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Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in Type 2 (non-insulin-dependent) diabetic and non-diabetic subjects

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Summary. The purpose of the present study was to examine 10-year cardiovascular morbidity and mortality in patients with newly-diagnosed Type 2 (non-insulin-dependent) diabetes mellitus and non-diabetic control subjects and to evaluate the effects of general risk factors, plasma insulin, urinary albumin excretion, lipoprotein abnormalities characteristic of Type 2 diabetes and the degree of hyperglycaemia in diabetic patients on cardiovascular mortality. Furthermore, the extent to which the above-mentioned factors could contribute to the excessive cardiovascular mortality observed in diabetic patients was examined. In the years 1979–1981, altogether 133 (70 men, 63 women) newly-diagnosed patients with Type 2 diabetes and 144 (62 men, 82 women) non-diabetic control subjects aged 45–64 years were studied. Both groups were re-examined in the years 1985–1986 and 1991–1992. The impact of different factors on cardiovascular mortality was examined by univariate analyses after adjustment for age and sex and by multiple logistic regression analyses. The age-standardized total and cardiovascular mortality rates were substantially higher in diabetic men (17.8 and 15.0%, total and cardiovascular mortality, respectively $p = 0.06$ and NS) and women (18.5 and 16.6%, $p < 0.01$ for both) than in non-diabetic control men (5.2% both total and cardiovascular mortality) and women (4.2 and 2.2%). Cardiovascular mortality was not related to the treatment modality (diet, oral drugs, insulin) at 5 years from diagnosis. Use of diuretics, beta-blocking agents or their combination at baseline did not make a significant contribution to cardiovascular mortality either. In multiple logistic regression analysis on diabetic patients, age, LDL triglycerides, smoking, blood glucose and ischaemic ECG at baseline had independent associations with cardiovascular mortality. Interestingly, urinary albumin excretion rate measured at 5-year examination also predicted 10-year cardiovascular mortality after adjustment for the effects of major risk factors including lipoprotein abnormalities, but its predictive power reduced to a non-significant level when the effect of plasma glucose was taken into account. The relative risk of cardiovascular mortality associated with diabetes was 8.2 after allowing for age alone, but it declined to 3.7 when all contributing factors from the baseline examination (except blood glucose) were taken into account. In conclusion, the present results indicate that LDL triglycerides and/or other changes in lipoprotein composition characteristic of Type 2 diabetes and manifesting as elevated serum triglycerides are atherogenic and they strongly predict increased cardiovascular mortality. Furthermore, it is hypothesized that the consequences of long-term hyperglycaemia could explain a large proportion of the remaining excessive cardiovascular mortality risk among Type 2 diabetic patients.

Key words: Cardiovascular disease, lipoprotein abnormalities, risk factors, albuminuria, insulin, mortality, diabetes mellitus.

Prospective population-based studies indicate that various manifestations of cardiovascular disease, including mortality from coronary heart disease (CHD), are substantially more common in diabetic patients than in the non-diabetic population [1–5]. This applies to both Type 1 (insulin-dependent) [6–7] and Type 2 (non-insulin-dependent) diabetic patients [1–5], even though most studies have dealt with Type 2 diabetes or no clear distinction has been made regarding the type of diabetes [8]. Only a small proportion of the excess occurrence of cardiovascular disease can be explained by the effects of diabetes on general risk factors of cardiovascular disease [8, 9]. Therefore, other factors associated with diabetes must be involved. These include hyperglycaemia and its consequences [8, 10], altered composition and metabolism of lipoproteins [11–13], and high plasma insulin level [14] or insulin resistance [15]. No previous prospective studies have been performed to explore the effects of lipoprotein abnormalities, characteristic of Type 2 diabetes, on cardiovascular mortality and incidence of myocardial infarction in patients

Table 1. Formation of study population and cardiovascular morbidity and mortality during 10-year follow-up period in diabetic and non-diabetic control subjects

Subject characteristics	Men			Women		
	Diabetic	Control	*p*	Diabetic	Control	*p*
Original study population *(n)*	70	62		63	82	
Age (mean ± SD years)	54.8 ± 5.7	52.9 ± 5.1	0.05	57.1 ± 5.1	54.3 ± 5.6	0.01
Deaths during 10-year follow-up *(n)*	20 (28.6%) [17.8%][a]	3 (4.8%) [5.2%][a]	0.06	16 (25.4%) [18.5%][a]	5 (6.4%) [4.2%][a]	0.01
Refused to participate in follow-up study *(n)*	2	1		3	7	
Study population at 10-year re-examination *(n)*	48	58		44	70	
Age (mean ± SD years)	65.6 ± 5.9	65.2 ± 5.2	NS	68.9 ± 5.2	66.2 ± 5.7	NS
Prevalence or incidence; n (%)						
Prevalence of myocardial infarction at baseline	13/70 (16.5)[a]	5/62 (9.7)[a]	NS	11/63 (17.7)[a]	4/82 (4.0)[a]	0.007
Cardiovascular mortality						
Total	16 (14.6)[a]	3 (5.2)[a]	NS	12 (16.6)[a]	1 (2.2)[a]	0.01
Coronary heart disease	14	2		6	0	
Stroke	2	1		5	0	
Other	0	0		1	1	
Incidence of first myocardial infarction[b]	18 (27.3)[a]	9 (19.2)[a]	NS	14 (12.2)[a]	2 (1.5)[a]	0.001
Incidence of first stroke[b]	8 (13.9)[a]	3 (5.1)[a]	NS	11 (13.9)[a]	2 (1.6)[a]	0.05

[a] Age-standardized, [b] Fatal and non-fatal cases included

with newly-detected Type 2 diabetes and in non-diabetic control subjects. The present study examined 10-year cardiovascular mortality and morbidity in relation to general risk factors, plasma insulin, urinary albumin and lipoprotein abnormalities determined at baseline in a group of patients with Type 2 diabetes followed-up from diagnosis, and in a comparable group of non-diabetic control subjects [16–18].

