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Albumin excretion in diabetic patients in the setting of acute myocardial infarction: association with 3-year mortality

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Abstract

Aims/hypothesis. Diabetes mellitus is associated with increased mortality in subjects with acute myocardial infarction (AMI). We aimed to estimate the risk of mortality in AMI patients with and without diabetes using the urinary albumin : creatinine ratio (ACR).
Methods. This is a prospective study of 121 consecutive, non-selected diabetic AMI patients, 121 age- and sex-matched non-diabetic AMI patients and 61 diabetic non-AMI outpatients as control subjects. All data were obtained during the first 7 days of hospitalisation and each AMI patient was followed for a period of exactly 3 years. Baseline ACR RIA measurements were made on the 1st, 3rd and 7th days of admission.
Results. Adjusted ACR values were significantly higher in the diabetic AMI patients than in the diabetic control outpatients ($p<0.0001$), and a significant difference was observed between the weekly ACR slopes for these two groups ($p<0.0001$). Microalbuminuria was more prevalent in the diabetic AMI patients than in the non-diabetic AMI patients on the 1st day (62% vs 46%, $p=0.01$) and 3rd day (41% vs 29%, $p=0.04$). Among the AMI patients with normoalbuminuria (ACR <30 μg/mg), the mortality rate was 11.6% for the patients without diabetes and 33.8% for those with diabetes ($p=0.001$). The mortality rate was much higher among the AMI patients with microalbuminuria (ACR ≥30 μg/mg) and similar for the diabetic (68.0%) and non-diabetic patients (74.3%). In a multivariable Cox model, ACR ($p<0.0001$) and diabetes status ($p=0.01$) were associated with adverse outcome even when several other clinical variables were included in the model. Furthermore, a negative interaction was found between diabetes and ACR ($p=0.01$).
Conclusions/interpretation. Microalbuminuria frequently occurs in diabetic and non-diabetic AMI patients during the first 3 days of admission to hospital and can be used to identify subjects at high risk of mortality.

Keywords Acute myocardial infarction · Albumin : creatinine ratio · Albumin excretion · Diabetes mellitus · Microalbuminuria · Mortality

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Abbreviations: ACR, albumin : creatinine ratio · AMI, acute myocardial infarction · CK-MB, myocardial band isoenzyme of creatine kinase · LVEF, left ventricular ejection fraction

Introduction

The prevalence of diabetes mellitus has been rising worldwide due to increasing obesity and decreasing physical activity [1, 2]. Diabetes affects 6 to 7% of the Western population [1, 2] but is present in as many as 30% of patients hospitalised with acute coronary syndromes, who also have a worse prognosis than patients without diabetes [3, 4]. In fact, diabetic subjects experience greater morbidity during the acute phase of myocardial infarction (AMI) and higher mortality in the post-infarction period [3, 5, 6]. This fact holds true even in the era of thrombolytics and primary percutaneous transluminal coronary angioplasty [7, 8].

Low-level urinary albumin has been shown to predict all-cause (largely cardiovascular) mortality in patients with diabetes [9, 10]. We recently demonstrated that the AER is increased in patients with AMI and it is strongly and independently associated with global and cardiovascular mortality [11, 12].

To our knowledge, no study to date has investigated the time-course and the predictive value of AER for mortality in diabetic patients during AMI. In particular, it is not known whether diabetes status and AER have an additive effect on the prognosis in this clinical setting.

This paper reports on a 3-year prospective study of an unselected sample of diabetic patients with AMI and an age- and sex-matched group of non-diabetic AMI patients. The aims of this study were: (i) to compare the urinary albumin levels in diabetic AMI patients with those in non-diabetic AMI patients and in diabetic control subjects without AMI; and (ii) to investigate whether the presence of microalbuminuria predicts mortality after AMI in diabetic and non-diabetic patients.

