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Long-term predictors of coronary artery disease and mortality in type 1 diabetes

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Summary

We assessed clinical and biochemical predictors of death and/or cardiovascular disease in 147 type 1 diabetes mellitus (DM) patients followed-up for 14 years. At follow-up, 28 of patients (19%) had died, and 25 patients (18%) had developed or died of coronary artery disease (CAD). At baseline, those who died had significantly higher serum creatinine ($p = 0.001$) and urine albumin/creatinine ratio ($p = 0.016$), greater prevalence of retinopathy ($p = 0.006$), lower serum apolipoprotein A1 ($p = 0.046$), and lower daily insulin dose ($p = 0.024$) than those who survived. CAD patients had a longer duration of diabetes ($p < 0.001$), were older at the onset of diabetes and at presentation ($p = 0.001$), and had higher prevalences of retinopathy ($p = 0.005$) and neuropathy ($p = 0.016$). The CAD group also had higher baseline serum creatinine ($p = 0.02$), lower HDL cholesterol ($p = 0.004$) and apolipoprotein A1 ($p = 0.007$) and higher LDL cholesterol ($p = 0.028$) and apolipoprotein B concentrations ($p = 0.027$). Under logistic regression analysis (adjusted for age and sex), baseline urine albumin/creatinine ratio ($p = 0.003$), presence of retinopathy ($p = 0.004$), serum creatinine ($p = 0.028$), and serum urea ($p = 0.034$) were the most powerful predictors of mortality, while duration of diabetes ($p < 0.0001$), baseline HDL cholesterol ($p = 0.012$), serum creatinine ($p = 0.02$), apolipoprotein B ($p = 0.038$), LDL cholesterol ($p = 0.039$), and systolic blood pressure ($p = 0.055$) were the strongest predictors of CAD. These findings emphasize the role of abnormal lipoprotein metabolism in the development of CAD in type 1 DM. Indicators of renal impairment and the presence of retinopathy seem to be of greater importance in predicting overall mortality.

Introduction

Although the prognosis of type 1 diabetes mellitus (DM) has improved considerably over the last 50 years, it still exceeds that of the general population. This has been highlighted in the recent BDA cohort and in other studies.[1–6] In younger type 1 DM patients, acute complications such as hypoglycaemia and ketoacidosis are the main causes of death,[1–3] while renal and cardiovascular disease are responsible for the majority of deaths in the older population.[1–6] Although it is well known that early mortality in type 1 DM patients is considerably increased, especially in patients with evidence of incipient or established nephropathy,[4,6–10] the precise metabolic abnormalities responsible for this increased risk are still poorly understood. Interventions to reduce early mortality could be assisted by more precise knowledge concerning predictors of mortality and cardiovascular disease, allowing a more focussed approach to intervention-based research and treatment.

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To examine the factors determining the progression of diabetic complications, we set up a prospective cohort study of DM patients in 1984 and investigated the cohort initially cross-sectionally and then prospectively after 4 and 10 years.[11–17] Baseline urine albumin/creatinine ratio and glycosylated haemoglobin (HbA1), smoking habits, treatment for hypertension and a history of hospital admission predicted the development of microalbuminuria.[11,12] Serum HDL concentration was lower and the LDL : HDL cholesterol ratio higher in the microalbuminuric group,[13] and the increase in albuminuria was correlated with baseline total serum cholesterol, LDL cholesterol and apolipoprotein B (apo B),[14] suggesting that an abnormal metabolism of apo B may be independently associated with the progression of albuminuria. Microalbuminuric type 1 DM patients had significantly higher fat and lower carbohydrate intake than a matched control group.[15] Stress testing on a treadmill predicted the development of microalbuminuria with a sensitivity of 80%,[16] and sialic acid, a marker for cardiovascular disease, was associated with both retinopathy and nephropathy.[17] Overall, these findings suggested a strong link between abnormal lipid metabolism and the development of microalbuminuria, a known risk factor for CAD and total mortality in the diabetic population.

The aim of this particular study was to investigate predictors of cardiovascular morbidity and total mortality in this cohort of well defined type 1 diabetic patients. Our hypothesis was that the factors we had previously identified as predicting microalbuminuria might also predict cardiovascular disease and death.