Subjects and methods

Subjects

The original study population consisted of 133 newly-diagnosed patients with Type 2 diabetes who were 45–64 years old at the time of diagnosis and 144 randomly selected non-diabetic subjects in the same age group, all of whom were investigated between 1 May 1979, and 31 December 1981. Both groups were recruited from a defined area of 180,000 inhabitants in the county of Kuopio in Eastern Finland.

Diabetic patients

General practitioners working in community health centres and private practitioners in the survey area were asked to refer newly-diagnosed diabetic patients with a fasting venous whole blood glucose level greater than or equal to 7.0 mmol/l and who were 45–64 years old to the outpatient department of Kuopio University Central Hospital. All patients were examined within 4 weeks after the detection of diabetes. Whenever necessary, those patients with hyperglycaemic symptoms were admitted to the hospital immediately after diagnosis.

The diagnosis of diabetes was confirmed by an oral glucose tolerance test using the diagnostic criteria recommended by the World Health Organization (WHO) [19], (a fasting venous whole blood glucose level greater than or equal to 7.0 mmol/l, a 2-h blood glucose level greater than or equal to 10 mmol/l, or both). Patients with secondary diabetes and those whose fasting blood glucose had exceeded 7.0 mmol/l for more than 6 months were excluded. All patients were non-ketotic at the time of diagnosis, and none needed insulin treatment during the follow-up period of at least 3 months from diagnosis. Of the 144 diabetic patients referred to the study, 11 were excluded. Five did not fulfill the diagnostic criteria of diabetes, one had hypothyroidism, three were outside the age limits, and two failed to complete the study. Thus, 133 patients with Type 2 diabetes were included in the study.

During the course of the study, it became evident that not all newly-diagnosed diabetic patients fulfilling the criteria were being recruited into the study. This information was obtained from a separate survey in which all medical records of the health centers in 10 communities of the survey area were reviewed in 1980 for the identification of subjects with diabetes and for information concerning the time of diagnosis, diagnostic criteria, mode of treatment, and the prevalence of angina pectoris, hypertension, and congestive heart failure [20]. From these data, it could be estimated that approximately 30% of all diabetic subjects possibly eligible for the study had been recruited for the present study. As reported elsewhere in detail [16, 21], the diabetic subjects included in the study did not differ significantly from those not included with respect to prevalence of cardiovascular disease history or distribution by age and sex.

Control subjects

A random control population sample of subjects who were 45–64 years old was selected from the population registers of the study area, taking into consideration the distribution of the population liv-

ing in rural and urban communities. Of 183 subjects originally contacted, 9 had diabetes, 1 had hypothyroidism, and 29 refused to participate in the study. Thus, the final control population consisted of 144 non-diabetic subjects.

Ten-year study population

Both diabetic and non-diabetic subjects were re-examined after 5 and 10 years from the first examination, in the years 1985–1986 and 1991–1992, respectively. The baseline and 10-year study populations are given in Table 1. During the 10-year follow-up, 36 diabetic patients (20 men and 16 women) and 8 control subjects (3 men and 5 women) died. Five diabetic subjects and 8 non-diabetic subjects refused to participate in the 10-year examination, but the data concerning cardiovascular mortality and morbidity was obtained from all subjects originally examined in 1979–1981.

Methods

Baseline examination

The methods used were similar for diabetic and non-diabetic control subjects. Medical history included a history of cardiovascular, renal, and any other significant long-term disease and the use of drugs. Chest pain symptoms suggestive of CHD were recorded in an interview using the questionnaire developed by Rose [22].

Anthropometric measurements

Standing height was measured without shoes to the nearest 0.5 cm. Body weight was measured with an electric weighing machine (model 708; Seca, Hamburg, Germany) with the subjects barefoot and dressed in shorts. Body mass index was calculated (body weight [kg]/height[m^2]).

Triceps and subscapular skinfolds were measured from the right with the Harpenden Caliper (John Bull, British Indicators, St. Albans, Herts., UK). Triceps skinfold was measured on the dorsal aspect of the arm at the middle point of the line from the acromion to the tip of the elbow, and subscapular skinfold beneath the apex of scapula. The mean value of two measurements was used.

Blood pressure

With the patient or subject in the sitting position after a 5-min rest, blood pressure was measured by one of the two specially trained nurses using a mercury sphygmomanometer (cuff size, 12.5 × 40.0 cm). Systolic and diastolic blood pressures were measured to the nearest

