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Short Communication

Silent myocardial infarction and its prognosis in a community-based cohort of Type 2 diabetic patients: the Fremantle Diabetes Study

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Abstract

Aims/hypothesis. Our study investigated the prognosis of Type 2 diabetic patients with silent myocardial infarction in a community-based cohort.
Methods. We analysed data from 1269 patients with Type 2 diabetes mellitus from a community-based observational study of diabetes care, control and complications. Silent myocardial infarction was defined as Q waves (Minnesota codes 1.1, 1.2) on a baseline electrocardiogram in the absence of a history or symptoms of CHD.
Results. Silent myocardial infarction was present in 3.9% of patients, or 44% of all Q-wave myocardial infarctions. The patients were subdivided into those with (i) no clinical or Q-wave evidence of myocardial infarction (Group 1), (ii) silent myocardial infarction (Group 2), (iii) self-reported CHD but no Q waves (Group 3), and (iv) self-reported CHD and Q waves (Group 4). Compared to Groups 3 and 4, Group 2 patients were more likely to be women, less likely to have smoked, and had higher serum HDL-cholesterol concentrations and higher blood pressure. Over an average of seven years, and after adjusting for other independent predictors of death, all-cause and CHD mortality were similar in Groups 1 and 2 and greater (twofold for all-cause and fourfold for CHD mortality) in Groups 3 and 4.
Conclusions/interpretation. Silent myocardial infarction is common in Type 2 diabetes and has a prognosis similar to that in patients without a history of CHD or Q waves. [Diabetologia (2004) 47:395–399]

Keywords Diabetes mellitus · Myocardial infarction · Silent · Electrocardiogram · Prognosis

In cross-sectional studies in the general population, 15 to 40% of patients with ECG evidence of past myocardial infarction (MI) do not give a history of typical cardiac symptoms [1, 2, 3]. Mortality rates in patients with such "silent" MIs have been reported as higher than, similar to, or lower than those in patients with known MI [1, 2, 3]. Although their numbers are relatively small and clinical details are often incomplete, diabetic patients included in population-based studies do not have an increased propensity to silent MI [4]. Thus, although various non-invasive and invasive tests (including coronary angiography) have been recommended in the assessment of diabetic patients at high risk of silent ischaemia even when the resting ECG is normal [5], there are no epidemiological data justifying such an approach. We therefore analysed data from a large, well-characterised, community-based cohort of patients to assess the prevalence, risk factors and prognosis of silent MI in patients with Type 2 diabetes.

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Abbreviations: MI, Myocardial infarction · FDS, Fremantle Diabetes Study · WA, Western Australia

Table 1. Comparison of patients with Type 2 diabetes in the four groups defined by self-reported CHD and Q-wave status