Subjects and methods

Patients. A total of 121 consecutive, unselected diabetic patients (four with Type 1 diabetes and 117 with Type 2 diabetes) and 121 age- and sex-matched non-diabetic patients matched for age and sex were studied. Subjects were admitted to the intensive care units at Bassano del Grappa, Adria and Conegliano General Hospitals (all in northeast Italy) for definite AMI and were prospectively studied. Subjects with urinary tract infections or other concomitant clinical situations that could affect urinary albumin were excluded. In order to compare the baseline AER values, a smaller group of 61 diabetic outpatients (three with Type 1 diabetes and 58 with Type 2 diabetes) who had been admitted to the Diabetic Office of the Internal Medicine Department at Conegliano General Hospital were assessed as control subjects. Having given written informed consent, the patients were interviewed by a physician, who completed a standard record form covering details of past medical history. The study was approved by the hospitals' ethics committees.

A diagnosis of AMI was made if two or more of the following criteria were fulfilled: (i) central chest pain lasting longer than 30 min; (ii) typical changes in serum enzymes (total creatine kinase, myocardial band isoenzyme of creatine kinase [CK-MB], aspartate aminotransferase, lactate dehydrogenase); and (iii) typical ECG changes with pathological Q-waves and/or localised ST-T changes in at least two contiguous leads. A patient was defined as having diabetes if there was written documentation that a physician had diagnosed Type 1 diabetes or Type 2 diabetes either before or at the time of the current myocardial infarction. Glycosylated haemoglobin was assayed for participants with diabetes at the local laboratory of each study centre.

Measurements. All clinical and laboratory data were obtained during the first 7 days of hospitalisation. Levels of serum enzymes were measured and a 12-lead ECG was recorded upon admission and every 4 h thereafter for the first 2 days of admission. These assessments were performed daily as of the 3rd day of admission. Venous blood was drawn for determination of blood glucose and serum levels of total and HDL cholesterol, triglycerides and creatinine. Blood pressure was measured by specially trained nurses, using a mercury sphygmomanometer with a cuff of appropriate size; the mean of three recordings was used. Heart rate was measured by palpation of the radial pulse. The presence and degree of heart failure was assessed on the 1st, 3rd and 7th days of admission according to Killip classification.

Left ventricular ejection fraction (LVEF) was assessed by two-dimensional echocardiography between the 3rd and 7th day of admission. Four- and two-chamber apical views were recorded on VHS cassettes and sent to Conegliano Hospital, where two physicians with no knowledge of patients' clinical data examined them. LVEF determination was performed according to Simson's method, and the mean of the two measurements was used [13]. Technically unsatisfactory echocardiographic images (n=35 among diabetic patients, n=33 among non-diabetic patients) were discarded from the analysis.

Urinary albumin excretion. Urinary albumin excretion was assessed in three 24-h urinary collections, which were performed on the 1st, 3rd and 7th days of admission. Urinary collections were made under the supervision of trained nurses to minimise errors in diuresis measurement. Immediately after completion, volumes were measured and urine specimens were frozen (−20 °C) and sent to the University of Padova (Padua, Italy). Here, urinary albumin was measured by RIA using a Human ALB.KIT-double antibody (Techno Genetics, Cassina De Pecchi, Milan, Italy) [14]. The detection limit of the method was 0.5 μg/ml and the between-batch coefficient of variation was 5%. For each 24-h urine sample, creatininuria was also measured using the Jaffe method [15]. Urinary albumin excretion was expressed as the ratio of albumin (μg/ml) : creatinine (mg/ml) (ACR [μg/mg]). Microalbuminuria was defined as an ACR of 30 μg/mg or higher for both men and women. All patients enrolled were included in the follow-up. Standard urinalysis was performed at the time of urinary sample collections. Creatinine clearance (ml/s) was measured on the 1st, 3rd and 7th days as follows: concentration of creatinine in urine × urine flow / concentration of creatinine in plasma. Diabetic non-AMI control subjects, who were not hospitalised, were requested to avoid any physical activity (i.e. work and sports activity) and to rest at home during the urine collection period.