Table 2. Baseline characteristic of study population

Variable	Men		Women	
	Diabetic ($n = 70$)	Control ($n = 62$)	Diabetic ($n = 63$)	Control ($n = 82$)
Body mass index (kg/m^2)	29.7 ± 0.6[a]	26.9 ± 0.4	31.3 ± 0.7[a]	27.2 ± 0.5
Skinfolds				
Triceps (mm)	19.8 ± 1.1[b]	16.0 ± 1.0	29.4 ± 1.2[a]	23.4 ± 1.0
Subscapularis	26.2 ± 1.4[c]	20.3 ± 1.3	31.3 ± 1.3[a]	26.1 ± 1.1
Waist/hip ratio[f]	0.99 ± 0.01[b]	0.96 ± 0.01	0.91 ± 0.01[a]	0.84 ± 0.01
Systolic blood pressure (mm Hg)	147 ± 2	146 ± 2	154 ± 2	147 ± 2
Diastolic blood pressure (mm Hg)	93 ± 1	91 ± 1	92 ± 1	90 ± 1
Drug treatment for hypertension (%)	41[d]	18	60[e]	24
Fasting blood glucose (mmol/l)	10.3 ± 0.4	5.1 ± 0.1	11.2 ± 0.5	4.8 ± 0.1
Fasting plasma insulin (mU/l)	24 ± 2[a]	16 ± 1	26 ± 2[a]	15 ± 1
Fasting plasma glucose[f] (mmol/l)	10.6 ± 0.5	5.8 ± 0.1	11.6 ± 0.5	5.7 ± 0.2
Glycated HbA_1 (%)[f]	8.9 ± 0.2	6.5 ± 0.2	9.7 ± 0.3	6.5 ± 0.3
Cholesterol (mmol/l)				
Whole serum	6.3 ± 0.2	6.7 ± 0.2	6.5 ± 0.2	6.7 ± 0.1
HDL	0.99 ± 0.03[a]	1.25 ± 0.04	1.17 ± 0.04[a]	1.41 ± 0.04
LDL	4.08 ± 0.11[b]	4.45 ± 0.14	4.26 ± 0.15	4.52 ± 0.11
VLDL	1.27 ± 0.12	1.00 ± 0.10	1.10 ± 10[b]	0.75 ± 0.05
Triglycerides (mmol/l)				
Whole serum	2.45 ± 0.39[b]	1.90 ± 0.20	2.37 ± 0.20[a]	1.38 ± 0.07
HDL	0.18 ± 0.01	0.15 ± 0.01	0.19 ± 0.01	0.16 ± 0.01
LDL	0.47 ± 0.03[b]	0.38 ± 0.06	0.48 ± 0.03[c]	0.35 ± 0.02
VLDL	1.80 ± 0.18	1.37 ± 0.52	1.70 ± 0.17[a]	0.87 ± 0.10

Results are mean ± SEM. [a] $p < 0.001$, [b] $p < 0.05$, [c] $p < 0.01$; analysis of covariance with group and age as factors. [d] $p < 0.01$, [e] $p < 0.001$; age-adjusted prevalence. [f] Measured at the 5-year examination. HDL, High density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein

2 mm Hg. Disapperance of Korotkoff sounds (phase V) was used for diastolic blood pressure. Hypertension was diagnosed as a predetermined blood pressure level (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg) and the history of antihypertensive drug treatment.

Resting electrocardiography

A conventional 12-lead resting ECG was recorded from each subject at each examination and interpreted according to the Minnesota code (Mc) [23].

Classification for the diagnosis of coronary heart disease

Ischaemic ECG abnormalities (Mc 1.1–3; 4.1–3, 5.1–3, and 7.1) included Q-QS abnormalities, various degrees of ST segment depression, T-wave changes, and left bundle branch block. The definite myocardial infarction class consisted of patients with major Q-QS abnormalities (Mc 1.1–2), who had suffered from myocardial infarction verified at the hospital, or both. All the patient records were checked to verify the correct diagnosis of myocardial infarction.

Oral glucose tolerance test and serum lipids

At the baseline, an oral glucose tolerance test was performed after a 12-h overnight fast. Samples for blood glucose and serum insulin determinations were taken before the test (fasting) and at 1 and 2 h after glucose. Samples for serum insulin were placed in pre-chilled tubes, centrifuged, and stored without delay at −20 °C until analysed.

Blood glucose was analysed by the glucose-oxidase method (Glox; Kabi Ab, Stockholm, Sweden). Serum insulin was analysed by radioimmunoassay (antiserum M 8309; Novo Industries, Copenhagen, Denmark). The variation coefficient of the method was 5.4 %, and sensitivity was 2 mU/l. Serum and lipoprotein lipids were determined from 12-h fasting samples. Lipoproteins were separated by ultracentrifugation at density 1.006 to remove VLDL, followed by precipitation of the infranatant fraction by dextran sulphate and magnesium chloride [24]. Enzymatic methods were used for the determination of cholesterol [25] and triglycerides [26] from whole serum, the top layer after ultracentrifugation of VLDL, and the supernatant after precipitation of LDL. LDL was calculated as the difference between whole serum and the sum of VLDL and HDL. The intra-assay variation for total cholesterol, HDL cholesterol, and triglycerides was 1.3 %, 0.95 %, and 3.1 % respectively, and the inter-assay variation was 3.3 %, 1.9 %, and 5.2 %, respectively.

At baseline 24-h urinary albumin was measured with an immunodiffusion method (Behringswerke, Mahrburg Lahn, Germany) as previously described [27].

Five-year and ten-year examinations

The methods used at the 5-year examination have been described elsewhere in detail [28–30]. At the 5-year examination 24-h urinary albumin was examined by turbidometry (Orion Diagnostica; Espoo Finland) by using IL Multistat III centrifugal analyzer (IL Laboratories Inc., Lexington Ky., USA), glucose was determined by a glucose dehydrogenase method (Merck Diagnostica, Darmstadt, Germany) and glycated haemoglobin A_1 (HbA_1) (normal range 5.5–8.5 %) by column chromatography (Quik-Sep Fast Haemoglobin Test System; Isolab, Akron, Ohio, USA) after incubation in 0.9 % NaCl solution for 12 h. Other biochemical determinations from the 5-year examination were not used for this study.

At 5-year examination for the determination of the waist/hip ratio the circumference of the waist was measured at the level of the umbilicus in the neutral breathing position. Pelvis circumference was measured at the level of the greater trochanters.

