

Survival after Myocardial Infarction in Patients with Type 2 Diabetes

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Abstract

Objective: To determine prospectively the survival of previously known diabetic patients admitted to coronary care unit with confirmed myocardial infarction (MI) over a one-year period and to assess the effects of gender, age, diabetes duration, hyperglycemia, hypertension, and anti-diabetic treatment on survival.

Methods: In this prospective cohort study, we followed 59 patients hospitalized with a confirmed myocardial infarction at 3 coronary care units, Peshawar (Pakistan), between May 1, 2000 and April 30, 2001, We analyzed survival using univariate and multivariate Cox Proportional hazards regression models to control for potentially confounding factors.

Results: A total of 17 (28.8%) subjects (7 male and 10 female) died. Survival was significantly associated with previous history of hypertension and duration of diabetes (HR = 3.40, 95% CI = 1.33-9.22, P = 0.001, and HR = 1.24, 95% CI = 1.05-1.45, P = 0.009, by Univariate Cox model, respectively). In multivariate analysis duration of diabetes was significantly associated with survival and Metformin treatment only, and Sulphonylurea & Metformin treatment together (P = 0.003, and 0.026, Multivariate Cox model, respectively).

Conclusion: Our results suggested that diabetes is associated with markedly increased mortality in the presence of hypertension after acute myocardial infarction and support for aggressive treatment of coronary risk factors among diabetic patients (JPMA 54:73;2004).

Introduction

There are significant ethnic and geographical variations in the prevalence and incidence of type 2 diabetes. The worldwide prevalence of diabetes is expected to more than double between 1994 and 2000, to 239 million people. 1 Recently Riste et al. (2001) reported that age standardized (35- 79 years) prevalence of known and newly diagnosed type 2 diabetics was 20% (17 -24%) in Europeans, 22% (18- 26%) in African Caribbean, and 33% (25 -21 %) in Pakistanis in Manchester, UK. A study conducted by Shera et al. 3 in rural areas of N. W.F.P, as part of the Pakistan National Diabetes Survey by WHO, indicated that the overall prevalence of type 2 diabetes and impaired glucose tolerance (IGT) in both sexes is 11.1% and 9.4%, respectively, and concluded that prevalence of diabetes mellitus in rural areas of N .W.F.P is rising. Type 2 diabetes increases the risk of coronary heart disease (CHD) by a factor of two to four. 4-6 Diabetes increases the case fatality rate of MI events 7 and pre- hospital mortality from acute coronary events is higher among people with diabetes. 8 Patients with diabetes who have MI are more likely to die than those without diabetes. 9-12 Furthermore, it is also well established that even newly diagnosed diabetic patients have an increased atherogenic cardiovascular risk

profile, such as increased concentration of total and LDL cholesterol, triglycerides, insulin, raised blood pressure and lower concentration of HDL cholesterol.^{13,14} In addition, it has been reported from large population-based studies^{10,15-17} and from two population-based MONICA registers^{18,19} that diabetic patients have worse short term and long-term prognosis after MI compared with non-diabetic patients. The aim of this study was to determine the survival rate in previously known type 2 diabetic patients with confirmed myocardial infarction after one-year duration in a developing region. Additionally, the study aimed to assess the effects of gender, age, diabetes duration, hyperglycemia, hypertension, high blood pressure on admission, anti-diabetic treatment, and acute treatment given at the time of admission on survival in diabetic patients.

Patients and Methods

In this prospective cohort study we enrolled previously known diabetic patients admitted to coronary care units of the Lady Reading Hospital (LRH), Khyber Teaching Hospital (KTH) and Hyatabad Medical Complex (HMC), Peshawar (Pakistan), for confirmed myocardial infarction between May 1, 2000 and April 30, 2001. We did not recruit individuals with type 1 diabetes or who lived outside the catchment area (3 miles radius from the individual hospitals), or those who were above 80 years of age. The local ethics committee of clinical research approved the study, and all patients provided written informed consent. Patients were considered to have diabetes if they had a previous history of disease (stated in medical records) or were on insulin and/or oral hypoglycemic agents before the MI for at least 1 year's duration. Subjects were considered to have MI if they fulfilled the World Health Organization (WHO) criteria for MI. The WHO classic definition of MI requires that at least two of the following three criteria are met: a history of typical symptoms of ischaemic chest discomfort, evolutionary electrocardiographic tracings involving the development of Q waves, and an increase in the creatine kinase level greater than twice the upper reference limit.²⁰