Follow-up. For 3 years after recruitment each AMI patient was called for an annual clinical check-up, such that each patient was followed-up for a period of exactly 3 years starting from the day of admission to the intensive care unit. For those who died during a hospital stay, the date and cause of death were obtained from hospital records (including the post-mortem report where available). Mortality data for those who died out of hospital were obtained from the family doctor. No patient dropped out during follow-up. Global mortality and total cardiovascular mortality were used as endpoints in this study. Any instances of coronary artery bypass graft surgery or percutaneous coronary angioplasty performed during the 3 years of follow-up were recorded and used as covariates in the multivariable survival models.

Statistical methods. Statistical analyses were performed using the Systat 7.0 for Windows package (SPSS, Evanston, Ill., USA) and JMP 3.1.4 for Windows (SAS Institute, Cary, N.C., USA). In the matching procedure, age was expressed in days. To correct for positively skewed distributions for ACR, log transformations were used as appropriate. ACR was analysed as a continuous variable, as quartiles and as a dichotomous variable using the cut-off value of 30 μg/mg, which is widely used in the literature as a threshold for microalbuminuria.

Table 1. Baseline characteristics of the patients with acute myocardial infarction

Characteristic	Diabetic AMI patients (n=121)	Non-diabetic AMI patients (n=121)	p value
Age (years)	69.8±10.9	69.8±11.0	
Sex (women)	53 (44)	53 (44)	
BMI (kg/m^2)	26.9±4.4	25.6±3.5	0.01
Current smoking	30 (25)	37 (31)	0.31
Hypertension	75 (62)	60 (50)	0.05
Systolic BP (mm Hg)	127±20	121±18	0.02
Diastolic BP (mm Hg)	77±12	75±10	0.08
Heart rate (beats/min)	80±17	75±16	0.02
History of angina	32 (26)	24 (20)	0.22
Previous myocardial infarction	33 (27)	21 (17)	0.06
Plasma glucose (mmol/l)	13.1±5.8	7.3±2.3	<0.0001
Total cholesterol (mmol/l)	5.52±1.31	5.39±1.13	0.43
Triglycerides (mmol/l)	2.03±1.29	1.51±0.92	<0.0001
Serum creatinine (mmol/l)	97.2±35.4	92.8±30.9	0.12
Creatinine clearance (ml/s)	1.25±0.72	1.28±0.60	0.37
Creatine kinase peak (U/l)	1470±1433	1539±1369	0.70
CK-MB peak (U/l)	174±187	182±161	0.71
Anterior myocardial infarction	42 (35)	45 (37)	0.69
Killip class>1	65 (54)	48 (40)	0.02
LVEF (%)[a]	47.7±12.8	52.0±11.9	0.02
Arrhythmias[b]	28 (23)	31 (26)	0.65
Thrombolysis	37 (31)	46 (38)	0.23
ACE inhibitors	61 (50)	52 (43)	0.24

Data are means ± SD or n (%). [a] Diabetic AMI patients (n=86), non-diabetic AMI patients (n=88); [b] tachyarrhythmias and/or bradyarrhythmias during the first week of hospitalisation. CK-MB, myocardial band isoenzyme of creatine kinase; LVEF, left ventricular ejection fraction

For continuous variables, comparison between groups were made using the unpaired Student's t test and repeated measures analysis of covariance with Tukey tests when data from all 3 days of observation were simultaneously assessed. The covariates used in each comparison are reported in the results section. The chi square test was used for categorical variables. Survival analyses using Cox proportional hazard regression models were completed to assess significant predictors of survival time. All of the risk factors considered significant based on univariable Cox analyses were entered into initial multivariable Cox models. These models were reduced by removing each variable that was non-significant and/or causing the least change in significance. This procedure was continued until no further variables could be removed without producing a significant change in the model [16]. These final models were determined to be the "parsimonious" multivariable models. Survival curves were constructed using the Kaplan–Meier method and compared by the log-rank test. Relative risks were derived from Cox regression models.