Methods

We recruited 172 patients with type 1 DM from the out-patient clinics of Portsmouth hospitals in 1984, with a view to setting up an observational study investigating the development of early diabetic complications. There was a deliberate selection policy for patients with a duration of diabetes of 5–20 years. Details of the cohort of patients have been published elsewhere.[11,12]

Exclusion criteria comprised a supine blood pressure $>160/95$ mmHg or current use of antihypertensive medication, serum creatinine >120 μmol/l, urine dipstix positive for protein, and any chronic disease other than diabetes which could potentially confound study findings.

At entry into the study, patients underwent a routine physical examination. Blood pressure was measured after 5 min rest in the supine position. Ankle reflexes were recorded as present or absent. Peripheral vascular disease was diagnosed by the absence of both pedal pulses or from a careful history presence of intermittent claudication. Retinopathy was graded through dilated pupils (1% tropicamide) as nil, mild background (occasional microaneurysm), moderate-severe background (conspicuous microaneurysms, haemorrhages/exudates), and proliferative (new vessels/vitreous haemorrhages).

Laboratory measurements

Venous blood was obtained before the morning dose of insulin, after at least an 8-h fast for estimation of blood glucose, creatinine, lipid, lipoprotein and glycated haemoglobin concentrations at entry into the study.

Early morning urine samples were tested for protein using Labstix (Ames Division). Urinary albumin concentration was determined by radioimmunoassay; inter-assay coefficient of variations (CV) was $<9\%$. Urinary creatinine was by an endpoint Jaffe reaction, with an inter assay coefficient of $<6\%$. Plasma glucose was measured on the Yellow Springs Analyser (Clandon Scientific). After removal of the 'labile fraction', glycated haemoglobin (HbA1) was measured by an electroendosmotic method using agar gel electrophoresis (Corning Medical), inter-assay coefficient of variation of $<4\%$. Serum creatinine was measured on the SMAC-II Analyser (Technicon). Genotyping of angiotensin-converting enzyme I/D polymorphism was carried out on DNA isolated from whole blood by using the 'salting out' procedure. The I/D polymorphism in intron 16 of the angiotensin-converting enzyme gene was detected by amplification of the polymerase chain reaction and analysis of the resulting fragment by agarose gel electrophoresis.[18] Serum cholesterol and triglycerides were assayed enzymatically with commercial test kits (Boehringer). Mean interassay CVs were as follows: cholesterol, 2.8% at 2.5 mmol/l and 3.6% at 8.9 mmol/l; triglycerides, 3.0% at 1.8 mmol/l and 2.8% at 3.0 mmol/l. High-density lipoprotein (HDL) was isolated after precipitation of apo-B containing lipoproteins by $MnCl_2$ and heparin, with excess Mn^{2+} chelated by Na_2 EDTA before the cholesterol assay. Low-density-lipoprotein cholesterol (LDL) was calculated by the Friedewald formula[19] except in patients with serum triglycerides >4.0 mmol/l, where LDL cholesterol level was measured directly after ultracentrifugation of plasma at a density of 1.019–1.063 g/ml. Serum concentrations of apolipoprotein A1 (apo A1) and apolipoprotein B (apo B) were determined by immunoturbidimetry.[20] Mean interassay CVs

were: apo A1, 3.5% at 0.72 g/l and 2.6% at 2.22 g/l; and apo B, 3.3% at 0.55 g/l and 3.3% at 1.53 g/l.

The cohort was followed over a 14-year period. Detailed examinations were done at 4 and 10 years, and these have been published elsewhere.[11–17] After 14 years, 147 patients were followed-up, at which time clinical details were ascertained with specific reference to presence of CAD. Patients that had moved out of the area were retrieved through the Office of National Statistics. Information about these patients was obtained from General Practitioner's records. Seven of the original 172 patients were untraceable through the Office of National Statistics, and eighteen were known to be alive, but no further information was obtainable. The diagnosis of CAD was established clinically using the Rose questionnaire[21] or electrocardiologically using Minnesota-coded 12-lead ECGs. Where patients had died, cause of death was ascertained from death certificates, hospital notes or postmortem examinations where available.

The study received local Ethics Committee approval.