Data on the incidence of cardiovascular disease concern the following end points: total cardiovascular mortality, and fatal and non-fatal myocardial infarction and stroke. The subjects who had suffered a myocardial infarction or stroke before the baseline examination were excluded from the respective incidence analyses. Causes of deaths were ascertained from patient records and death certificates, and non-fatal events from patient records, in addition to medical history and clinical examination at the 10-year examination. As at the baseline, the definite myocardial infarction class consisted of patients with new major Q-QS abnormalities (Mc1.1–2), or who had suffered from myocardial infarction verified at the hospital, or both.

Statistical analyses

The difference between the groups concerning continuous variables was analysed by the Student's *t*-test for unpaired samples or by analysis of covariance. Whole serum triglycerides, VLDL triglycerides, LDL triglycerides, urinary albumin and insulin were analysed after logarithmic transformation. Age standardization was performed by the direct standardization method using the Finnish male and female populations from the comparable age groups as the standard populations. The significance of differences between the standardized rates were analysed by a test of proportions based on standardized normal distribution. Multiple logistic regression analyses (note that the follow-up period was almost equal for all subjects studied) were performed on diabetic patients and on the whole study population to find out the independent contribution of different variables to cardiovascular mortality. The final analyses included the factors which had a significant association in univariate analyses after adjustment for age and sex and those known to be related to cardiovascular disease, e.g. LDL cholesterol, HDL cholesterol, blood pressure and body mass index. LDL triglycerides were included in the final model instead of total triglycerides, VLDL cholesterol or VLDL triglycerides because they had the strongest independent association. This analysis had the highest likelihood ratio test statistics and correct classification percent.

Results

Table 2 gives the baseline characteristics of the study population and fasting plasma glucose and glycated HbA_1 level as well as waist/hip ratio at the 5-year examination. The details of these variables have been reported previously [16–18, 29]. Briefly, at the time of diagnosis diabetic patients were more obese than their non-diabetic counterparts. Additionally, prevalence of hypertension was significantly higher among diabetic patients (63 % vs 38 % in men, $p = 0.005$, and 70 % vs 42 % in women, $p = 0.002$, age-standardized prevalence), but no significant difference was found in the mean blood pressure levels between diabetic and non-diabetic subjects. Metabolic control judging from blood or plasma glucose (at 5-year examination) values was roughly similar in diabetic patients at the baseline and after 5 years. Fasting plasma insulin was higher in both sexes of diabetic patients than in the corresponding non-diabetic subjects. No significant difference was observed between diabetic and non-diabetic subjects in serum total cholesterol, but LDL cholesterol tended to be lower in diabetic patients than in non-diabetic subjects. HDL cholesterol was reduced in

Table 3. Age, serum lipids and lipoproteins, metabolic control, urinary albumin, fasting insulin, body mass index, blood pressure, and ECG abnormalities and smoking in relation to 10-year cardiovascular mortality (CVD) in diabetic and non-diabetic subjects

Variable	Diabetic patients			Control subjects		
	Without CVD ($n = 97$)	With CVD ($n = 28$)	p[a]	Without CVD ($n = 136$)	With CVD ($n = 4$)	p[a]
Age (years)	54.7 ± 1.1	58.8 ± 1.2	0.012	54.2 ± 0.47	56.0 ± 2.9	NS
Cholesterol (mmol/l)						
Total	6.34 ± 0.14	6.86 ± 0.27	0.053	6.67 ± 0.010	7.52 ± 0.79	NS
LDL	4.14 ± 0.12	4.41 ± 0.18	NS	4.48 ± 0.09	4.83 ± 0.63	NS
VLDL	1.11 ± 0.08	1.47 ± 0.23	0.056	0.84 ± 0.053	1.63 ± 0.60	0.038
HDL	1.10 ± 0.03	0.98 ± 0.05	0.082	1.35 ± 0.029	1.06 ± 0.19	NS
Triglycerides (mmol/l)						
Total	2.28 ± 0.15	2.94 ± 0.37	0.019	1.56 ± 0.094	3.08 ± 1.03	0.016
LDL	0.44 ± 0.02	0.59 ± 0.06	0.006	0.36 ± 0.013	0.62 ± 0.13	0.011
VLDL	1.67 ± 0.14	2.12 ± 0.33	0.058	1.05 ± 0.085	2.30 ± 1.07	0.06
HDL	0.17 ± 0.008	0.22 ± 0.02	0.009	0.16 ± 0.08	0.16 ± 0.06	NS
Baseline blood glucose (mmol/l)	10.2 ± 0.3	12.2 ± 0.7	0.012	4.9 ± 0.05	6.2 ± 0.56	0.001
5-year-plasma glucose (mmol/l)	11.3 ± 0.4	14.5 ± 0.9	0.001	5.7 ± 0.11	7.3 ± 1.7	0.038
5-year HbA_1 (%)	9.1 ± 0.2	10.0 ± 0.4	0.014	6.6 ± 0.10	7.4 ± 0.10	NS
Baseline urinary albumin (mg/24 h)	31 ± 8	47 ± 14	0.068	–	–	
5-year urinary albumin (mg/24 h)	28 ± 7	50 ± 16	0.004	–	–	
Fasting insulin (mU/l)	22.2 ± 1.4	31.1 ± 3.5	0.09	15.4 ± 0.7	16.0 ± 4.4	NS
Body mass index (kg/m^2)	30.1 ± 0.5	30.8 ± 1.0	NS	27.0 ± 0.4	26.9 ± 2.3	NS
Systolic blood pressure (mm Hg)	149 ± 2	152 ± 3	NS	147 ± 1.6	139 ± 3.8	NS
Diastolic blood pressure (mm Hg)	93 ± 1	93 ± 2	NS	91 ± 1	86 ± 4	NS
Prevalence of abnormal ECG (%)	12/82 (15)	16/43 (37)	0.004	18/140 (13)	2/4 (50)	0.09
Prevalence of smoking (%)[b]	40	68	0.01	24	75	0.05