Data are presented as means ± SD for continuous measures, unless otherwise specified and as number of subjects (%) for categorical variables. All p values are two-tailed and p values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics. The main clinical characteristics of the diabetic and non-diabetic AMI patients are reported in Table 1. Diabetic AMI patients had higher mean values for BMI, systolic blood pressure, heart rate and triglycerides and a lower mean LVEF than non-diabetic AMI patients. Heart failure (Killip Class >1) was more frequent among diabetic than non-diabetic AMI patients. The other clinical variables, including treatment with thrombolytics or ACE inhibitors, did not differ significantly between the two groups. Diabetic control outpatients were similar to the diabetic AMI patients with respect to age and sex (age 69.5±8.8 years, 27 females [44%]). However, duration of diabetes was longer in the control group (14.0±9.5 vs 9.3±8.2 years, p=0.001) and glycosylated haemoglobin level was higher (7.9±1.5% vs 7.0±1.3%, p=0.01). Systolic BP (153±22 vs 127±20 mm Hg, p<0.0001) and diastolic BP (86±11 vs 77±12 mm Hg, p<0.0001) were also higher among diabetic outpatients than diabetic AMI patients. Furthermore, serum creatinine was lower in the control group (61.9±17.7 vs 97.2±35.4 mmol/l, p<0.0001) and, accordingly, creatinine clearance was higher (2.14±0.96 vs 1.25± 0.72 ml/s, p<0.0001). None of the diabetic outpatients showed clinical signs of heart failure during the week of study. In the diabetic AMI group, 50% of subjects used insulin and 26% used oral antidiabetic agents; the corresponding values in the diabetic non-AMI group were 32% (p=0.008) and 63% (p<0.0001) respectively.

Albumin : creatinine ratios. Among the diabetic patients, the prevalence of microalbuminuria was much higher in the AMI patients than in the non-AMI

Table 2. Albumin : creatinine ratio measured on the 1st, 3rd and 7th days of the study

Characteristic	Diabetic AMI patients[a]	Non-diabetic AMI patients	Diabetic control subjects	Diabetic AMI patients vs non-diabetic AMI patients, adjusted *p* value	Diabetic AMI patients vs diabetic control subjects, adjusted *p* value
1st day ACR (μg/mg)	122.8±16.0	91.6±13.7	27.2±5.6	0.33	<0.0001
3rd day ACR (μg/mg)	52.8±8.0	36.5±6.7	20.5±4.2	0.08	0.001
7th day ACR (μg/mg)	33.3±5.7	24.5±4.5	20.4±4.1	0.75	0.03

Data are means ± SEM. [a] Repeated measures adjusted F=1.1, p=0.28 vs non-diabetic AMI patients; linear polynomial test for trend p=0.39 vs non-diabetic AMI patients; repeated measures adjusted F=18.7, p<0.0001 vs diabetic control subjects; linear polynomial test for trend p<0.0001 vs diabetic control subjects

control outpatients on the 1st day (62% vs 28%, p<0.0001) and 3rd day (41% vs 20%, p=0.004) of admission. This difference was not significant by the 7th day (28% vs 20%, p=0.21). ACR was significantly higher in the diabetic subjects with AMI than in the diabetic control group, even after adjusting for blood pressure, creatinine clearance, Killip class and administration of the various drugs (including insulin and oral antidiabetic agents) (Table 2). The Tukey test showed that the between-group differences were significant for all 3 days of measurement. Diabetic AMI patients had high ACR values on the 1st day of admission, which gradually decreased to the 7th day, whereas the diabetic control subjects had stable ACR values, producing a significant linear difference between the weekly ACR slopes for the two groups (Table 2).