	Group 1	Group 2	Group 3	Group 4
Number	897	50	257	64
Age (years)[c]	62.6±11.5[e,f]	67.7±11.0	68.1±8.7	67.1±9.9
Sex (% male)[b]	47.5[f]	36.0[e,f]	53.7	62.5
Diabetes duration in years[c]	3.0 (0.9, 8.0)[e,f]	5.0 (1.0, 10.3)	5.0 (1.9, 11.0)	6.5 (2.6, 12.1)
BMI (kg/m^2)	29.7±5.6	29.1±5.6	29.4±4.9	29.2±5.0
Systolic blood pressure (mmHg)	150±24[d]	157±22	153±23	151±24
Diastolic blood pressure (mmHg)	81±11	83±9	79±12	81±10
Antihypertensive treatment (%)[c]	41.2[e,f]	56.0[e,f]	75.5	85.9
Postural hypotension (%)[a]	11.0	8.2	11.6	9.7
Fasting plasma glucose (mmol/l)[b]	8.3 (6.9, 10.6)[f]	8.4 (6.8, 11.4)	8.5 (6.8, 11.3)	9.3 (7.8, 11.7)
HbA_1c (%)[b]	7.3 (6.4, 8.6)[e,f]	7.9 (6.8, 9.2)	7.7 (6.6, 9.1)	8.4 (7.0, 9.2)
Total serum cholesterol (mmol/l)	5.4±1.1	5.5±1.0	5.5±1.2	5.4±1.0
Serum HDL-cholesterol (mmol/l)[b]	1.07±0.33[e]	1.12±0.30[e]	1.01±0.30	1.02±0.34
Serum triglycerides (mmol/l)	1.9 (1.1, 3.2)[e]	1.7 (1.1, 2.8)	2.0 (1.2, 3.6)	2.0 (1.2, 3.5)
Lipid-lowering treatment (%)[c]	7.7[e,f]	2.0[e,f]	20.3	15.6
Urinary albumin: creatinine >3.0 mg/mmol (%)[c]	37.5[e,f]	51.0	49.2	55.7
Neuropathy (%)[b]	29.3[e]	26.5	39.3	25.0
Retinopathy (%)	15.3	22.4	17.7	16.9
QT_c interval ($QT/\sqrt{(R\text{-}R)}$) ($sec^{0.5}$)	0.421±0.028[f]	0.408±0.025[f]	0.419±0.035[f]	0.436±0.128
Smoking				
Current (%)[b]	15.4	14.0	14.6	12.7
Ex (%)[b]	37.8	32.0	46.9	55.6
Never (%)[b]	46.8[e,f]	54.0[f]	38.6	31.7
Alcohol intake >3 standard drinks/day (%)	8.0	2.1	7.2	3.3
Exercise in the past 2 weeks (%)[b]				
Any	74.1[e]	66.0	65.1	75.0
None	25.8	34.0	34.9	25.0
Death (%)[c]				
All-cause	18.2[e,f]	26.0[e]	42.0	42.2
Cardiac	5.8[e,f]	10.0[e]	23.7	21.9

Diabetes duration, fasting plasma glucose and HbA_1c are reported as median (inter-quartile range), and serum triglycerides as geometric mean (SD range)

[a] >20 mmHg fall in systolic blood pressure on standing; [b] $p<0.05$, [c] $p<0.001$ by ANOVA, Kruskal-Wallis H-test or chi-square test; [d] $p<0.05$ vs Group 2; [e] $p<0.05$ vs Group 3; [f] $p<0.05$ vs Group 4

Subjects and methods

Subjects

The Fremantle Diabetes Study. This was a prospective observational study of diabetic patients from a postcode-defined community of 120,097 people in Fremantle, Western Australia (WA). The Fremantle Diabetes Study (FDS) protocol was approved by the Human Rights Committee, Fremantle Hospital. All patients gave informed consent prior to participation. We identified 2258 eligible subjects between 1993 and 1996, and recruited 1426 (63%) to annual assessments. The present sample comprised 1269 Type 2 diabetic patients. Identification and recruitment methods, sample characteristics including classification of diabetes, and details of non-recruited patients have been described elsewhere [6].

Clinical and laboratory methods

Baseline assessment. We recorded detailed patient data and did a full clinical examination. We also did biochemical tests on fasting blood and urine samples using standard automated methods [6]. Patients were classified as having known CHD if a self-reported history and/or symptoms of MI, angina, coronary artery bypass grafting or angioplasty were identified by standard questions asked by trained interviewers. Baseline ECGs were coded by a trained, independent observer using the Minnesota system [7]. We included codes 1.1 and 1.2 as indicative of definite or probable Q-wave MI and defined silent MI as a definite or probable Q-wave MI without a history or typical symptoms of CHD. We excluded minor Q-waves (1.3) and other ECG abnormalities not specific for CHD. Other vascular complications were classified as described previously [6].

Outcome variables. A government register records details of all deaths in WA and is part of the larger WA Health Services Research Linked Database. These sources provided all-cause and CHD mortality data from the beginning of the study until death or until the end of June 2002.

