Hyperglycemia and Compositional Lipoprotein Abnormalities as Predictors of Cardiovascular Mortality in Type 2 Diabetes

A 15-year follow-up from the time of diagnosis

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OBJECTIVE — We studied the 15-year cardiovascular mortality and morbidity of newly diagnosed patients with type 2 diabetes and of nondiabetic control subjects and the predictors of cardiovascular mortality in diabetic patients.

RESEARCH DESIGN AND METHODS — We performed a 15-year prospective study of 133 middle-aged patients with newly diagnosed type 2 diabetes and 144 control subjects. Cardiovascular risk factors were assessed in both groups at baseline and after 5 and 10 years.

RESULTS — Total mortality was markedly higher in patients with type 2 diabetes (total: 44.3 vs. 12.9% for men, age-adjusted odds ratio [OR] 5.0, $P < 0.001$; 44.4 vs. 11.0% for women, OR 5.2, $P < 0.001$), which was due to increased cardiovascular mortality (ORs for men and women: 6.2 and 11.2, respectively, $P < 0.001$ for both). The incidences of fatal and nonfatal myocardial infarction and stroke were likewise higher in diabetic patients. In univariate analyses and various multiple logistic regression analyses, hyperglycemia was a constant predictor of cardiovascular mortality assessed at the time of diagnosis or at 5- or 10-year examinations. Moreover, lipoprotein abnormalities characteristic of type 2 diabetes (low HDL cholesterol, high LDL triglycerides or apolipoprotein B levels, and low LDL cholesterol/apolipoprotein B ratio as a marker for LDL size) were predictive of cardiovascular death in these analyses.

CONCLUSIONS — This long-term study of a well-characterized group of newly diagnosed patients strengthens the view that the prognosis in middle-aged subjects is markedly impaired and that both hyperglycemia and compositional lipoprotein abnormalitiesare predictors of cardiovascular mortality in patients with type 2 diabetes.

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The various clinical manifestations of atherosclerotic vascular diseases are markedly increased in patients with type 2 diabetes (1–8). The heavy burden of cardiovascular diseases is the major cause of the shortened life span of these patients. Cardiovascular disease also leads to prematurely lost working capacity in middle-aged patients and to increased disability in the elderly. It is well described that conventional risk factors for cardiovascular diseases, e.g., smoking, hypertension, and elevated LDL cholesterol, are also operative in patients with type 2 diabetes (2), but the pattern of these risk factors does explain only a fraction of the excess occurrence of atherosclerotic diseases in type 2 diabetes. Therefore, the studies focusing on the role of other factors that are more peculiar to type 2 diabetes, such as hyperglycemia and compositional lipoprotein abnormalities, are warranted.

Although there are some data supporting the impact of hyperglycemia as a risk factor (4,6–9), this view has not been universally accepted (10). Further, although low HDL cholesterol and elevated serum total triglycerides have predicted various cardiovascular events (5), the predictive value of compositional changes of lipoproteins or apolipoprotein abnormalities typical of type 2 diabetes have rarely been measured in prospective studies. A further drawback of previous studies is that they seldom followed the patients from the time of the clinical diagnosis of diabetes. Importantly, in most studies, the risk factors have been measured only once, which may not be an accurate reflection of, e.g., long-term glycemic control or lipid abnormalities.

In this study, we have followed for 15 years a carefully characterized group of patients with newly diagnosed type 2 diabetes and a nondiabetic control population. According to the results, the prognosis of the middle-aged patients with newly diagnosed type 2 diabetes is markedly impaired and comparable to many more severe diseases. Further, the results support the concept of hyperglycemia and compositional changes of lipoproteins being peculiar risk factors for cardiovascular deaths in patients with type 2 diabetes.

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Abbreviations: apo, apolipoprotein; CVD, cardiovascular death; ECG, electrocardiogram; IDL, intermediate-density lipoprotein; Mc, Minnesota code; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Study population

The formation and representativeness of the baseline, 5-year, and 10-year study populations have been described earlier in

Table 1—*Clinical characteristics of type 2 diabetic patients and control subjects at baseline*

Baseline study	Diabetic	Control	*P* value
n	133	144	—
Age (years)	55.7 ± 0.8	54.3 ± 0.5	0.003
Men (%)	70 (53)	62 (43)	0.111
Smoking history (%)	62 (47)	36 (25)	<0.05
BMI (kg/m^2)	30.4 ± 0.5	27.1 ± 0.4	<0.001
Systolic blood pressure (mmHg)	150 ± 2	147 ± 2	0.165
Diastolic blood pressure (mmHg)	93 ± 1	91 ± 1	0.067
Frequency of hypertension (%)	88 (66)	57 (40)	<0.001
Serum cholesterol (mmol/l)	6.43 ± 0.12	6.70 ± 0.10	0.085
LDL cholesterol (mmol/l)	4.49 ± 0.09	4.17 ± 1.10	0.013
HDL cholesterol (mmol/l)	1.07 ± 0.03	1.34 ± 0.03	<0.05
VLDL cholesterol (mmol/l)	1.19 ± 0.08	0.86 ± 0.05	0.001
Total serum triglycerides (mmol/l)	2.41 ± 0.14	1.60 ± 0.10	<0.05
VLDL triglycerides (mmol/l)	1.75 ± 0.12	1.08 ± 0.09	<0.001
LDL triglycerides (mmol/l)	0.47 ± 0.02	0.37 ± 0.01	<0.001
Albuminuria (30 mg/24 h) (%)	28 (21)	2 (1.4)	<0.001
Fasting glucose (mmol/l)	10.7 ± 0.3	5.0 ± 0.1	<0.001
1-h glucose (mmol/l)	18.0 ± 0.4	6.8 ± 0.2	<0.001
2-h glucose (mmol/l)	17.5 ± 0.5	5.9 ± 0.1	<0.001
Fasting serum insulin (mU/l)	24.8 ± 1.4	15.4 ± 0.7	0.003
Myocardial infarction (%)	24 (18)	9 (6.3)	<0.01
Ischemic ECG (%)	43 (32.3)	20 (13.9)	<0.001

Data are *n*, means ± SEM, or *n* (%).

detail (4,11–13). Briefly, the original study population comprised 133 patients with newly diagnosed type 2 diabetes aged 45–64 years and 144 nondiabetic control subjects from the same age-group, all of whom were randomly selected from the population register during 1979–1981. Both groups were recruited from a defined area of 180,000 inhabitants in the county of Kuopio in eastern Finland. Approval for the study was given by the ethics committee of the Kuopio University and Kuopio University Hospital. Informed consent was obtained from all the subjects studied.