The prevalence of microalbuminuria was lower in the non-diabetic AMI patients than in the diabetic AMI patients (46%, 29% and 17%, p=0.01, p=0.04 and p=0.57 respectively vs diabetic AMI patients). Univariable repeated measures ANOVA revealed that ACR was lower in the non-diabetic AMI patients than in the diabetic AMI patients (F=4.0, p=0.04) but the between-group differences were no longer significant after adjusting for BMI, BP and Killip class (Table 2). No significant difference was observed between these two groups with respect to the weekly ACR slopes (Table 2).

Three-year mortality according to diabetes status and albumin : creatinine ratio. During the 3 years of follow-up, 58 patients in the diabetic AMI group (48%, 24 men and 34 women) and 36 patients in the non-diabetic AMI group (30%, 15 men and 21 women) died (p=0.004). Among the diabetic subjects, the causes of death were: reinfarction (n=7), stroke (n=6), heart failure or cardiogenic shock (n=16), sudden death (n=11), other cardiovascular causes (n=13) and non-cardiovascular causes (n=5). Among the non-diabetic patients, causes of death had a similar distribution (p=0.26 vs diabetic patients): reinfarction (n=2), stroke (n=2), heart failure or cardiogenic shock (n=12), sudden death (n=8), other cardiovascular causes (n=4) and non-cardiovascular causes (n=8).

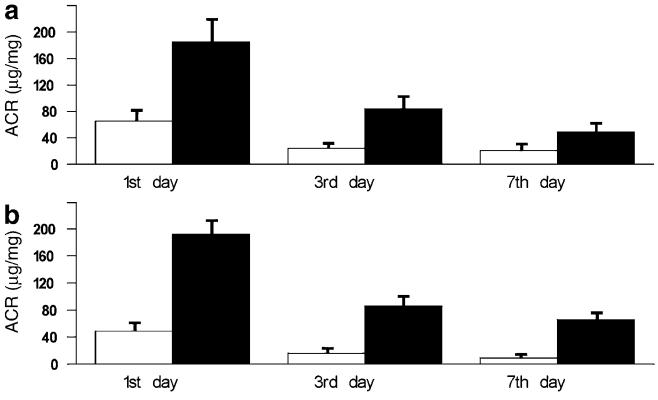

Fig. 1. ACR in diabetic patients (**a**) and non-diabetic patients (**b**) with AMI measured on the 1st, 3rd and 7th days of admission to hospital. The graphs of the two groups show patients who died (black bars) and those who survived (open bars). Values are expressed as means ± SEM. Results of repeated measures analysis of covariance adjusting for CK-MB peak, Killip class, ACE inhibitor and thrombolytic therapy: F=10.6, p=0.001 in diabetic patients and F=30.4, p<0.0001 in non-diabetic patients

Diabetic AMI patients used calcium-channel blockers less frequently than non-diabetic AMI patients (27% vs 45%, p=0.02) during follow-up, while nitrates (70% vs 71%, p=0.92), beta-blockers (30% vs 34%, p=0.61) and ACE-inhibitors (46% vs 48%, p=0.79) were used by a similar number of patients in the two groups. Compared with the AMI patients who died, survivors were more likely to use beta-blockers (32% vs 16%, p=0.004) and calcium-channel blockers (37% vs 19%, p=0.003), and less likely to use nitrates (70% vs 85%, p=0.008) and insulin (5% vs 29%, p<0.001). There was no difference between these two groups with respect to the use of ACE inhibitors (47% vs 52%, p=0.46).

Throughout the first week after admission for AMI, ACR was consistently higher in the patients who died than in those who survived, both among diabetic and non-diabetic individuals (Fig. 1). Secondary analysis showed that the between-group differences were significant for all three measurements (p<0.001 for each

day for diabetic subjects and $p<0.0001$ for each day for non-diabetic subjects). Similar differences were found when deaths from cardiovascular causes alone were considered ($p<0.001$ for diabetic patients and $p<0.0001$ for non-diabetic patients). Figure 2 shows the all-cause mortality rate in diabetic and non-diabetic AMI patients stratified into quartiles according to ACR value on the 3rd day. Both diabetic and non-diabetic subjects exhibited a progressive rise in mortality rate with increasing ACR value ($p<0.0001$ for χ^2 test for both groups). Mortality rate ranged from 0% for the non-diabetic patients in the lowest ACR quartile to 73.3% for the diabetic patients in the highest ACR quartile. Similar results were obtained using measurements taken on the 1st day and the 7th day of admission.