1. Study Tool A 32 item structured questionnaire was used to collect initial information on study subjects at the time of their admission to respective CCU. Eleven questions were on subjects' demographics, 7 were on subject's past medical history regarding diabetes and its treatment, and the remaining 14 questions were related to their acute medical condition (MI symptoms/ presentation, diagnosis, investigation and treatment) given at the time of admission for which they were admitted to the hospital. The baseline questionnaire was pilot tested in KTH coronary care unit, before the actual study started in May 2000. A retrospective, 2 months (February and March) patients' data was extracted from the CCU admission register, to collect the relevant information and the questionnaires were filled. A total of 72 patients with confirmed MI were admitted to the CCU, during February 1999. Of those 72 patients, 9 were diabetic at the time of admission and 2 patients with diabetes died during their initial stay in the hospital. A total of 86 patients with confirmed MI were admitted to the CCU, during March 1999. Of those 86 patients, 11 were diabetic at the time of admission and 3 patients with diabetes died during their initial stay in the hospital. A follow-up structured questionnaire was used to collect information on subjects' outcome (dead/ alive) after one year of the study period. It consisted of 12 questions, 5 questions were on subjects' identity with respect to baseline questionnaire and 7 were on subjects' state of health after their discharge from the hospital till that time. The follow-up

questionnaire was completed by the author herself. 2. Statistical Analysis The data were analyzed and the summary statistics were carried out by two statistical packages, SPSS for Windows, version 10.0 and STATA version 9.0. The results for all continuous variables are given in the form of averages (SD) and 95% confidence intervals (CI) and for categorical variables in percentage or proportions. Survival curves were obtained using STATA. Univariate and multivariate analysis were performed to determine association between different co-variables. Cox Proportional Hazard models were applied to assess the relative effects on outcome (death or survival only) of different variables (history of hypertension, duration of diabetes, blood glucose level (BGL), highest blood glucose level, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and anti-diabetic treatment) and other potential confounders and covariates. To determine the relative contribution of blood pressure measures, based on a background model of age, gender, 3 separate Cox regression models were constructed, adding duration of diabetes, history of hypertension and highest blood glucose level, respectively, as independent variables.

Results

A total of 1148 patients were admitted to three CCUs, LRH (628), KTH (313) and HMC (217), with an episode of MI, during one-year period between May 1, 2000 and April 30, 2001. Of these 1148 MI patients, 160 (13.9%) were diabetic at the time of admission to CCU, with at least one-year duration. Forty-six (4%) patients were hyperglycaemic at the time of admission to CCU without a prior history of diabetes and 28 (2.4%) had a positive family history of diabetes but were non-diabetic. A total of 160 questionnaire forms were filled for diabetic patients at three CCU, LRH (91), KTH (42) and HMC (27). Of these 160, 46 (28.8%) patients were excluded from follow-up because they were not residing within Peshawar district, and 114 (71.2%) patients were included in the study as they were local residents. Of these 114, 87 (76.3%) patients were considered for follow-up, as they were living within the inclusion area (3 miles radius from individual hospital) and 27 (23.7%) were excluded. Of these 87, 59 (67.8%) patients were followed up after a year and 28 (32.2%) were lost to follow-up (Figure 1). [(0)] Table 1 . Baseline characteristics of study subjects on continuous variables. Baseline characteristics and summary statistics were measured using the data collected from 160 diabetic patients at the time of admission in three CCUs (Table 1). The proportion of admission of patients with diabetes at LRH, KTH and HMC CCUs were 14.5%, 13.2% and 13.4%, respectively, during 1 May 2000 to 30 April 2001, with an overall proportion of 13.9%. Eighty-two, (51.2%) of those who were interviewed at the time of admission were female and 78 (48.8%) were male, with an overall mean age of 55.7 (S.D. 9.7) years. Their mean duration of diabetes at the time of admission was 5.2 (S.D. 2.4) years. Mean duration of stay at hospital was 2.5 (S.D. 1.9) days for the study cohort. A total of 132 (82.5%) patients (68 females and 64 males) were admitted with first episode of MI while 28 (17.5%) patients (14 females and 14 males) had other (second, third, fourth, etc.) episodes. Figure 2 illustrates the distribution of anti-diabetic treatment, between male and female that the patients were on at the time of admission. A total of 130 (91.3%) patients (64 male and 66 female) were taking sulphonylurea (SU), 77 (48.1%) patients (41 male and 36 female) were on metformin (MFN), 54 (33.8%) patients (30 male and 24 female)