The diabetic patients (70 men, 63 women) were referred to the study by general practitioners working in the community health centers of the survey area. The diagnosis of diabetes was made in the clinical setting (11), and it was confirmed by an oral glucose tolerance test using the diagnostic criteria of the World Health Organization (14). Subjects whose fasting blood glucose had exceeded 7.0 mmol/l for more than 6 months; subjects with secondary diabetes, thyroid diseases, alcoholism, renal insufficiency, or overt carcinoma; and subjects in institutional care were not eligible for the study. All diabetic patients were nonketotic at the time of diagnosis and none needed insulin treatment during the follow-up period of at least 3 months. After the baseline examination, patients were referred to the primary health care. They were invited for the 5- and 10-year follow-up studies during the periods between August 1985 and February 1986 and between September 1991 and May 1992. The 15-year follow-up study consists of mortality and morbidity data comprising all the fatal and nonfatal events through 31 December 1995.

Methods

The history of cardiovascular and other diseases and the use of drugs were registered at all examinations. BMI was calculated as weight (kg)/height squared (m^2). A conventional 12-lead resting electrocardiogram (ECG) was recorded from each subject at each examination and interpreted according to the Minnesota code (Mc) (15). Ischemic 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 myocardial infarction class consisted of patients with major Q-QS-abnormalities (Mc 1.1-2) and/or those who had suffered from myocardial infarction verified at the hospital. Stroke was defined as a clinical syndrome consisting of neurological findings persisting >24 h and verified at a hospital (15). All the patient records were checked to verify the correct diagnosis of myocardial infarction. Data on the incidence of cardiovascular diseases concern the following endpoints: total cardiovascular mortality, fatal and nonfatal myocardial infarction, and fatal and nonfatal stroke. The subjects who had suffered myocardial infarction and stroke were excluded from the respective incidence analyses. Causes of deaths were ascertained from the patient records and death certificates. Nonfatal events were ascertained from patient records at follow-up examinations (5-, 10-, and 15-year examinations) and by medical history and clinical examination at the baseline, 5-, and 10-year examinations.

Oral glucose tolerance tests were performed (at baseline, 5-, and 10-year examinations) by using a glucose dose of 75 g. Blood samples for glucose and insulin were drawn before the glucose dose and 1 and 2 h afterwards. The oral glucose tolerance test was not done for those diabetic patients with insulin treatment at 5- and 10-year follow-up examinations. Those control subjects who showed glucose values within the diabetic range (mostly marginally elevated 2-h glucose levels) at the follow-up examinations (n = 13 at the 5-year and n = 17 at the 10-year examination [12–13]) were included in the control group in all analyses.

Glucose determinations were performed at baseline from venous whole blood by a glucose oxidase method (Kabi AB, Stockholm, Sweden), at the 5-year examination from plasma samples by a glucose dehydrogenase method (Merck, Darmstadt, Germany), and at the 10-year examination from plasma samples by a glucose oxidase method (Daiichi, Kyoto, Japan). There were no significant differences between the results of these three methods for glucose.

Insulin samples were drawn into chilled EDTA tubes. After separation of plasma, samples were frozen immediately at −70°C until the determination, which was carried out by a double-antibody radioimmunoassay (baseline: Antiserum M8309, Novo, Copenhagen, Denmark; 5- and 10-year examinations: Phasedeph, Pharmacia, Uppsala, Sweden). The detection limit of the assays was 2.5 mU/l, and the coefficient of variation between duplicate aliquots measured simultaneously was 5.1–6.1%.

HbA_{1c} was measured at the 5-year and 10-year examinations (not measured at

Table 2—*Follow-up characteristics of type 2 diabetic patients and control subjects*