Table 1 Baseline data for 147 type 1 diabetic patients

Age (years)	32.3 (±11.9)
Male : female	82 : 65
Age at onset of DM (years)	15.1 (±8.8)
Duration of DM (years)	16.8 (±9.2)
BMI (kg/m^2)	24.0 (±3.6)
Smoking (% of patients)	19%
Retinopathy (% of patients)	9.5%
Insulin dose (units/day)	53.5 (±21.1)
Systolic blood pressure (mmHg)	128.3 (±15.7)
Diastolic blood pressure (mmHg)	76.9 (±7.6)
Glucose (mmol/l)	12.2 (±7.6)
HbA1 (%) (normal <7.5%)	10.8 (±2.4)
Serum creatinine (μmol/l)	77.6 (±1.3)
Urine albumin/creatinine ratio (mg/mmol)*	1.7 (1.4–2.2)
Serum cholesterol (mmol/l)	5.4 (±0.9)
Serum LDL cholesterol (mmol/l)	3.6 (±0.9)
Serum HDL cholesterol (mmol/l)	1.18 (±0.43)
Serum triglycerides (mmol/l)*	1.76 (1.24–2.49)
Serum apolipoprotein B (g/l)	1.00 (±0.20)
Serum apolipoprotein A1 (g/l)	1.44 (±0.28)

Data are means (±SD) except *geometrical mean (95%CI).

Statistical analysis

Variables that were not normally distributed were logarithmically transformed and are defined by the geometrical mean plus 95%CI. Categorical data were defined as binary variables. The baseline variables in the groups of patients who died or had evidence of CAD were compared with the alive and CAD-free groups by using the Mann–Whitney or Fisher's two-sided exact test. Logistic regression models were used to examine which baseline variable (explanatory variables) predicted the death (all cause mortality) or CAD (cardiovascular death or alive with CAD) (=the outcome variable). The models used included those baseline variables which showed significant association with total mortality or CAD in univariate logistic regression analysis or which were a priori considered to be potentially important predictors of death or CAD. To avoid the problems of multicolinearity, independent variables included in the same model showed correlation coefficients with each other of <0.4. Results of logistic models are presented as odds ratios that relate to a change of one unit in the predictor variable. A p value of 0.05 or less was considered statistically significant.

Results

Data were available for 147 (85%) of the 172 patients after 14 years. Characteristics of the patients lost to follow-up were not significantly different from the ones followed-up. One hundred and nineteen (81%) patients were alive and 28 (19%) patients had died over the 14 years. Ten patients had died of cardiovascular disease, three of renal failure, four of chest-related infections, and two of cancer. Two patients had committed suicide, and seven had other non-diabetic/vascular causes of death.

Table 1 summarizes the baseline characteristics of the 147 patients included in the study. On average, this was a young cohort of type 1 DM patients with a relatively long duration of diabetes at study entry. The population was not overweight, and was normotensive. Nearly 10% of the patients had established retinopathy, but none had macroalbuminuria.

All-cause mortality

Baseline characteristics of the patients who died are summarized in Table 2. Patients who died were older at entry in the study, and more likely to be female. At baseline, they had a higher rate of microvascular complications, in particular retinopathy, and elevated albumin/creatinine ratio and serum creatinine. Although HbA1 and serum glucose concentrations were similar in both groups, patients still alive were on a higher baseline daily insulin dose. Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein B

Table 2 Comparison of baseline characteristics of those patients alive or dead (all causes)