were on both (SU and MFM) drugs, and II (8.9%) patients (5 male and 6 female) were on insulin injections. [(1)] [(2)] [(3)] Table 3. Multivariate analysis using Cox Proportional Regression model with adjusted hazard ratios, p values and 95% confidence intervals for all cause mortality by outcome variables. patients (77 male and 81 female) received beta-blockers, 139 (86.8%) patients (67 male and 72 female) received both Aspirin and beta-blockers, 119 (74.4%) patients (54 male and 65 female) received thrombolysis, and only 5 (3.1%) patients (1 male and 4 female) received either insulin injection or OHA. The number of admissions to three CCUs, throughout the year, by calendar month in the study cohort (n = 160), between male and female, is shown in Figure 4. The majority, 111 (68.3%) of patients (55 male and 56 female) was admitted during the spring/summer period (April to May) as compared to 49 (31.7%) patients (23 male and 26 female) who were admitted during the autumn/winter Period (September to March). We reported one-year follow-up data for 59 patients, 17 (19.1%) died later during the following 12 months. Of these 17 diabetic patients, 2 (11.8%) died within a month, 7 (41.2%) within 6 months, and the remaining 8 (47%) died after 6 months of their initial episode of MI. In all patients death was associated with severe chest pain, admission to hospital and in the majority of patients death occurred within 24 to 48 hours. Sudden/ street deaths were not included in our cohort, as their relatives could give a history. Figure 5 presents the observed Kaplan Meier, survival curves for the one-year follow-up period for study subjects. All study subjects had been put into two groups according to their history of hypertension. Eighteen (30.5%) patients with history of hypertension (hyper 0) had 1 deaths while 5 deaths occurred in 41 (69.5%) patient without a history of hypertension (hyper 1). As shown in the graph a clear association was found between history of hypertension and survival. Cox Proportional Hazards Model (PHM) 1. Univariate Analysis In the univariate Cox model based on baseline variables are shown in Table 2. A high mortality was associated with history of hypertension (HR = 3.40, p 0.001) and systolic and diastolic blood pressure measurement (HR = 1.02, p = 0.010 and 1.05, p = 0.001 respectively) at the time of admission to CCU. Age, gender MI episode and raised blood glucose level were not associated with high mortality in diabetic patients. Highest blood glucose level (HR = 101, P = M65) during stay, pulse rate (HR = 102, P = M78) and blood urea level (HTR ~ 102, P = M83) at the time of admission were not very strong predictors of mortality in diabetic patients. 2. Multivariate Analysis A backward stepwise approach was chosen Model 1 included SU treatment as an independent (exposure) variable, but not MFN and other baseline variables (duration, history of hypertension and highest blood glucose level) with the following degree of fit" LR X2 (13 d.f.) = 2684, P = 0.0028. SU treatment at the time of admission was not a predictor of mortality (HR = 0.56, p = 0.224, Table 3, model 1) The three variables that were highly significant in the univariate analyses, became non significant (history of hypertension P = 0.089; duration of diabetes', P = 0.056, and highest blood glucose level, P = M63) in this model. A model 2 was fitted with MFN treatment as an independent variable with all other variables but not SU. The degree of fit for the second model was as follows LR X2, (13 df) = 4222, P = 0.0044. MFN treatment at the time of admission was not a predictor of mortality (HR = 0.69, p = 0.670, Table 3, model 2). Duration of diabetes, highest blood glucose level and history of hypertension became more significant in this model, on the basis of individual LR tests (P = 0.003, 0.001 and 0.010 respectively). In model 3 (Table 3) both 'SU and MFN treatment' was used as an independent variable with other variables. The degree of

fit for this model 3 was as follows LR'X2, (13 d.f.) = -4.522, P=0.021 SU and MFN treatment at the time of admission was not a predictor of mortality (HR = 232, p = 0.256, Table 3, model 3) History of hypertension became less significant in this model, on the basis of individual LR tests (P = 0.026) Similarly thrombolysis as an acute treatment given to patients at the time of admission was not a predictor of mortality (HR = 1.51, p = 0.702, Table 3, model 4).