	Diabetic	Control	*P* value
5-year study			
n	111	133	—
BMI (kg/m²)	28.6 ± 0.4	27.2 ± 0.4	0.010
Waist circumference (mm)	98 ± 1	91 ± 1	<0.001
Systolic blood pressure (mmHg)	144 ± 2	140 ± 2	0.064
Diastolic blood pressure (mmHg)	85 ± 1	80 ± 1	0.615
Serum cholesterol (mmol/l)	6.48 ± 0.14	6.68 ± 1.35	0.264
LDL cholesterol (mmol/l)	3.91 ± 0.09	4.23 ± 0.09	0.264
HDL cholesterol (mmol/l)	1.04 ± 0.03	1.26 ± 0.03	<0.001
HDL_2 cholesterol (mmol/l)	0.74 ± 0.02	0.96 ± 0.03	<0.001
HDL_3 cholesterol (mmol/l)	0.30 ± 0.09	0.30 ± 0.09	0.927
VLDL cholesterol (mmol/l)	1.54 ± 0.11	1.19 ± 0.05	0.003
Total serum triglycerides (mmol/l)	2.72 ± 0.02	1.72 ± 0.09	<0.001
VLDL triglycerides (mmol/l)	2.10 ± 0.20	1.17 ± 0.07	<0.001
LDL triglycerides (mmol/l)	0.49 ± 0.02	0.42 ± 0.02	0.002
ApoB (g/l)	1.60 ± 0.04	1.62 ± 0.05	0.767
$ApoA_1$ (g/l)	1.54 ± 0.03	1.71 ± 0.03	0.001
LDL cholesterol/apoB	2.51 ± 0.05	2.73 ± 0.05	0.003
HDL cholesterol/$apoA_1$	0.74 ± 0.03	0.93 ± 0.03	0.002
Albuminuria (>30 mg/24 h) (%)	23 (20.7)	9 (6.8)	0.001
HbA_{1c} (%)	9.2 ± 0.2	5.8 ± 0.1	—
Fasting glucose (mmol/l)	11.7 ± 0.4	5.8 ± 0.1	—
1-h glucose (mmol/l)	19.3 ± 0.5	9.2 ± 0.3	—
2-h glucose (mmol/l)	19.8 ± 0.5	7.6 ± 0.3	—
Fasting insulin (mU/l)	22.4 ± 2.1	17.9 ± 1.7	0.101
Treatment of diabetes (diet/oral drugs/insulin) (%)	60/63/5 (47/49/4)	—	—
10-year study			
n	93	128	—
BMI (kg/m²)	29.0 ± 0.5	28.4 ± 0.4	0.372
Waist circumference (mm)	98 ± 1	94 ± 1	0.020
Systolic blood pressure (mmHg)	153 ± 3	149 ± 2	0.395
Diastolic blood pressure (mmHg)	85 ± 1	80 ± 1	0.208
Serum cholesterol (mmol/l)	6.36 ± 0.14	6.37 ± 0.10	0.945
LDL cholesterol (mmol/l)	4.05 ± 0.10	4.22 ± 0.09	0.215
HDL cholesterol (mmol/l)	1.11 ± 0.03	1.31 ± 0.03	<0.001
VLDL cholesterol (mmol/l)	1.20 ± 0.11	0.85 ± 0.04	0.001
Total serum triglycerides (mmol/l)	2.51 ± 0.18	1.78 ± 0.09	<0.001
VLDL triglycerides (mmol/l)	1.88 ± 0.17	1.21 ± 0.08	<0.001
LDL triglycerides (mmol/l)	0.40 ± 0.01	0.37 ± 0.02	0.013
ApoB (g/l)	1.16 ± 0.03	1.06 ± 0.02	0.007
$ApoA_1$ (g/l)	1.25 ± 0.02	1.34 ± 0.02	0.002
LDL cholesterol/apoB	3.61 ± 0.86	4.09 ± 0.75	<0.001
HDL cholesterol/$apoA_1$	0.84 ± 0.02	0.94 ± 0.02	<0.001
$ApoA_1$/apoB	1.15 ± 0.03	1.34 ± 0.04	<0.001
Albuminuria (<30 μg/min) (%)	38 (41)	16 (13)	<0.001
Fasting glucose (mmol/l)	12.2 ± 0.4	6.0 ± 0.1	<0.001
Fasting plasma insulin (mU/l)	15.2 ± 0.6	11.9 ± 0.8	0.001
HbA_{1c} (%)	9.0 ± 0.2	5.5 ± 0.1	—
Treatment of diabetes (diet/oral drugs/insulin) (%)	18/59/21 (18/60/21)	—	—

Data are *n*, means ± SEM, or *n* (%).

baseline) by liquid cation exchange chromatography with reference range 4.0–6.0% (fast protein liquid chromatography system; Pharmacia).

Serum lipids were determined after a 12-h overnight fast from fresh serum samples by enzymatic methods. Lipoprotein fractionation was performed by using ultracentrifugation and selective precipitation, as previously described (16).

Serum apolipoproteins A_1 ($apoA_1$) and B (apoB) were determined by commercial immunochemical methods at the 5-year (Orion Diagnostica, Espoo, Finland) and 10-year (Kone Diagnostics, Espoo, Finland) examinations. Both methods are based on the measurement of immunoprecipitation at 340 nm (16), but because of the different reagents used, the absolute levels are not comparable between the examinations. The interassay coefficients of variation were <5% for both reagents.

At baseline, 5-year, and 10-year examinations, morning urine samples were screened for the presence of nitrites, leucocytes, erythrocytes, and protein. The abnormal urine samples were further studied by examining the urine sediment and bacterial culture. Those subjects with evidence of infection were treated accordingly. For the collection of 24-h or overnight urinary samples, subjects were given detailed oral and written instructions on the use of plastic containers. The urine volume was measured, and the urine aliquots were stored at −70°C until analysis. The analysis was performed within 2–3 months, except for the 10-year samples, which were analyzed within 1 week. At the baseline study, the urinary albumin was measured by immunodiffusion (Behringwerke, Marburg, Germany) with a lower limit of assay of 0.8 mg/l after concentration of the sample. Urinary albumin concentration was measured at the 5-year examination with turbidometry (Orion Diagnostica) by using Multistat III centrifugal analyzer (IL Laboratories, Lexington, CT), with the lower limit of the assay being 8 mg/l. At the 10-year examination, the urinary albumin excretion was measured from timed overnight samples by kinetic rate nephelometry on the Beckman Array Protein Analyzer using microalbumin reagent (all from Beckman, Brea, CA), with lower limit of the assay being 2.0 mg/l.

All the laboratory measurements mentioned above were analyzed within 2 weeks after they were taken.

Statistical analysis

The differences between the two groups concerning continuous variables were analyzed by the Student's *t* test for unpaired samples or the Mann-Whitney *U* test, when appropriate. The χ^2 test, Fisher's test, or Mantel-Haenzel's test for linear association was used to analyze the differences between the groups for the frequency data.