[a] Analysis of covariance with age and sex as factors. [b] Current and ex-smokers included

Table 4. Relation of cardiovascular mortality to selected lipoproteins and other risk factors in diabetic subjects ($n = 28$) and in total study population ($n = 32$)

Variables	Diabetic subjects		Total study population	
	Coefficient/ Standard error	Significance	Coefficient/ Standard error	Significance
Age	5.34	0.021	6.44	0.0112
Systolic pressure	0.099	0.75	1.21	0.27
LDL cholesterol	0.794	0.37	1.77	0.18
HDL cholesterol	0.472	0.49	0.021	0.89
LDL triglycerides	3.90	0.048	6.22	0.013
Smoking	8.84	0.003	12.01	0.0005
Body mass index	0.791	0.37	0.756	0.38
Fasting insulin	1.68	0.19	1.53	0.22
Blood glucose	4.19	0.041	–	–
Ischaemic ECG at baseline	5.01	0.025	7.05	0.0079
Diabetes	–	–	3.66	0.056

diabetic patients whereas they had an increased VLDL cholesterol compared to that of non-diabetic control subjects. Serum total, VLDL and LDL triglycerides were elevated in diabetic subjects.

At the time of diagnosis of diabetes, the prevalence of myocardial infarction was higher in diabetic than in non-diabetic subjects (Table 1). Cardiovascular mortality during 10-year follow-up was substantially higher in diabetic (28 of 133) than in non-diabetic subjects (4 of 144). The most common cause of death in both diabetic men and women was CHD. Incidence of myocardial infarction was also higher in diabetic than in non-diabetic subjects. Total cardiovascular mortality was similar in diabetic men and women, but the incidence of myocardial infarction tended to be higher in diabetic men.

Table 3 summarizes different baseline characteristics in relation to cardiovascular mortality during the 10-year follow-up for both groups. In diabetic subjects, cardiovascular mortality was significantly associated with age, elevated total and LDL and HDL triglycerides, hyperglycaemia (blood glucose at baseline, plasma glucose at 5 years, and glycated HbA_1 at 5 years), presence of abnor-

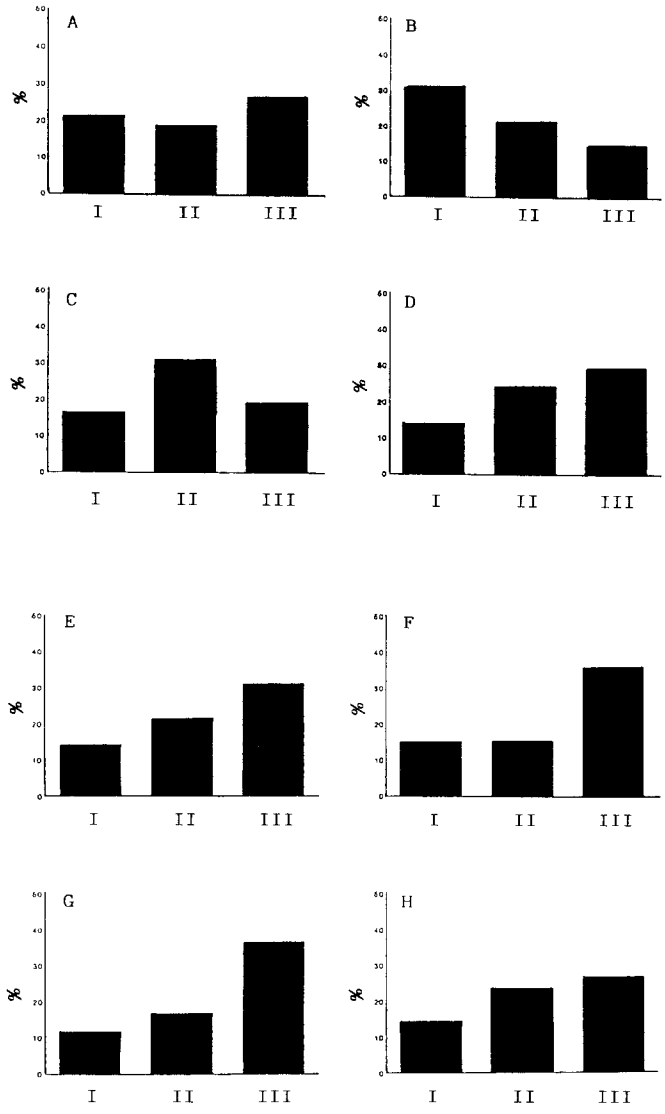

Fig. 1. A–H. Cardiovascular mortality in diabetic subjects according to the tertiles of serum and lipoprotein lipids; I lowest, II middle, III highest tertile. **A,** total cholesterol, **B,** HDL cholesterol, **C,** LDL cholesterol, **D,** VLDL cholesterol, **E,** total triglycerides ($p = 0.058$), **F,** HDL triglycerides ($p = 0.025$), **G,** LDL triglycerides ($p = 0.0068$), **H,** VLDL triglycerides

mal ECG and positive smoking history (including current and ex-smokers) at baseline examination. In addition, serum total and VLDL cholesterol and fasting insulin levels tended to be higher and HDL cholesterol lower in subjects who died during the follow-up than in those who survived. Blood pressure level, or skinfold thicknesses at baseline did not predict cardiovascular mortality in this study. Cardiovascular mortality was not significantly related to baseline urinary albumin excretion, but 5-year urinary albumin excretion rate was higher in diabetic patients with CVD ($n = 20$) than in others ($n = 91$). Waist/hip ratio measured at 5-year examination had no relation to 10-year cardiovascular mortality (data not shown).