Data analysis

The data were analysed using SPSS for Windows (SPSS, Chicago, Ill., USA). Data are presented as proportions, means ± SD, geometric means (SD range) or, for non-normally dis-

Table 2. Multivariate predictors of mortality in patients with Type 2 diabetes using Cox proportional hazards regression analysis

	All-cause mortality		CHD mortality	
	HR (95% CI)[a]	*p* value	HR (95% CI)[a]	*p* value
Age (10 year increase)	2.16 (1.83–2.55)	<0.001	2.22 (1.74–2.83)	<0.001
Sex				
Female	1			
Male	1.67 (1.28–2.17)	<0.001		
BMI (1 kg/m^2 increase)	0.97 (0.94–1.00)	0.027		
Diastolic blood pressure (10 mmHg increase)			0.83 (0.71–0.98)	0.032
Ln (urinary albumin:creatinine)[b]	1.21 (1.12–1.31)	<0.001	1.19 (1.05–1.36)	0.008
Neuropathy				
No	1		1	
Yes	1.70 (1.30–2.21)	<0.001	1.89 (1.27–2.83)	0.002
Retinopathy				
No	1		1	
Yes	1.89 (1.41–2.52)	<0.001	2.11 (1.37–3.26)	0.001
Current smoking				
No	1			
Yes	1.47 (1.03–2.11)	0.034		
Exercise (%)				
None	1			
Any	0.64 (0.49–0.84)	0.001		
MI group				
Group 1	1		1	
Group 2	1.09 (0.58–2.03)	0.80	1.75 (0.69–4.48)	0.24
Group 3	1.91 (1.45–2.50)	<0.001	3.91 (2.60–5.89)	<0.001
Group 4	2.32 (1.47–3.65)	<0.001	4.23 (2.18–8.19)	<0.001

[a] HR, hazard ratio (95% confidence intervals). [b]A 2.72-fold increase in urinary albumin:creatinine corresponds to an increase of 1 in this line. MI, myocardial infarction

tributed variables, median (inter-quartile range). Two-sample comparisons were by Fisher's exact test, Student's *t* test, or Mann-Whitney *U* test. Multiple comparisons were by ANOVA or Kruskal-Wallis H test or chi-squared tests. A two-tailed level of significance of *p* equal to 0.05 was used. Cox proportional hazards modelling was used to identify predictors of all-cause and CHD mortality, with inclusion of variables that were significant at a *p* value of less than 0.2 in initial univariate analysis. Forward conditional modelling was used with *p* values for entry and removal criteria set at less than 0.05 and greater than 0.10 respectively.

Results

Baseline patient characteristics. The patients in this study had a mean age of 64.1±11.1 years, a median diabetes duration of 4.0 (1.0, 9.0) years and 49.2% were men. There were 114 patients with definite or probable Q-wave MIs (9.0% of the total cohort) and 50 of these MIs (43.9%) were silent. We defined four groups of patients: no history or symptoms of CHD, no ECG evidence of definite or probable MI (Group 1); silent MI (Group 2); self-reported CHD but no ECG evidence of MI (Group 3); and both self-reported CHD and ECG evidence of MI (Group 4; Table 1). Patients in Groups 2, 3 and 4 had similar age and diabetes duration, whilst those in Group 1 were the youngest and most recently diagnosed. Group 2 had the greatest proportion of women. Patients in Group 2 tended to have the highest blood pressures, but also the highest serum HDL-cholesterol and the lowest serum triglyceride concentrations. Group 2 patients were also the least likely to have ever smoked. For unadjusted all-cause and CHD mortality, Group 2 patients had rates that were similar to those in Group 1 but which were greater than those in Group 4.

Silent MI and outcome. The average follow-up was 7.0 years (range 0.1–9.2 years), representing 8916 patient-years. There were 312 deaths (24.6% of the sample) during this period. Deaths from CHD (132) comprised 42.3% of all-cause mortality. We had complete baseline data on 253 (81%) of all deaths (112 of which were from CHD). Most deaths excluded from analysis had incomplete ascertainment of neuropathy and/or retinopathy. Removal of these variables from analyses increased subject numbers but did not affect overall results.