Discussion

Our study was the first follow-up study for previously known diabetic patients with MI, conducted in Pakistan. Previously a cross-sectional survey was conducted by Hashim et al. 21 to determine the prevalence of macrovascular complications associated with diabetes and their relation with age, duration of diabetes and metabolic control IHD (198%; male (221%) females (175%)) associated with diabetes was the commonest complication in Wah Cantt, Rawalpindi (Pakistan) and the prevalence increase with increasing age Zarger et al 22 retrospectively studied the trends of mortality in diabetes in Kashmir Valley of India They collected data by screening the hospital records of all diabetic patients who were admitted to the hospital and died between 1987 and 1996. According to their findings the most common cause of death in diabetic patients was infections (33.8%), followed by chronic renal disease (30.9%), coronary artery disease (16.4%), cerebrovascular disease (13.7%), hypoglycaemia (7.8%), diabetic ketoacidosis (6.7%), and hyperosmolar coma (2.2%). No comparable data are available on the survival of previously known diabetic patients admitted to the hospital with an episode of MI in the developing region. Therefore its comparison with similar studies in the developing region is not possible but similar studies in the developed regions will be discussed. The study of mortality in diabetes is overwhelmed with many difficulties. Most epidemiological data are from countries with more advantaged healthcare and disease surveillance systems. Statistically evaluated and well-collected data from our country are scant. Impact of Diabetes and History of Hypertension on Survival in Myocardial Infarction Karlson and their colleagues²³ have reported a one- group prospective study involving patients with diabetes admitted to CCU with an episode of MI in Sweden. They recruited 427 patients with known diabetes who were admitted to the CCU with an episode of MI over the period of 21 months. Study patients were followed to relate the 1-year risk of death to whether they had a history of hypertension (44%) or not (56%). Their results showed that patients with diabetes and hypertension had a 1-year mortality rate of 22% as compared with 26% in diabetic patients without a history of hypertension (p>0.2). Therefore it was concluded that a history of hypertension does not affect the prognosis adversely among diabetic patients with MI. Our results differ from the findings reported by Karlson and colleagues. Our results demonstrated a higher mortality and poor survival of diabetic patients if they had a 'history of hypertension' (HR = 3.40, P = 0.001, multivariate analysis) at the time of admission. Our results are in positive agreement with the findings reported in another separate study by Karlson and their colleagues.²⁴ They also studied the relationship between hypertension and DM and their impact on the survival after myocardial infarction. They followed 1274, hypertensive patients prospectively, who were admitted to CCU, with MI between 1986 and 1987. One hundred and eighty-seven (15%) patients had a previous history of diabetes at the time

of admission to CCU. After one-year follow-up, mortality in hypertensive patients without diabetes was 16% whereas in hypertensive patients with diabetes mortality was 24% ($P < 0.5$, univariate analysis). Our study results also demonstrated that highest blood glucose level ($HR = 1.01$, $P = 0.065$, univariate Cox model) during hospital stay and blood urea levels ($HR = 1.02$, $P = 0.078$, univariate Cox model) at the time of admission were not predictors of poor survival in this cohort of diabetic patients with MI. Our results did not show a significant relationship between age, gender and duration of diabetes with poor survival or higher mortality. These findings could be due to a small sample size. To minimize the case definition problem, we only included diabetic patients who were on anti-diabetic treatment or who had diabetes for at least one-year's duration at the time of admission. To reduce the measurement error self-reporting of diabetes or diabetes with only diet restriction were not included. To reduce error from recording single measurements of blood glucose level, we used the highest blood glucose level recorded during patients' stay at the hospital. To reduce selection bias we used standard criteria for inclusion of subjects in our study. For myocardial infarction we used the WHO definition of MI (Methods section) used in the MONICA study.²⁰