Cardiovascular mortality was also analysed in relation to the treatment of diabetes at 5-year examination, but no significant difference was found between the patients on diet therapy only (11 of 57, 19.3 %) and those who were receiving oral antidiabetic drugs (13 of 61, 21.3 %) or insulin (1 of 4, 25.0 %) at 5-year examination. Use of diuretics (13 of 55, 23.6 % vs 15 of 78, 19.2 %; patients with CVD vs without CVD, respectively), beta-blocking agents (15 of 52, 28.8 % vs 13 of 81, 16.0 %) or their combination did not show a significiant association with cardiovascular mortality, although the cardiovascular mortality tended to be higher (NS) in patients with the combination therapy (10 of 34, 29.4 %) than in others (18 of 99, 18.2 %).

Only four non-diabetic subjects died from a cardiovascular cause during 10-year follow-up. High total, VLDL, and LDL triglycerides, high VLDL cholesterol, high fasting glucose level and smoking history predicted cardiovascular mortality among them.

None of the risk factors included in Table 3 predicted myocardial infarction in diabetic subjects during the 10-year follow-up (data not shown). The results were similar whether or not subjects with myocardial infarction at baseline were excluded from analyses. In non-diabetic subjects, the incidence of myocardial infarction was associated with a high LDL cholesterol (5.34 ± 0.42 vs 4.41 ± 0.08 mmol/l, $p = 0.049$, subjects with myocardial infarction vs subjects without), high blood glucose (5.4 ± 0.26 vs 4.9 ± 0.06 mmol/l, $p = 0.012$) and sex (10 of 62 vs 2 of 82, $p = 0.003$, men vs women), but not with other variables shown in Table 3.

Table 4 shows the results on multiple logistic regression analyses concerning the relation of cardiovascular mortality to selected lipoproteins and other risk factors in diabetic subjects as well as in the total study population. In diabetic subjects, among different lipoprotein fractions, LDL triglycerides were most strongly associated with cardiovascular mortality. When LDL triglycerides were included into the model the impact of other lipoproteins and lipids examined were substantially reduced. From the other factors, age, smoking history, high blood glucose and ischaemic ECG at baseline significantly predicted cardiovascular mortality.

Multiple logistic regression analysis was also carried out on diabetic patients including factors presented in Table 4 and urinary albumin of the baseline examination, but urinary albumin did not make a significant contribution ($p = 0.21$). In multiple logistic regression analysis on diabetic patients (20 with CVD; 91 without CVD) including the same factors shown in Table 4 except plasma glucose but determined at 5-year examination, urinary albumin made an independent contribution to cardiovascular mortality ($p = 0.028$). However, after further adjustment for plasma glucose, the independent effect of urinary albumin decreased to a non-significant level ($p = 0.12$). In this analysis the most powerful predictors of cardiovascular mortality were plasma glucose ($p = 0.004$), age ($p = 0.028$), plasma insulin ($p = 0.056$) and smoking ($p = 0.083$).

Figure 1 demonstrates the relation of cardiovascular mortality in diabetic subjects according to different lipoprotein lipid tertiles. The trends over tertiles were significant for HDL and LDL triglycerides, in addition cardiovascular mortality was almost significantly associated with total triglycerides in this analysis.

Figure 2 shows cardiovascular mortality in diabetic subjects by tertiles of fasting blood glucose at baseline in two treatment categories (diet and oral drugs or insulin at 5-year examination). Cardiovascular mortality was increased three-fold in patients included into the highest tertile compared to the lowest blood glucose tertile irrespective of treatment. The same was true with respect to plasma glucose and glycated HbA_1 determined at 5-year examination (data not shown).

In the total study population, the factors predicting cardiovascular mortality were similar to those found in diabetic subjects. Furthermore, in this model diabetes had a significant predictive value regarding cardiovascular mortality (Table 4).

When adjusted for age alone the relative risk of cardiovascular mortality associated with diabetes was 8.2, but it declined to 3.7 when all factors (except blood glucose) were added to the model, suggesting that a substantial proportion of increased risk in diabetic subjects is mediated through lipoprotein abnormalities and other risk factors (Fig. 3).

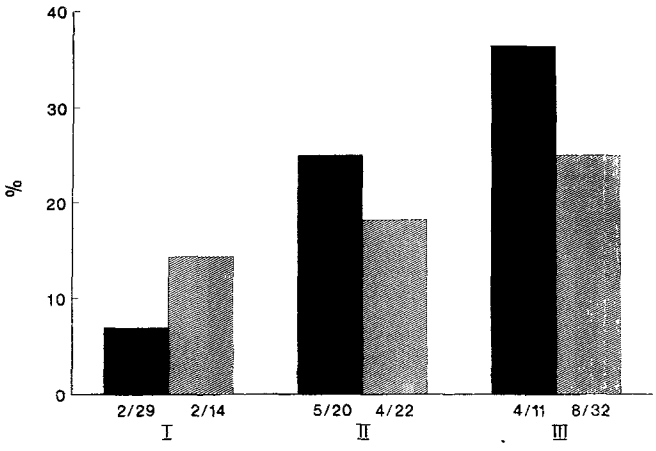

Fig. 2. Cardiovascular mortality by tertiles of blood glucose at baseline in diet (■) and drug-treated (▨) diabetic subjects. Drug treatment was obtained from the 5-year examination. Number of cases in each group is expressed below the bars. I tertile; blood glucose ≤ 8.6 mmol/l; II tertile; blood glucose 8.7–11.8 mmol/l; III tertile; blood glucose ≥ 11.9 mmol/l