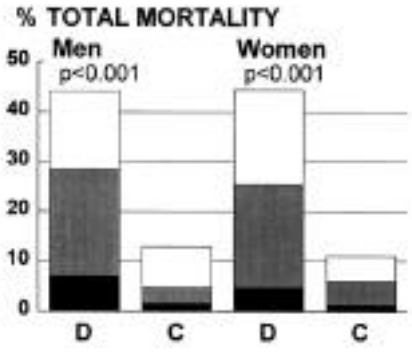

Figure 1—*Total mortality in diabetic (D) and control (C) subjects by sex from the time of diagnosis to the 5-year (■), 10-year (■ + ■), and 15-year follow-up (total height of the bar).*

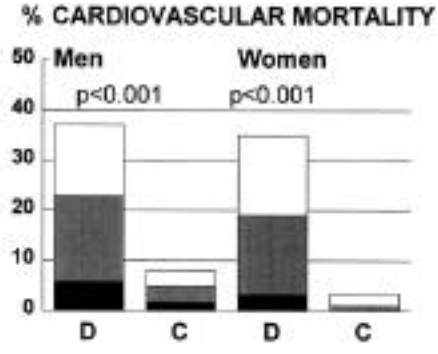

Figure 2—*Cardiovascular mortality in diabetic (D) and control (C) subjects by sex from the time of diagnosis to the 5-year (■), 10-year (■ + ■), and 15-year follow-up (total height of the bar).*

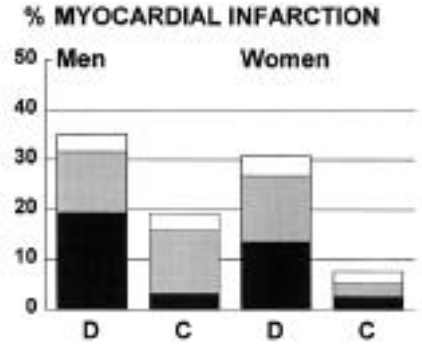

Figure 3—*Incidences of new fatal or nonfatal myocardial infarction in diabetic (D) and control (C) subjects by sex from the time of diagnosis to the 5-year (■), 10-year (■ + ■), and 15-year follow-up (total height of the bar).*

Logistic regression analysis was performed to assess the independent predictive effect of various selected variables. When used as continuous variables, serum triglyceride and its subfractions and insulin levels were analyzed after logarithmic transformation to eliminate skewness and kurtosis, but untransformed units are presented. All the data were analyzed by SPSS[7] for Unix[7] (SPSS, Chicago). *P* values <0.05 were considered statistically significant.

RESULTS — Baseline and 5- and 10-year follow-up characteristics of the diabetic and control populations were published earlier (4,11–13) and are summarized in Tables 1 and 2. No difference in mean age or sex distribution was found between the groups. At baseline, the diabetic patients had a higher mean BMI ($P < 0.001$) than did the nondiabetic subjects. The mean fasting blood glucose at the time of diagnosis of diabetes was 10.7 mmol/l. Fasting serum insulin levels were higher in the diabetic than in the control subjects ($P < 0.001$). Arterial hypertension (based on combined criteria of treatment with antihypertensive drugs or measured blood pressure >160/95 mmHg), myocardial infarction, and ischemic ECG changes were more common in the diabetic than in the control subjects, whereas no significant difference in actual blood pressure levels was observed. Total and LDL cholesterol levels were somewhat lower in diabetic patients, and they had markedly lower HDL cholesterol ($P < 0.001$) and higher VLDL cholesterol and total, VLDL, LDL, and HDL triglycerides ($P < 0.001$). At the time of diagnosis, diabetic patients already had a higher frequency of albuminuria than nondiabetic subjects ($P < 0.001$).

At baseline, all diabetic patients were treated with diet only. The frequency of drug treatment increased with time: at the 5-year examination, 56 (51%) of patients were treated with oral drugs and 5 (5%) with insulin; and at the 10-year examination, only 15 (17.0%) were treated with diet only, 53 (60%) with oral drugs, and 20 (22.8%) with insulin (10 received additional oral hypoglycemic drugs, i.e., combination therapy).

At the 5- and 10-year examinations (Table 2), the differences in mean body mass between the groups were reduced, but waist circumference remained greater in diabetic than in control subjects. At the 5- and 10-year examinations, no significant differences in total and LDL cholesterol levels were observed between the diabetic and nondiabetic groups, whereas the same abnormalities found at the baseline study in HDL cholesterol and lipoprotein triglycerides were found in diabetic patients. The decrease in HDL cholesterol in diabetic patients was due to a lower level of HDL_2 subfraction, as no difference in HDL_3 cholesterol levels was observed between the groups. Likewise, $apoA_1$ levels were lower but apoB levels higher in diabetic than in control groups at 5 years and 10 years. Further, LDL cholesterol/apoB and HDL cholesterol/$apoA_1$ ratios were markedly lower in diabetic than in control subjects at both examinations.

Total and cardiovascular mortality

The total mortality (Fig. 1) during the 15-year follow-up was 44.3% (31 of 70) in diabetic men and 12.9% (8 of 62) in control men (age-adjusted odds ratio [OR] 5.0, $P < 0.001$). For women, the total mortality was 44.4% (28 of 63) in diabetic and 11.0% (9 of 82) in control women (OR 5.2, $P < 0.001$). The excess mortality rates in diabetic subjects were mainly due to cardiovascular deaths (CVDs) (Fig. 2) being 37.1% (26 of 70) in diabetic men compared with 8.1% (5 of 62) in control men (OR 6.2, $P < 0.001$) and 34.9% (22 of 63) in diabetic women compared with 3.7% (3 of 82) in control women (OR 11.4, $P < 0.001$).