AMI patients were subsequently stratified into four groups according to diabetes status and the absence or presence of microalbuminuria. Figure 3 shows the Kaplan–Meier curves for 3-year mortality for the four groups. The mortality rate was dramatically increased in patients with ACR values greater than or equal to 30 μg/mg on the 3rd day (68.0% among diabetic patients, and 74.3% among non-diabetic patients). The mortality rate was much lower in patients with ACR values lower than 30 μg/mg on the 3rd day, and was significantly different between patients with and without diabetes (33.8% vs 11.6% respectively, $p=0.001$). Similar mortality trends were observed for measurements made on the 1st day and the 7th day (log-rank test $p<0.0001$ for both).

Multivariable analyses. Based on separate Cox survival analyses, both diabetes status and ACR were associated with 3-year all-cause mortality (Table 3). Multivariable Cox survival models in which both diabetes status and ACR level were included showed that both of these two predictors were still significantly associated with adverse outcome even after adjustment for seven other clinical variables in the final parsimonious survival model. The predictive power of ACR for mortality remained significant when subjects were

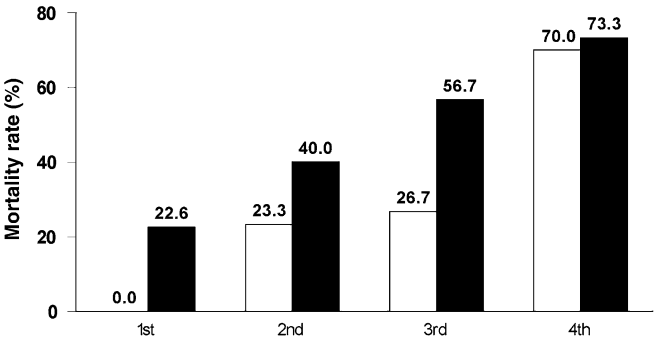

Fig. 2. All-cause mortality rates in diabetic AMI patients (black bars) and non-diabetic AMI patients (open bars) after 3 years of follow-up stratified into quartiles according to ACR values measured on the 3rd day of admission

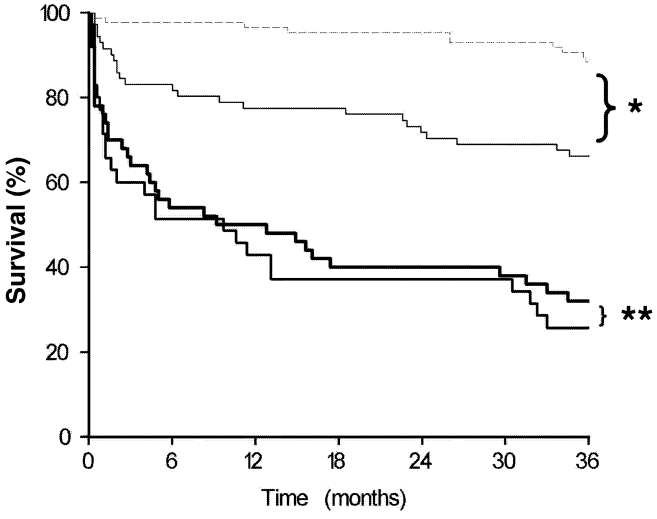

Fig. 3. Kaplan–Meier curves of 3-year all-cause mortality in AMI patients stratified according to diabetes status and the presence of microalbuminuria (ACR ≥30 μg/mg) on the 3rd day of admission. Log-rank test: $\chi^2=79.6$, $p<0.0001$. * $p=0.001$, ** $p=0.53$. Interrupted line, non-diabetic patients with normoalbuminuria; thin solid line, diabetic patients with normoalbuminuria; medium solid line, non-diabetic patients with microalbuminuria; thick solid line, diabetic patients with microalbuminuria