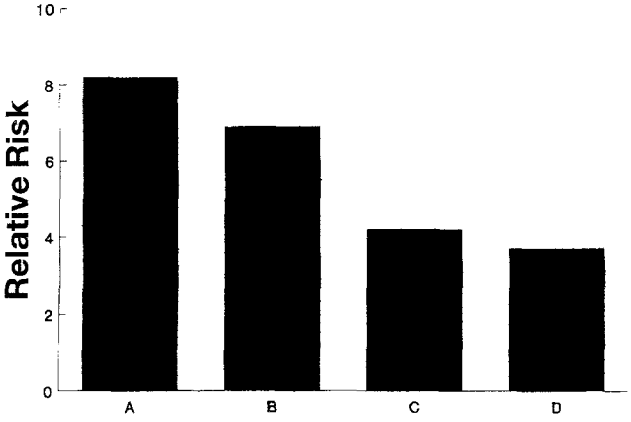

Fig. 3. Relative risk of cardiovascular death associated with diabetes, (**A**); adjusted for age, (**B**); for age and ischaemic (abnormal) ECG at baseline, (**C**) for age, abnormal ECG, and systolic blood pressure, LDL-cholesterol, HDL-cholesterol, ln (logarithmic transformation) triglycerides, smoking and body mass index, and (**D**) adjusted for the factors mentioned above except triglycerides, and for ln plasma insulin and ln LDL triglycerides. The multiple logistic regression analyses were based on 28 cases among diabetic patients and 4 cases among non-diabetic subjects

Discussion

The main finding of this 10-year follow-up study on cardiovascular mortality and morbidity in a representative group of newly-diagnosed middle-aged patients with Type 2 diabetes and non-diabetic control subjects was a pronounced excess of cardiovascular mortality and incidence of myocardial infarction among diabetic subjects. Furthermore, a strong relation of cardiovascular mortality to lipoprotein abnormalities characteristic of Type 2 diabetes was noted. As to the representativeness of the study population, all diabetic subjects fulfilled the WHO criteria for diabetes [19] at baseline, and at 5-year examination they were mostly being treated with diet or oral antidiabetic agents except five who were receiving insulin. Additionally, 97% of diabetic subjects had a well-preserved insulin secretion capacity [29] confirming their correct classification as patients with Type 2 diabetes. Our study population comprised approximately 30% of all patients with newly-diagnosed diabetes in the 45–64-year-old age group in whom this diagnosis was made during the baseline study period in the study area. We were able to confirm by a separate survey that the group of diabetic subjects included in our study cohort was representative of all newly-diagnosed diabetic patients in this age group [20, 21]. Non-diabetic control subjects of the same age group were recruited through the population registers. There does not, therefore, appear to be any indication for selective bias in the formation of the study groups. Furthermore, as distinct from most previous studies our group of patients with Type 2 diabetes was well characterized and homogeneous with respect to the known duration of diabetes.

The higher frequency of cardiovascular deaths and myocardial infarction in both sexes of our diabetic patients is consistent with previous prospective studies in various study populations using different diagnostic criteria for diabetes [1–5, 8]. In former studies it has been shown that the impact of general risk factors is roughly similar in diabetic and non-diabetic subjects, and the increased risk for atherosclerotic vascular disease among diabetic subjects is not substantially reduced after allowing for the effect of serum total cholesterol, smoking, blood pressure, obesity and ECG abnormalities [8, 9]. The data on serum triglycerides and cardiovascular mortality among diabetic populations are rather limited [31–34], and no long-term follow-up studies examining the impact of different lipoprotein fractions on cardiovascular mortality are available so far. In the cross-sectional results of the WHO Multinational Study serum total triglyceride level was associated with the prevalence of myocardial infarction [31], and Standl and Janka [32] reported an independent association between high serum triglyceride level and major macrovascular complications including death,

gangrene, and myocardial infarction in a prospective study on diabetic subjects. In the Paris Prospective Study [33] hypertriglyceridaemia was the only factor which in multiple regression analysis was associated with coronary mortality in subjects with impaired glucose tolerance or diabetes. HDL cholesterol, however, was not included among the baseline data of the Paris Prospective Study. In a recent Swedish study [34], high serum triglycerides were also associated with CHD morbidity when diabetic and non-diabetic men were analysed together.

In the present prospective study we were able to demonstrate that besides serum total triglycerides, compositional abnormalities of lipoproteins, evidently associated with disturbed catabolism of VLDL [13, 35], were related to cardiovascular mortality. Among different lipoprotein fractions examined, LDL triglycerides most consistently predicted cardiovascular deaths. The finding concerning LDL triglycerides (and other risk factors) was consistent both in diabetic and non-diabetic subjects, and therefore multiple logistic regression analysis was also made after combining both groups. In this analysis, diabetes still made a significant contribution to cardiovascular mortality, but the relative risk associated with diabetes was substantially decreased after allowing for lipoprotein abnormalities and other risk factors. The results on multiple logistic regression analysis after combining the groups should, however, be interpreted cautiously due to the small number of deceased cases from cardiovascular causes among non-diabetic subjects.