Incidence of myocardial infarction and stroke

The incidence of new fatal or nonfatal myocardial infarction (Fig. 3) during the 15-year follow-up was 35.1% (20 of 57) in diabetic men, 19.3% (11 of 57) in control men (OR 2.2, $P = 0.069$), 30.8% (16 of 52) in diabetic women, and 5.1% (4 of 78) in control women (OR 6.3, $P < 0.001$). The incidence of new fatal or nonfatal stroke (Fig. 4) was 15.9% (11 of 69) in diabetic men compared with 6.6% (4 of 61) in control men (OR 2.6, $P = 0.122$) and 25.0% (15 of 60) in diabetic women compared

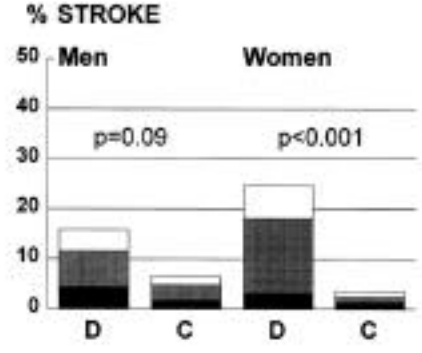

Figure 4—*Incidences of new fatal or nonfatal stroke in diabetic (D) and control (C) subjects by sex from the time of diagnosis to the 5-year (■), 10-year (■ + ■), and 15-year follow-up (total height of the bar).*

Table 3—*Age, sex, BMI, waist circumference, blood pressure levels, albuminuria, fasting insulin levels, and ischemic ECG as predictors of subsequent CVD during the 15-year follow-up in patients with newly diagnosed type 2 diabetes*

	CVD⁻	CVD⁺	*P* value
Baseline variables			
n	85*	48	—
Age (years)	56.9 ± 0.8	53.8 ± 0.5	0.003
Men (%)	52	54	0.789
Smoking history (%)	35 (41)	27 (56)	0.094
BMI (kg/m²)	30.6 ± 0.5	30.2 ± 0.8	0.679
Systolic blood pressure (mmHg)	150 ± 2	150 ± 3	0.814
Diastolic blood pressure (mmHg)	93 ± 1	92 ± 1	0.514
Albuminuria (30 mg/24 h)	20%	23%	0.647
Fasting serum insulin (mU/l)	23.4 ± 2.5	27.2 ± 2.5	0.189
Ischemic ECG (%)	19 (22)	24 (50)	0.001
5-year study variables			
n	81†	40	—
BMI (kg/m²)	28.7 ± 0.5	28.4 ± 0.8	0.707
Waist circumference (mm)	98 ± 2	97 ± 4	0.675
Systolic blood pressure (mmHg)	143 ± 2	147 ± 3	0.321
Diastolic blood pressure (mmHg)	86 ± 1	84 ± 1	0.294
Albuminuria (30 mg/24 h) (%)	11 (15)	12 (32)	0.031
Fasting plasma insulin (mU/l)	20.1 ± 1.9	27.0 ± 5.2	0.128
Treatment of diabetes (%)			
Diet	73	27	0.083 for trend
Oral drugs	57	43	—
Insulin	60	40	—
10-year study variables			
n	77†	21	—
Albuminuria (>20 μg/min) (%)	41	53	0.366
Treatment of diabetes (%)			
Diet	89	11	0.360 for trend
Oral drugs	76	24	—
Insulin (with or withour oral drugs)	76	24	—

Data are means ± SEM, unless otherwise indicated. *Baseline study population with respect to 15-year follow-up and CVD status as end points; †5- and 10-year study populations, respectively.

with 3.7% (3 of 81) in control women (OR 7.7, $P = 0.002$).

Predictors of 15-year CVD in diabetic patients: univariate analysis

Age, sex, anthropometric variables, blood pressure levels, albuminuria, fasting insulin, ischemic ECG, and treatment of diabetes. Table 3 shows the associations of these variables with 15-year CVD in diabetic patients. In the univariate analysis, statistically significant predictors were age and ischemic ECG changes (baseline study), whereas body weight, waist circumference, and blood pressure levels showed no constant association. Although fasting insulin levels tended to be higher in subjects with CVD, this difference did not reach statistical significance. Albuminuria was a significant predictor of CVD when measured at the 5-year study, but this relationship was not evident at the baseline and 10-year examinations. The mode of treatment of diabetes was not significantly associated with CVD.

Metabolic control. Metabolic control was consistently worse in subjects with CVD than in those without (Table 4). This relationship was statistically significant whether measured from baseline or from 5-year fasting or postload glucose levels (except the 1-h glucose level at 5 years). Further, the 5-year HbA_{1c} level was a nearly significant predictor ($P = 0.05$), and the 10-year HbA_{1c} was highly significant ($P = 0.009$).

The baseline fasting glucose (tertile limits 8.6 and 11.9 mmol/l) and HbA_{1c} at the 5-year examination (tertile limits 7.8 and 10.5%) were divided into the tertiles. CVD tended to be higher with increasing tertiles of fasting blood glucose (27.7, 38.1, and 43.2%; $P = 0.08$ for trend) and of HbA_{1c} (27.5, 33.3, and 49.5%; NS).

Diabetic dyslipidemia. When analyzed from the baseline examination, HDL cholesterol was lower and LDL triglycerides were higher in subjects with CVD than in those without (Table 5). The associations with other lipids and lipoproteins did not reach statistical significance. When analyzed from the 5-year examination, low HDL cholesterol was a nearly significant predictor of CVD ($P = 0.058$), with this effect being due to lowered HDL_2 cholesterol ($P = 0.041$). The impact of LDL triglycerides at the 5-year examination was not statistically significant, but the VLDL triglycerides were higher in subjects with CVD than in those without ($P = 0.028$). Note that even if LDL cholesterol per se was not a predictor of CVD, the marker of LDL size—the LDL cholesterol/apoB ratio—was lower in subjects with CVD than in subjects without CVD.

Predictors of fatal and nonfatal myocardial infarction and stroke in diabetic patients. As to myocardial infarction and stroke, the impact of previous risk factors was seen, but they were markedly attenuated and did not reach statistical significance, except for the association between hyperglycemia and stroke (data not shown).