To assess whether cases have been missed out due to misdiagnosis at presentation to Accident and Emergency/ Casualty and admitted to medical units rather than CCU, a retrospective check of medical wards admission was done. A total of 151 and 191 patients were admitted to Male 'Medical A' and Female 'Medical A' wards of LRH, during the months of April and May 2001, respectively. Of these 151 and 191 patients, only one patient was admitted to the ward with chest pain but not had diabetes. The error rate therefore does not seem to be very large. A number of strengths in the approach taken to this study can be highlighted, in addition to a number of factors, which may be judged as both strengths and possible limitations. Of major importance is the extent of data collection. The major issue was the location of the research (Peshawar, Pakistan) and collecting data prospectively (1-2 monthly) from the respective hospitals. The data extraction was undertaken by a single individual to ensure consistency in interpretation of the discharge summaries and case records (if needed) and also ensured that each record should be examined the same way. The strengths of our study are its prospective design, confirmed MI cases, confirmed diagnosis of DM for at least one or more years' duration and the relatively homogenous nature of the cohort which minimizes confounding by several variables, like access to medical care, educational attainment and socioeconomic status. The death certificates verified deaths, which occurred in the hospital, while those outside were from direct interview with relatives. The main limitation of this study, both as an internal feature and in terms of comparability with other studies, is its relatively small follow-up size. The majority of studies which have generated sufficiently large patient numbers and long follow-up are those which used Registry based data, and paradoxically, the main draw back here is the lack of comorbidity and baseline data in developing regions like Pakistan. Overall 28 (32.2%) patients were lost to follow-up, which could have an important effect on the results. The size of the follow-up was small as the method used for follow-up was door-to-door interview; logistically it was difficult and partly due to lack of complete addresses not available from the discharge summaries and records. Because of the size, most of the analysis performed and described in the results section which involved stratification of the data, the small number resulted in wide confidence intervals, which suggests a degree of uncertainty about the strength of

interpretation. The number of patients in three hospitals (CCU) differs, but this is partly explained by the greater capacity and catchment area of LRH (27; >45%) as compared to HMC (12; 20%). The number of patients successfully followed up over the study period (one-year) differs as well and this was partly due to an easy access to a well-defined housing estate covered by HMC catchment area (12; 100%) as compared to other hospitals. Other limitations include the use of self-reporting of subjects' health status as an outcome other than essential outcome (alive/ dead) and lack of data on glycemic control after their initial admission to CCU . However, tight control of glucose levels has not been conclusively documented to be associated with cardiovascular end-points results in either type 1 or type 2 diabetes.⁵ Our results may not be generalizable to the general population or for those patients with diabetes and an episode of MI, who could not afford hospital admission or could not reach in time to the CCU. However so far no observational (population-based) or experimental (like DIAGAMI trial to determine the survival in insulin treated diabetic patients) study has been done in this population to look for survival in patients with diabetes after an initial episode of MI. We did not collect data on certain variables like smoking history, physical activity, socioeconomic status, and body mass index (BMI, height, weight and hip- waist ratio). These parameters would be of value to look at their relationship with outcomes in patients with diabetes as they are closely associated with type 2 diabetes² and will have some effects on the health related outcomes in previously known diabetics with MI. The proportion of patients with diabetes presented with MI had almost equal distribution among three CCUs (14.5% at LRH, 13.2% at KTH and 13.4% at HMC). We assume that the rate of diabetic patients admission to CCUs with MI is relatively small as compared to glucose intolerance (diabetes and IGT) in both sexes in this region (21.4%).³ It may indicate that we have a higher rate of instant deaths (sudden) in diabetic patients with MI. We do not have information on case fatality before admission, and the risk of sudden cardiac death is known to be higher in the first few hours after coronary occlusion.²⁵ Our results therefore apply only to patients who survived long enough to reach hospital.

Conclusion

The information generated by this study has made an initial contribution to the research question of one-year survival of patients in Pakistan with previously known diabetes admitted to CCU with an episode of MI, and whether survival is different in a developing region as compared with developed regions. Differences in survival in our study appear to be most heavily influenced by the previous history of hypertension with diabetes and to some extent the duration of diabetes. Our study indicated poor survival in patients with diabetes with confirmed MI, in Peshawar (Pakistan), to which our local health services must respond, but that is not different from rate reported elsewhere. These findings support the need for aggressive primary and secondary prevention measures to be tested out in individuals and populations with diabetes, education about diabetes and hypertension, modification of behavioral risk factors, early diagnosis, effective glycaemic and blood pressure control are essential preventive measures. Primary and community health care professionals have a crucial role to play here. To reduce human costs associated with diabetes and hypertension, effective educational programmes and in

particular the future need for more large observational and experimental studies has to grow effectively.

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