Table 3. Univariable and multivariable analyses of predictors of 3-year all-cause mortality based on Cox regression models in patients with acute myocardial infarction using data collected on the 3rd day of admission

Variables	RR (95% CI)[a]	*p* value	RR (95% CI)[a]	*p* value
ACR	2.8 (2.2–3.7)	<0.0001	2.2 (1.7–2.9)	<0.0001
Thrombolysis	0.3 (0.2–0.6)	<0.0001	0.2 (0.1–0.5)	<0.0001
CK-MB peak	1.4 (1.1–1.6)	0.001	1.6 (1.3–2.0)	0.0001
Systolic BP	0.8 (0.7–1.0)	0.14	0.7 (0.5–0.9)	0.006
Age	2.2 (1.7–2.8)	<0.0001	1.6 (1.2–2.1)	0.0009
LVEF (*n*=174 of 242)	0.5 (0.4–0.6)	<0.0001	0.7 (0.5–0.9)	0.01
History of angina	1.3 (0.8–2.0)	0.31	1.7 (1.1–2.7)	0.03
Diabetes mellitus	1.9 (1.2–2.8)	0.003	1.7 (1.1–2.6)	0.02
Killip class (1–4)	2.5 (2.0–3.1)	<0.0001	1.5 (1.1–2.0)	0.01
Interaction between diabetes and ACR	0.4 (0.2–0.8)	0.003	0.5 (0.3–0.8)	0.01

Units of variables as reported in Table 1. [a] Increased risk of mortality for a 1-SD increase in continuous variables. CK-MB, myocardial band isoenzyme of creatine kinase; LVEF, left ventricular ejection fraction; RR, relative risk

divided according to age (<65 years: n=74, χ^2=11.9, p=0.0006; ≥65 years: n=168, χ^2=22.6, p<0.0001). When ACR was excluded from the model, the predictive power of diabetes status for mortality increased (χ^2=10.2, p=0.001). It is noteworthy that ACR was by far the strongest predictor of all the variables considered. Furthermore, a negative interaction was found between diabetes and ACR, both at a univariable and a multivariable level (Table 3). Thrombolytic therapy favourably affected outcome. Sex, BMI, current smoking, pre-existing hypertension, prior myocardial infarction and anterior site of AMI were all significant predictors of mortality based on univariable tests, but they did not reach statistical significance when entered into multivariable models. The same multivariable analyses performed using data from the 1st and 7th days of admission produced similar results (1st day: diabetes status: χ^2=6.0, p=0.01; ACR: χ^2=24.3, p<0.0001; 7th day: diabetes status: χ^2=5.2, p=0.01; ACR: χ^2=21.5, p<0.0001). Similar associations were found for cardiovascular mortality.

Discussion

The results of the present study indicate that ACR is dramatically increased during the first 3 days after AMI in diabetic patients, and that during this period microalbuminuria is more common in diabetic than in non-diabetic individuals. Although we cannot provide direct evidence that the increase in ACR is due to AMI (as no ACR values prior to AMI are available), the marked difference in ACR between diabetic AMI patients and diabetic non-AMI outpatients on the 1st and 3rd days of admission support this concept. Furthermore, microalbuminuria strongly predicts cardiovascular and all-cause mortality in the setting of AMI. The association between microalbuminuria and the risk of mortality was independent of other cardiovascular risk factors. When the two groups of AMI patients were stratified into quartiles according to ACR values, the mortality rate ranged from 0% for the non-diabetic AMI patients in the lowest ACR quartile to 73.3% for the diabetic AMI patients in the highest ACR quartile. Our group has previously reported that low-level urinary albumin predicts in-hospital and 1-year mortality in subjects admitted to hospital for AMI [11, 12]. The present study is the first to examine the additional prognostic information provided by albuminuria for 3-year mortality over that already available from clinical and instrumental findings in diabetic patients with AMI. The present results are consistent with those recently observed in a population of hypertensive subjects with left ventricular hypertrophy who were enrolled in the LIFE study [17]. In this study, Wachtell and colleagues demonstrated a strong association between ACR and the risk of cardiovascular mortality in both diabetic and non-diabetic individuals.