Predictors of CVD in nondiabetic control subjects at the baseline examination

Eight subjects (5.6%) had CVD during the 15-year follow-up. Although the number of subjects was very small, smoking history (62.5 vs. 22.8%; $P = 0.02$) and fasting blood glucose (5.7 ± 0.3 vs. 4.9 ± 0.1 mmol/l; $P = 0.01$) emerged as statistically significant predictors. Further, total cholesterol tended to be higher (7.18 ± 0.57 vs. 6.66 ± 0.10 mmol/l; $P = 0.22$) and HDL cholesterol lower (1.15 ± 0.11 vs. 1.35 ± 0.03 mmol/l; $P = 0.10$) in subjects with CVD than in those without. Interestingly, total triglycerides were also significant predictors of CVD in control subjects (1.56 ± 0.10 vs. 2.35 ± 0.57; $P = 0.03$), as were VLDL triglycerides (1.71 ± 0.56 vs. 1.05 ± 0.09 mmol/l; $P = 0.05$) and even LDL triglycerides (0.51 ± 0.08 vs. 0.36 ± 0.01 mmol/l; $P = 0.02$). Blood pressure levels were not associated with CVD in control subjects (systolic blood pressure, 152 ± 10 vs. 147 ± 2 mmHg; $P = 0.436$; diastolic blood pressure, 91 ± 4 vs. 91 ± 1 mmHg; $P = 0.82$).

Table 4—*Glycemic control measured at baseline and at 5- and 10-year follow-up examinations as a predictor of subsequent CVD up to the 15-year follow-up in patients with newly diagnosed type 2 diabetes*

	CVD$^-$	CVD$^+$	*P* value
Baseline variables			
n	85*	48	—
Fasting glucose (mmol/l)	10.1 ± 0.3	11.8 ± 0.6	0.018
1-h glucose (mmol/l)	17.3 ± 0.5	19.2 ± 0.8	0.025
2-h glucose (mmol/l)	16.8 ± 0.6	18.7 ± 5.9	0.056
5-year study variables			
n	81†	40	—
HbA_{1c} (%)	8.9 ± 0.3	9.9 ± 0.5	0.054
Fasting glucose (mmol/l)	11.2 ± 0.4	13.3 ± 0.6	0.005
1-h glucose (mmol/l)	18.8 ± 0.5	20.3 ± 0.8	0.120
2-h glucose (mmol/l)	18.9 ± 0.7	21.5 ± 0.9	0.020
10-year study variables			
n	77†	21	—
HbA_{1c} (%)	8.7 ± 0.2	10.1 ± 0.5	0.009
Fasting glucose (mmol/l)	12.0 ± 0.4	13.0 ± 0.9	0.271
1-h glucose (mmol/l)	20.3 ± 0.6 (*n* = 65)	21.4 ± 0.9 (*n* = 16)	0.391
2-h glucose (mmol/l)	20.0 ± 0.8	21.7 ± 1.4	0.317

Data are means ± SEM. *Baseline study population with respect to 15-year follow-up and CVD status as end points, †5- and 10-year study populations, respectively.

Multivariate analyses in diabetic patients

The independent roles of risk factors as predictors of 15-year CVD in diabetic patients were assessed by multiple logistic regression analyses. These were constructed for each examination. Age, sex, and BMI were included for each model as putative determinants, and other variables were included if the *P* value was <0.10 in univariate analyses. For dyslipidemia, of the variables with high intercorrelation, the most significant predictor was taken into the final model.

Age was a constant predictor of CVD in diabetic patients in all examinations (Table 6), whereas male sex and BMI were not. At baseline examination, ischemic ECG changes at baseline showed an independent predictive value for CVD. Hyperglycemia assessed by fasting glucose levels at the baseline and at the 5-year examination and by HbA_{1c} at the 10-year examination was constantly predictive of CVD. From the lipid values, the highest predictive value could be attributed to LDL triglycerides (baseline), VLDL triglycerides (5-year examination), and apoB (10-year examination). Interestingly, albuminuria was not an independent predictor of CVD in multivariate analysis after adjusting for the effects of hyperglycemia. Further, we studied the possible interactions between the lipoprotein and hyperglycemia variables by including the interaction term (the product of these variables) in the model. No statistically significant interactions were observed.

Excess cardiovascular mortality in diabetic patients

The odds ratio of CVD for diabetic patients versus control subjects was 8.2 when adjusted for age and sex (assessed only at the baseline examination) (Fig. 5). Further adjustment for conventional risk factors (LDL cholesterol, smoking, hypertension, and ischemic ECG) reduced the odds ratios to 6.3. Finally, when adjusted for HDL cholesterol and fasting glucose level, the respective odds ratio was reduced to 2.1.

CONCLUSIONS

The major finding of this study is that hyperglycemia assessed by repeated measurements of glucose and HbA_{1c} values is a strong and constant predictor of CVD in type 2 diabetic patients and the same applies to diabetic dyslipidemia, i.e., variables reflecting disturbed VLDL metabolism and decreased LDL size.

Although the patients in our study were recruited from primary care at the time of clinical diagnosis of diabetes and were initially treated with diet only, the 15-year total mortality was 44% in diabetic patients, which was markedly higher than in the general population. The relative contribution of diabetes to cardiovascular mortality was greater in women than in men, as also shown in many earlier studies (18). The burden of atherosclerotic diseases in type 2 diabetic patients is dependent on the frequency of these diseases in the background population (19,20), but the high mortality and morbidity rates necessitate viewing this common disease as one of the major health problems.

The 10-year follow-up of this study population was the first to demonstrate that hyperglycemia is an independent predictor of CVD in type 2 diabetic patients (4). Another study also carried out in the eastern part of the Finland has shown that HbA_{1c} is an independent predictor of 8-year CVD in patients with a longer known duration of type 2 diabetes (8). Further study on elderly type 2 diabetic patients showed that HbA_{1c} predicted fatal and nonfatal events during a relatively short follow-up time of 3.5 years (6). Furthermore, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (3) showed that glycohemoglobin concentrations predicted 8-year coronary heart disease mortality after controlling for smoking and blood pressure. On the other hand, in some studies either this association has not been shown or significant univariate associations have been reduced to nonsignificant levels after adjustment for other risk factors (1,3,5).