	Alive ($n = 119$)	Dead ($n = 28$)	p
Age (years)	30.7 (±11.7)	36.8 (±13.1)	0.238
Male : female	71 : 48	11 : 17	0.041
Age at onset of DM (years)	14.5 (±8.6)	17.3 (±13.1)	0.131
Duration of diabetes (years)	16.2 (±9.0)	19.5 (±9.8)	0.081
BMI (kg/m^2)	24.2 (±3.6)	23.3 (±3.8)	0.268
Smoking (*n*, % of patients)	26 (21.8%)	2 (7.1%)	0.057
Retinopathy (*n*, % of patients)	7 (5.9%)	7 (25.0%)	0.006
Neuropathy (*n*, % of patients)	23 (22.5%)	3 (33%)	0.353
Insulin dose (units/day)	57.5 (±1.7)	48.1 (±4.1)	0.024
Systolic blood pressure (mmHg)	127.5 (±1.4)	131.5 (±3.3)	0.239
Diastolic blood pressure (mmHg)	76.7 (±0.0)	77.5 (±1.3)	0.626
Serum glucose (mmol/l)	12.5 (±7.8)	11.4 (±5.5)	0.486
HbA1c (%) (normal <7.5%)	10.7 (±2.6)	11.1 (±1.3)	0.482
Serum creatinine (μmol/l)	76.8 (±1.4)	81.0 (±2.9)	0.001
Urine albumin/creatinine ratio (mg/mmol)*	1.8 (1.4–2.4)	3.6 (2.0–6.4)	0.016
Serum cholesterol (mmol/l)	5.4 (±1.0)	5.2 (±0.7)	0.453
Serum LDL cholesterol (mmol/l)	3.32 (±0.13)	3.69 (±0.26)	0.257
Serum HDL cholesterol (mmol/l)	1.19 (±0.5)	1.07 (±0.15)	0.382
Serum triglycerides (mmol/l)*	1.89 (1.28–2.8)	1.17 (0.6–2.2)	0.333
Serum apolipoprotein B (g/l)	1.0 (±0.2)	1.02 (±0.2)	0.734
Serum apolipoprotein A1 (g/l)	1.46 (±0.22)	1.28 (±0.47)	0.046
ACE genotype (II : ID : DD)	23 : 50 : 29	2 : 2 : 5	0.196

Data are means (±SD) except * geometrical mean (95%CI).

concentration, age at onset of diabetes, duration of diabetes, body mass index, smoking or blood pressure measurements did not differ between the two groups. Mean apolipoprotein A1 concentration, however, was lower in those who died.

Under univariate logistic regression analysis, urine albumin/creatinine ratio, retinopathy, creatinine and serum urea predicted total mortality (Table 3). In multivariate models (adjusted for age and sex), retinopathy was the only independent predictor of all-cause mortality (OR 5.66, 95%CI 1.00–32.00).

Table 3 Logistic regression models examining predictors of total mortality in patients with type 1 diabetes (adjusted for age and sex with separate models for each predictor variable)

Predictor variable	Odds ratio (95%CI)	p
Urine albumin/ creatinine ratio	2.67 (1.12–6.41)	0.003
Retinopathy	5.33 (1.69–16.78)	0.004
Serum creatinine (μmol/l)	1.012 (1.01–1.05)	0.028
Serum urea	1.13 (1.01–1.27)	0.034

Cardiovascular disease and cardiovascular death

Baseline characteristics of those patients who subsequently suffered from or died of coronary artery disease (CAD group) are summarized in Table 4. Lower serum HDL, apolipoprotein A1, high LDL and apolipoprotein B and raised serum creatinine concentrations and urine albumin/creatinine ratio were seen in the CAD group. This group had a higher rate of microvascular complications (retinopathy and neuropathy). Moreover the CAD group developed diabetes at a later age, and had a longer duration of diabetes. There was no difference in the rate of CAD between men and women. Both groups were of similar age and weight, were receiving a similar insulin dose and had similar glycaemic control and smoking habits.

Univariate logistic regression models revealed that duration of diabetes, serum HDL cholesterol, creatinine concentration, apolipoprotein A1, LDL cholesterol and systolic blood pressure predicted CAD (Table 5). In multivariate models (adjusted for age and sex), duration of diabetes (OR 1.15, 95%CI 1.00–1.34) and serum creatinine (OR 1.09, 95%CI 1.01–1.18) remained independent predictors of cardiovascular disease.