A number of studies performed before the introduction of fibrinolysis for the treatment of patients with AMI consistently showed a higher mortality rate in diabetic patients [3, 5, 6]. Although current treatment of AMI with fibrinolytic agents and aspirin has led to a marked improvement in the prognosis for AMI [18, 19], diabetic patients remain a subgroup at high risk of mortality, both in hospital and after discharge, and diabetes still doubles the case fatality rate [5, 7, 20]. The results of the present study confirm this, as diabetes status in itself accounted for an increase in the risk of 3-year global mortality by a factor of 1.9. The risk was 1.2 times higher in the diabetic subjects without microalbuminuria, but 3.5 times higher in the subjects with ACR values above or equal to 30 μg/ml.

The increased mortality in diabetic patients may be accounted for by several mechanisms, and it is in this context that new information on this topic must be evaluated. Among factors such as more extensive coronary atherosclerosis in diabetic subjects, alterations in the fibrinolytic system that facilitate reocclusion after fibrinolysis [21, 22], diabetic cardiomyopathy with systolic or diastolic dysfunction [23], and autonomic imbalance [24], particular emphasis has been placed on endothelial dysfunction leading to impaired myocardial perfusion [25]. Albuminuria is considered to be a marker of widespread endothelial dysfunction enhancing atherogenesis, and several studies have shown that the mortality risk is 2.3 to 4 times higher in diabetic patients with microalbuminuria than in those without [26, 27, 28]. Thus, it is possible that the glomerular albumin leak reflects a widespread atherosclerosis-mediated capillary vasculopathy [25, 26, 27, 29]. Although we have no ACR values for the patients prior to AMI, it is reasonable to assume that the large difference in ACR between the diabetic AMI group and the diabetic control group is accounted for by AMI. Therefore, it is conceivable that the inflammatory injury and haemodynamic changes related to AMI [12] caused a greater leakage of urinary albumin in subjects with diabetes and associated glomerular damage. A recent study has demonstrated an association between C-reactive protein (a sensitive marker of inflammation) and microalbuminuria [30], and previous results from our laboratory indicate that C-reactive protein is a strong independent predictor of mortality in subjects with AMI [31]. The negative interaction between diabetes and ACR with respect to mortality suggests that microalbuminuria is the overriding factor in the setting of AMI because it reflects a heavily compromised clinical situation, and microalbuminuria was more common among the diabetic individuals than the non-diabetic individuals. In contrast, within the AMI patients with normal ACR, diabetes still retained an independent predictive power for mortality.

Albuminuria has been associated with adverse changes in several cardiovascular risk factors [27, 29]. A critical question within this context is whether the

relationship between increased ACR and mortality merely reflects the association between albuminuria and other predictors of mortality. However, in our analyses, ACR remained a strong predictor of mortality even after adjustment for these factors, suggesting that ACR is an independent additive component in the relationship between albuminuria and mortality in patients with AMI. A possible limitation of this study is that the majority of enrolled patients were elderly subjects, and thus the present results may not apply to younger individuals. However, the predictive power of ACR for mortality was also present in subjects younger than 65 years of age.

In conclusion, the present data show that microalbuminuria is common in diabetic AMI patients and provides prognostic information additional to that provided by other well-known indicators of risk. This relatively inexpensive and widely available test can help to identify subjects at high risk of mortality, for whom additional preventive and therapeutic measures are advisable.

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