The close association between cardiovascular deaths and elevated LDL triglycerides could be due to a direct impact of LDL particles enriched with triglycerides on atherogenesis. Previously, it was shown that LDL triglycerides are associated with coronary atherosclerosis evaluated by coronary angiography [36, 37]. In our study population LDL triglycerides also predicted the appearance of peripheral atherosclerosis at 5-year examination [30]. Furthermore, LDL particles enriched with triglycerides have been suggested to be particularly susceptible to oxidative modification which may enhance their atherogeneticity [38]. In addition, evidence from experimental studies suggests that LDL enriched with triglycerides may be involved in atherogenesis [39]. On the other hand, the association between LDL triglycerides and cardiovascular mortality could be explained by other lipoprotein abnormalities in Type 2 diabetes. Among these are VLDL remnants and intermediate density lipoproteins (IDL) arising during catabolism of VLDL to IDL and LDL, and small dense LDL particles which are inversely related to serum triglycerides [40, 41]. Furthermore, glycation of lipoprotein may have a role in accelerated atherosclerosis in diabetes [42]. Interestingly, HDL cholesterol had no significant independent association with cardiovascular deaths in this study. This suggests that the increased risk associated with low HDL may be partially mediated through disturbed VLDL metabolism which is intimately associated with low HDL cholesterol [43]. Finally, our results suggest that an increased risk for cardiovascular disease associated with high serum triglycerides in diabetic subjects or more generally in insulin resistance states could be ascribed to lipoprotein compositional abnormalities lying behind hypertriglyceridaemia and insulin resistance [15].

Hyperinsulinaemia [14] and insulin resistance [15] have been connected with increased occurrence of atherosclerosis. In this study population, diabetic women with CHD disease at baseline had higher fasting and post-glucose insulin levels than those without CHD [17]. Furthermore, high fasting insulin levels predicted the appearance of peripheral atherosclerosis at 5-year examination independent of lipoprotein abnormalities and other risk factors [30]. At 10-year examination, in multiple logistic regression analyses the independent impact of insulin did not reach statistical significance. A high plasma insulin level is a reflection of insulin resistance, but it may directly affect atherogenesis through stimulation of the proliferation of arterial smooth muscle cells [44] and down regulating HDL receptors [45].

Cardiovascular morbidity and mortality in the non-diabetic population have been shown to relate to blood glucose level in a non-linear manner [2, 8], but the degree of hyperglycaemia as a risk factor in diabetic subjects is unresolved. In the present study, fasting blood glucose at baseline and fasting plasma glucose and glycated HbA_1 levels at 5 years were higher in diabetic subjects who died during the follow-up than in those who survived. According to our study cardiovascular mortality was three times higher in diabetic subjects with highest blood glucose levels at baseline (or at 5-year examination) than in those with lowest blood glucose levels. This finding in conjunction with some previous observations [46] and experimental evidence suggests that poor metabolic control of diabetes may, through several mechanisms [8, 10, 47, 48], accelerate both the atherosclerotic process and thrombus formation among diabetic subjects. Judging from the present study it can be hypothesized that the consequences of hyperglycaemia could explain a large proportion of excessive cardiovascular mortality in diabetic patients not attributable to conventional risk factors and other factors analysed.

Albuminuria has a strong predictive value for cardiovascular mortality in Type 2 diabetes [49–51]. Judging from our results, an increased albumin excretion rate predicts lipoprotein abnormalities favouring atherogenesis [28]. Thus, it is conceivable that these lipoprotein abnormalities partly explain the accelerated atherosclerosis associated with albuminuria in Type 2 diabetes. In the present study, 5-year albuminuria predicted 10-year cardiovascular mortality, but the independent impact of urinary albumin disappeared after including plasma glucose into the model. Therefore, the long-term hyperglycaemia could result in the endothelial damage [52] and increased vascular permeability [53], and consequently not only in microvascular lesions and increased albumin excretion rate, but also in accelerated atherosclerosis and thrombogenesis.

Smoking appeared to be an important risk factor for cardiovascular mortality in diabetic subjects. Similar results have been reported previously [3, 4], but in some studies the impact of smoking on the diabetic population has remained smaller than expected [9].

We also analysed the relation of lipoprotein abnormalities and other risk factors to the incidence of myocardial infarction during the 10-year follow-up. In diabetic subjects, none of the variables examined was significantly associated with the incidence of myocardial infarction. This result is consistent with that seen at the 5-year examination [30], and could be explained by the fact that other factors such as increased susceptibility to thrombus formation [46] or those associated with the diabetic state itself [10, 47, 48] might have had a central role in precipitating myocardial infarction in diabetic patients with asymptomatic or symptomatic CHD. Additionally, attempts to reduce risk factor levels might have played a role because diabetic patients were effectively treated for hypertension and they had received dietary advice to reduce the intake of saturated fats and cholesterol, and stopping smoking was also particularly frequent among diabetic subjects [12, 30]. In non-diabetic subjects, high LDL cholesterol and high fasting blood glucose predicted myocardial infarction.

It remains to be established to what extent the pronounced excess mortality in Type 2 diabetic subjects is preventable. According to our results much effort should be put to the treatment of hyperglycaemia and correction of lipoprotein abnormalities in patients with Type 2 diabetes by weight reduction, other dietary means and physical activity which have been shown to work in the clinical setting [54, 55]. Furthermore, stopping smoking should be encouraged. The more active use of pharmacological agents for normalization of atherogenic lipoprotein profile [56], and insulin therapy for both hyperglycaemia and dyslipidaemia [12], are complementary and potentially useful methods for patients with a high risk for atherosclerotic vascular disease, but to what extent they could improve the long-term prognosis of Type 2 diabetic patients is still unresolved.

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