Variables associated with all-cause mortality in univariate analysis were greater age, male sex, single marital status, only primary school education, longer diabetes duration, lower BMI, higher systolic blood pressure, taking antihypertensive medication, not taking lipid-lowering therapy, greater serum creatinine and microalbuminuria, retinopathy, neuropathy, having smoked, no regular exercise and MI group ($p \leq 0.046$). In a Cox proportional hazards model, age, sex, BMI, microangiopathy, exercise, current smoking and MI group remained (Table 2). There was no significant interaction between sex and MI group. Patients in Group 2 were no more likely to die than those in Group 1. Patients in Groups 3 and 4 were twice as likely to die as those in Group 1.

There were univariate associations between CHD death and greater age, single marital status, longer diabetes duration, lower BMI, higher systolic blood pressure, taking antihypertensive medication, greater HbA_1c, microvascular complications, no regular exercise and MI group ($p \leq 0.037$). In a Cox model, age, diastolic blood pressure, microvascular complications and MI group remained (Table 2). There was no interaction between sex and MI group. Patients in Group 2 were no more likely to die from CHD than those Group 1, while patients in Groups 3 and 4 were approximately four times as likely to die as those in Group 1.

Discussion

Using the comprehensive FDS database, this large study of the association between diabetes and silent MI found that nearly half of our patients with ECG evidence of a transmural MI were unaware of its occurrence. This proportion is greater than in the general population, with most studies reporting that 40% or less of MIs are silent [1, 2, 3]. As in previous smaller scale studies [8, 9], our diabetic patients with silent MI were more likely to be women and hypertensive. They were also less likely to have smoked and more likely to have had favourable serum lipid profiles. After adjustment for major vascular risk factors and other predictors of death, the prognosis in the silent MI group was significantly better than for Type 2 diabetic patients with known CHD.

Although smoking was a risk factor for silent MI in population-based studies [1], this was not so in our cohort. This could reflect the relatively small proportion of current smokers (15%), but current smoking was an independent predictor of all-cause mortality. Our Group 2 patients had higher serum HDL-cholesterol concentrations than those in Groups 3 and 4, and treatment for dyslipidaemia was less frequent, but why these factors were associated with atypical presentation of MI is unclear. Microalbuminuria has not usually been included in analyses of factors predictive of silent MI, but was as common in Group 2 patients as in Groups 3 and 4, which is consistent with its strong independent association with CHD.

The previously reported association between autonomic neuropathy and silent MI was questioned in a recent review [4]. We found no association between postural blood pressure changes, the corrected electrocardiographic QT interval and silent MI, while peripheral sensory neuropathy and other microvascular complications were no more frequent in Group 2 than in the other groups. The mechanisms underlying unrecognised ischaemia in diabetes remain controversial [4]. If autonomic neuropathy is contributory, the phenotype of our Group 2 patients suggests that it could be one of a number of factors.

All-cause mortality in our Group 2 patients was similar to that in Group 1 after adjustment for other risk factors, and less than half that in the patients with symptomatic CHD. For CHD death, the pattern was similar, albeit with wider confidence intervals due to the smaller number of endpoints. The prognosis of silent MI in Type 2 diabetes has not been investigated previously. Studies in the general population yielded varying results. In the Honolulu Heart Program [2], mortality rates were 1.5 to 1.7 times higher in silent than in clinically evident MIs. An Israeli study showed that the 7-year mortality associated with clinical MIs was more than four times that in the silent MI group [1]. In another study [3], silent and clinical MI had the same all-cause mortality. These heterogeneous results might reflect differences in study design and methods of analysis, but genetic and environmental factors could have played key roles.

Major Q waves are an important marker of unrecognised cardiac disease [10] but the limitations of using only a resting ECG in CHD classification have been acknowledged [1, 9]. Coding errors can also confound analysis of ECG data. Echocardiography, exercise ECGs and other more invasive cardiac investigations would have provided valuable additional data in our study. However, its relatively large scale and community-based nature meant that results of such tests were not consistently available, even in patients with known CHD.

Although we do not suggest that risk factor modification and further cardiac investigation are less important for Type 2 diabetic patients with unrecognised MI than for those with known MI, the prognosis in the former group appears as good as in patients with neither ECG nor clinical evidence of CHD. Because this relatively favourable outlook remained after adjustment for conventional CHD risk factors, there could be other as yet unidentified but important influences on diabetes-associated macrovascular disease.

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