Discussion

The principal findings of this long-term prospective study are that abnormal lipoprotein metabolism,

Table 4 Comparison of baseline characteristics of patients alive without cardiovascular disease and those alive with cardiovascular disease or cardiovascular death

	Alive, no CAD ($n = 112$)	CAD (or CAD death) ($n = 25$)	p
Age (years)	29.7 (±11.4)	41.5 (±11.0)	0.222
Male : female	61 : 51	15 : 10	0.391
Age at onset of diabetes (years)	14.6 (±8.7)	17.0 (±8.5)	0.001
Duration of diabetes (years)	15.1 (±8.2)	24.5 (±9.7)	<0.001
BMI (kg/m^2)	23.9 (±3.5)	25.2 (±3.9)	0.102
Smoking (*n*, % of patients)	23 (21.5%)	5 (20.0%)	0.558
Retinopathy (*n*, % of patients)	5 (4.5%)	6 (24%)	0.005
Neuropathy (*n*, % of patients)	17 (18.7%)	7 (50%)	0.016
Insulin dose (units/day)	56.0 (±20.0)	56.0 (±19.2)	0.998
Systolic blood pressure (mmHg)	127.2 (±15.4)	133.9 (±15.7)	0.052
Diastolic blood pressure (mmHg)	76.7 (±7.6)	78.2 (±6.6)	0.375
Serum glucose (mmol/l)	12.7 (±7.6)	9.7 (±5.8)	0.068
HbA1 (%) (normal <7.5%)	10.8 (±2.5)	10.2 (±1.3)	0.218
Serum creatinine (μmol/l)	76.2 (±1.3)	79.8 (±3.3)	0.020
Urine albumin/creatinine ratio (mg/mmol)*	1.83 (1.4–2.5)	2.54 (1.3–5.0)	0.380
Serum cholesterol (mmol/l)	5.35(±0.96)	5.42 (±0.78)	0.844
Serum LDL cholesterol (mmol/l)	3.35 (±0.06)	4.15 (±1.3)	0.028
Serum HDL cholesterol (mmol/l)	1.25 (±0.41)	0.78 (±0.38)	0.004
Serum triglycerides (mmol/l)*	1.67 (1.1–2.5)	1.71 (0.9–3.1)	0.960
Serum apolipoprotein B (g/l)	0.98 (±0.19)	1.14 (±0.16)	0.027
Serum apolipoprotein A1 (g/l)	1.47 (±0.23)	1.18 (±0.5)	0.007
ACE genotype (II : ID : DD)	20 : 45 : 26	3 : 7 : 4	0.979

Data are means (±SD) except * geometrical mean (95%CI).

Table 5 Logistic regression models examining significant predictors of cardiovascular morbidity or death in the patients with type 1 diabetes (adjusted for age and sex, with separate models for each predictor variable)

Predictor variable	Odds ratio (95%CI)	p
Duration of diabetes (years)	1.12 (1.06–1.19)	<0.0001
HDL cholesterol (mmol/l)	0.04 (0.003–0.49)	0.012
Serum creatinine (μmol/l)	1.01 (1.00–1.03)	0.024
Apolipoprotein B (g/l)	65.5 (1.26–330.9)	0.038
LDL cholesterol (g/l)	2.67 (1.05–6.76)	0.039
Systolic blood pressure (mmHg)	1.03 (1.0–1.06)	0.055

duration of diabetes, the presence of retinopathy and renal impairment predict cardiovascular disease or death in patients with type 1 diabetes. Measurements of blood pressure, renal function and plasma lipid concentrations that at the onset of the study were considered to be within the accepted reference range, were independently associated with an increase in mortality and CAD. This observation supports the concept of vigorous intervention to modify these risk factors. Moreover, our findings suggest that measurement of total cholesterol and apolipoprotein B concentrations in isolation is an inadequate indication of coronary risk, and emphasizes the importance of measuring HDL cholesterol concentration.

The strength of this study, compared with previous reports on vascular morbidity and death in type 1 diabetes is the long follow-up period of 14 years, a more detailed biochemical profile including lipoproteins and apolipoproteins at entry into the study in a well-defined group and a cohort that is typical of the type 1 diabetic population. However, the relatively small sample size and selection bias are potential limitations. This study was not designed to investigate specific interventions and the cohort was treated with the routine use of anti-hypertensive and lipid-lowering medication according to local policies. The diagnosis of CAD was made by using a validated (Rose) questionnaire 21 and a standard 12-lead ECG,

although coronary angiography would have been preferable.

