8.4, were used to perform all statistical analyses.

Results

Mean age was 64 ± 11 years (27% women). More than 2/3 were hypertensive and hyperlipidemic, almost a quarter were current smokers, and 13% had previous revascularization. DM was documented in 5,279 (37%) of the study population, of whom 304 were treated by diet only, 4,002 by oral hypoglycemic medications, and 973 by insulin. Patients with DM had a greater prevalence of risk factors and comorbidities that increased progressively with treatment status of DM (Table 1).

During a median follow-up of 78 months (IQR 40 to 119), 3,225 patients (23%) of the study population died (20% of non-DM, 30% of DM treated with insulin at presentation and intermediate values in other groups, p <0.001, Table 1). In a multivariate model, after adjustment for age, gender, body mass index, hypertension, smoking status, hyperlipidemia, creatinine level, family history of premature CAD, and previous coronary interventions, DM and its treatment status were significantly and progressively associated with long-term mortality (Table 2). Additional adjustment for the indication for coronary angiography did not affect the model significantly. Overall cumulative 1-year crude mortality rates were 0.8% for patients without ACS at presentation (n = 6,911 patients), 4.7% in the UAP/NSTEMI ACS group (n = 5,730), and 9.4% in patients with acute STEMI (n = 1,696). The short-term 1-year survival of patients with DM compared with non-DM was significantly worse in those who underwent coronary angiography due to UAP/NSTEMI (p = 0.002) and STEMI (p = 0.012) but not in the non-ACS group (p = 0.334) (Figure 1). However, at long-term follow-up, survival of patients in each of the 3 angiographic indications was significantly worse in DM compared with non-DM (all pairwise p values <0.0001), and the differences in survival between patients presenting with UAP/NSTEMI versus STEMI disappeared in the long term (Figure 2). In addition, medically treated diabetic patients who presented with stable symptoms had, in the long-term, survival rates that were similar or even worse than nondiabetic patients who presented with ACS (HR 1.21, 95% CI 1.08 to 1.35, p = 0.001).

Figure 3 presents the adjusted HRs for long-term mortality, after adjusting for both the coronary presentation and DM status. The relative risks for mortality increased with the angiographic indication and a continuum of risk was seen in relation to the treatment status of DM in each of the angiographic subgroups. The magnitude of effect of the DM status on long-term mortality was similar for each of the 3 angiographic indications (Figure 3). Outcomes in insulin and non−insulin-treated DM were also examined following propensity score matching and remained significantly different (p = 0.0007; Figure S1 and details can be found in Supplementary Material).

Discussion

In patients referred for coronary angiography in the contemporary era, DM was associated with a long-term risk