Important strengths in the present study corroborate the previous observations linking hyperglycemia with cardiovascular events. First, the patients have been followed from the time of clinical diagnosis. Second, this is the only study that has measured the effects of risk factors (e.g., level of glycemia) at multiple time points. Third, the follow-up time is markedly longer than in any previous study. Further, we have used several indicators of hyperglycemia, including fasting and postload glucose levels and HbA_{1c}. It is known that metabolic control of type 2 diabetes deteriorates with increasing known duration of the disease, irrespective of the mode of treatment (13,21); therefore, the longer the known duration of the disease, the greater the likelihood that the harmful effects of hyperglycemia become underestimated. This underestimation is even more likely if the level of glycemia is measured only once, as is the case in most previous studies. Additionally, the long follow-up time of the present study is likely to exclude the possibility that hyperglycemia merely reflects the effects of clinical or subclinical diabetic complications or comor-

Table 5—*Serum lipids, lipoproteins, apoA$_1$ and apoB and lipoprotein size indexes as predictors of subsequent CVD during the 15-year follow-up in patients with newly diagnosed type 2 diabetes*

	CVD$^-$	CVD$^+$	*P* value
Baseline variables			
n	85*	48	—
Serum cholesterol (mmol/l)	6.35 ± 0.15	6.58 ± 0.19	0.357
LDL cholesterol (mmol/l)	4.09 ± 0.13	4.30 ± 0.14	0.303
HDL cholesterol (mmol/l)	1.12 ± 0.03	0.99 ± 0.03	0.005
VLDL cholesterol (mmol/l)	1.13 ± 0.10	1.29 ± 0.14	0.347
Total serum triglycerides (mmol/l)	2.31 ± 0.17	2.59 ± 0.24	0.325
VLDL triglycerides (mmol/l)	1.69 ± 0.15	1.85 ± 0.21	0.306
LDL triglycerides (mmol/l)	0.43 ± 0.03	0.54 ± 0.04	0.004
5-year study variables			
n	81†	40	—
Serum cholesterol (mmol/l)	6.41 ± 0.17	6.61 ± 1.40	0.502
LDL cholesterol (mmol/l)	3.91 ± 0.12	3.90 ± 0.15	0.676
VLDL cholesterol (mmol/l)	1.44 ± 0.13	1.74 ± 0.19	0.182
HDL cholesterol (mmol/l)	1.07 ± 0.03	0.97 ± 0.04	0.058
HDL$_2$ cholesterol (mmol/l)	0.77 ± 0.03	0.67 ± 0.04	0.041
HDL$_3$ cholesterol (mmol/l)	0.30 ± 0.01	0.30 ± 0.02	0.979
Total serum triglycerides (mmol/l)	2.51 ± 0.27	3.15 ± 0.38	0.172
VLDL triglycerides (mmol/l)	1.91 ± 0.25	2.48 ± 0.35	0.028
LDL triglycerides (mmol/l)	0.48 ± 0.03	0.52 ± 0.03	0.143
ApoB (g/l)	1.56 ± 0.05	1.69 ± 0.07	0.159
ApoA$_1$ (g/l)	1.56 ± 0.03	1.50 ± 0.04	0.274
LDL cholesterol/apoB	2.57 ± 0.06	2.37 ± 0.08	0.039
HDL cholesterol/apoA$_1$	0.74 ± 0.01	0.67 ± 0.01	0.168
10-year study variables			
n	77†	21	—
Serum cholesterol (mmol/l)	6.31 ± 0.16	6.57 ± 0.25	0.444
LDL cholesterol (mmol/l)	4.01 ± 0.11	4.22 ± 0.24	0.388
HDL cholesterol (mmol/l)	1.13 ± 0.04	1.04 ± 0.05	0.254
VLDL cholesterol (mmol/l)	1.17 ± 0.12	1.31 ± 0.15	0.612
Total serum triglycerides (mmol/l)	2.40 ± 0.20	2.94 ± 0.36	0.224
VLDL triglycerides (mmol/l)	1.78 ± 0.19	2.25 ± 0.34	0.148
LDL triglycerides (mmol/l)	0.39 ± 0.02	0.45 ± 0.02	0.033
ApoB (g/l)	1.11 ± 0.03	1.31 ± 0.06	0.004
ApoA$_1$ (g/l)	1.25 ± 0.02	1.25 ± 0.05	0.980
LDL cholesterol/apoB	3.70 ± 0.10	3.28 ± 0.19	0.060
HDL cholesterol/apoA$_1$	0.86 ± 0.03	0.78 ± 0.03	0.020

Data are means ± SEM. *Baseline study population with respect to 15-year follow-up and CVD status as end points, †5- and 10-year study populations, respectively.

bidities—in other words, that the sicker persons would be more likely to be hyperglycemic and therefore more likely to succumb within the relatively short observation time. On the other hand, this study cannot address the concept that the level of glycemia or its control more reflects the genetic burden for an individual or metabolic covariates rather than it does the noxious effects of glucose per se (10). More definite answers could be obtained from the prospective intervention studies aiming at correction of hyperglycemia (20), but the studies performed so far have not shown an unequivocal reduction in cardiovascular events (22–23); in fact, a trend toward an increase in events was observed in a group treated intensively with insulin in the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (23). The theoretical possibilities concerning why hyperglycemia would increase CVD not reviewed herein are numerous, e.g., glycation of collagen or other vessel-wall proteins and lipoproteins, increased production of free radicals and heightened oxidative stress, changes in vascular reactivity, and increased thrombus formation (17,24–27).

Another major contributor to cardiovascular mortality was diabetic dyslipidemia, i.e., low HDL cholesterol or HDL$_2$ cholesterol (determined at baseline or at 5 years, respectively) and elevated VLDL triglycerides (determined at 5 years). However, more evident contributors than absolute concentrations of the lipoproteins were the variables reflecting compositional abnormalities, e.g., elevated LDL triglycerides, apoB, and the LDL cholesterol/apoB ratio. In general, LDL cholesterol is considered the most atherogenic lipoprotein species. However, it is also possible that LDL enriched with triglycerides—itself or as a reflection of other lipoprotein abnormalities characteristic of disturbed catabolism of VLDL, remnant particles, intermediate-density lipoprotein (IDL), or small dense LDL—may be among the most atherogenic lipoprotein particles(28).Further, as a support of the concept of atherogenicity of LDL triglycerides, they also predicted CVD in control subjects, despite the small number of cases.