There are limited data examining the longitudinal association between dyslipidaemia and CAD in type 1 diabetes. HDL cholesterol and triglyceride concentrations predicted CAD in a study of type 1 DM subjects.[22] However, the authors followed their cohort for a relatively short period of time (4 years). In cross-sectional studies, lower HDL cholesterol and apolipoprotein A1 concentrations have been observed in some[23–25] but not in other studies.[26] None of these studies investigated predictive markers of CAD, thereby reducing statistical power and interpretation, and three of the four studies consisted of a fairly small sample size of 40–78 DM patients.[23,24] The mechanism of cardiovascular protection may relate both to an involvement of HDL in plasma cholesterol transport and to a range of non-lipid transport functions of HDL.[2]

Abnormalities in lipoprotein metabolism in established diabetic nephropathy have been described previously.[7,13,28–30] The increase in albuminuria was related to baseline serum concentrations of total cholesterol, LDL cholesterol and apo B. Moreover, apo B independently predicted the progression of albuminuria.[13] Only one longitudinal study has previously investigated the role of lipids and macrovascular complications in type 1 diabetes. A large cohort of more than 3000 patients was followed up over a 10-year period.[8] Total cholesterol was a predictor for total mortality, and even though they assessed their patients for end-stage diabetic complications (by means of a questionnaire), they did not investigate predictors of CAD, nor were lipoproteins measured.

We have confirmed that renal function predicts early mortality. Specifically, albumin creatinine ratios and serum creatinine concentrations were predictors of overall mortality. This finding is not unexpected, and confirms the observation of other investigators; however other confounding factors such as serum lipid concentrations were not measured in these previous studies.[4–10] Although these previous studies[4,7] followed their cohorts for more than 20 and 5 years, respectively, they examined biochemical and biophysical risk factors in a cross-sectional approach rather than longitudinally which weakened statistical interpretation. The underlying mechanism leading to increased cardiovascular mortality in the nephropathic DM patients may be generalized vascular dysfunction affecting the glomeruli, the retina and intima of large vessels simultaneously.[31–33]

In our cohort, systolic hypertension preceded CAD. This has also been observed in other studies.[3,5,9,10,25,31–35] Systolic hypertension increases cardiovascular mortality 3.5-fold in men and 2.5-fold in women, compared to normotensive patients.[33] In type 1 DM, hypertension seems to be integrally linked to nephropathy.[5,7] Once microalbuminuria or proteinuria is present, higher systolic blood pressures have been observed and this group has a marked higher rate of CAD and total mortality.[7]

We observed that diabetic microvascular complications, particularly retinopathy, predicted cardiovascular disease and death. Similar results have been described previously,[3,32] although they were not confirmed in another study.[4] In this last study, half of the patients were assessed via a questionnaire and the presence of retinopathy may have been underestimated. Preliminary results suggest that retinopathy may be a sensitive marker for generalized endothelial dysfunction which increases susceptibility to CAD.[36] In this study we measured reactive hyperaemic blood flow responses in the forearm in a group of DM patients with varying degrees of retinopathy, and observed that retinopathy was the only independent correlate of reactive hyperaemia.

In the general population, male sex is a strong predictor for CAD, but in the diabetic population, females are equally affected.[3,4,10] The mechanism behind this observation is not clear. Smoking is a strong risk factor for CAD, but in our cohort there was a smaller proportion of smokers in the group that later developed CAD. In the type 1 diabetic population, the impact of smoking on CAD and death has similarly been conflicting.[31,37]

The deletion polymorphism in the gene for angiotensin-converting enzyme is a risk factor for CAD in the general population.[38] In our cohort, we were previously unable to show any relation of genotype for angiotensin-converting enzyme with the development of microalbuminuria.[12] This might have been due to small sample size (only eight developed microalbuminuria). Even though glycaemic control predicted the development of microalbuminuria in our cohort,[12] there was no statistically significant relationship between initial HbA1 and the development of CAD. Since this was an observational study, many factors, such as attitudes towards the optimization of normoglycaemia, have changed over 14 years of follow-up, and the initial HbA1 may not be an adequate measurement of glycaemic control over these years.

In summary, reversible or modifiable risk factors such as dyslipidaemia, renal impairment and systolic hypertension are integrally linked to the risk of cardiovascular mortality and death in type 1 diabetes. Interventional studies are required to specifically examine in type 1 diabetes whether treatment aimed at specifically improving these

variables (in isolation or synergistically) at an early stage can alter the natural history of events.

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