Interestingly, elevated apoB at the 10-year examination was a strong predictor of CVD. ApoB is the major protein constituent of VLDL and its metabolic products, IDL and LDL (29). Further, from the various risk factors determined at the 10-year examination, elevated LDL triglycerides and apoB were most strongly associated with the ultrasonographically assessed carotid intima-media thickness in diabetic patients(30), a quantitative estimate of atherosclerosis. The content of immunologically detectable apoB in human aortic intima has a positive correlation with serum apoB concentration (31), and these particles can be found even in lesion-free human aortic intima (32). Therefore, our results give further support to the view that these apoB-containing particles are likely to play a fundamental role in the development of atherosclerosis in patients with type 2 diabetes. Moreover, this relationship is not solely mediated by a tendency to thrombosis favored by disturbances in triglyceride metabolism (33).

Although absolute LDL cholesterol levels were not predictive of CVD (4), the LDL cholesterol/apoB ratio was predictive in diabetic patients. This ratio has been previously implicated to be a crude marker of LDL size (34–36). Small dense LDL linked with elevated triglycerides has been impli-

Table 6—*Adjusted odds ratios from multiple logistic regression analyses on the impact o selected predictors of CVD during the 15-year follow-up in patients with newly diagnosed typ 2 diabetes*

	Odds ratio	95% CI	*P* value
Baseline variables (*n* = 133)			
Age (years)	1.11	1.02–1.20	0.01
Male sex (0 = no, 1 = yes)	0.96	0.09–3.26	0.95
BMI (kg/m^2)	1.01	0.33–3.26	0.78
Smoking history (0 = no, 1 = yes)	2.53	0.80–8.12	0.12
Lg-LDL triglycerides (mmol/l)*	8.70	1.03–73.0	0.03
Fasting glucose (mmol/l)	1.13	0.93–1.10	0.04
Ischemic ECG (0 = no, 1 = yes)	3.00	1.24–7.22	0.01
5-year study variables (*n* = 111)			
Age (years)	1.14	1.04–1.24	0.01
Male sex (0 = no, 1 = yes)	1.85	0.71–4.82	0.21
BMI (kg/m^2)	0.97	0.88–1.08	0.29
Albuminuria (0 = no, 1 = yes)	1.86	0.62–5.53	0.27
Lg-VLDL triglycerides (mmol/l)	3.60	0.94–13.8	0.06
Fasting glucose (mmol/l)	1.16	1.13–16.4	0.02
10-year study variables (*n* = 93)			
Age (years)	1.11	0.99–1.25	0.07
Male sex (0 = no, 1 = yes)	1.45	0.41–4.89	0.64
BMI (kg/m^2)	1.03	0.76–1.59	0.62
HbA_{1c} (%)	1.52	1.25–2.00	0.01
Lg-apoB (g/l)†	16.1	0.96–267	0.05

*When substituted with HDL cholesterol, *P* = 0.09, odds ratio 0.24; †when substituted with Lg-LDL-triglycerides, *P* = 0.050, odds ratio 8.72. Lg, logarithmic.

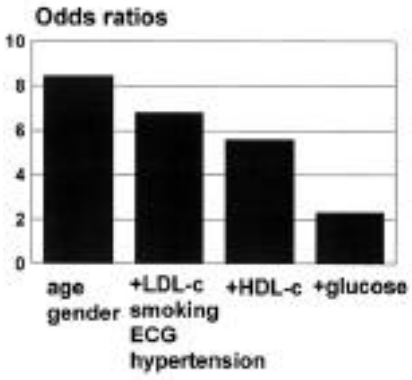

Figure 5—*The increased risk (odds ratios, diabetic vs. nondiabetic subjects) for CVD from the time of diagnosis to the 15-year examination. Left bar is adjusted for age and sex only. Second bar from the left is adjusted for age, sex, LDL cholesterol, smoking, ischemic ECG, and hypertension. Third bar is adjusted for all previous variables plus HDL cholesterol. Fourth bar is adjusted for all previous variables plus fasting glucose level.*

cated as a fundamental component of dyslipidemia in type 2 diabetes, and it has been suggested that these particles are more atherogenic than larger LDL particles(37). However, no previous prospective study has assessed the role of LDL size in predicting atherosclerotic vascular diseases in diabetic patients. The method used in our study to assess LDL size is crude. This would, however, decrease the likelihood of finding a predictive association with CVD. Therefore, it is probable that this association was, if anything, underestimated in this study. Taken together, our findings demonstrate that the closely interwoven components of diabetic dyslipidemia, elevated triglyceride-rich lipoproteins, and low concentrations of HDL cholesterol and small LDL contribute to CVD in patients with type 2 diabetes. Furthermore, this contribution is independent of the degree of hyperglycemia.

Of the other risk factors, smoking emerged as a strong predictor of CVD in diabetic patients at baseline (4), but the relationship became less evident at later examinations. This may be due to the selective mortality, but more important, it may also be due to the fact that stopping smoking was common in diabetic patients. These results indirectly suggest that quitting smoking is also an effective measure to prevent CVD in type 2 diabetes.

Albuminuria was predictive of CVD, but only as assessed at the 5-year examination. Note, however, that we assessed at each examination urinary albumin from one collection only, and the known high interassay variation of urinary albumin excretion may have decreased the predictive accuracy of this variable. On the other hand, albuminuria is closely associated with a clustering of risk factors, hypertension, dyslipidemia, and hyperglycemia (38), shown also in this study (39). Therefore, it is likely that excess risk of CVD associated with albuminuria is, to a large extent, mediated through this adverse profile of risk factors.

The fact that hypertension and blood pressure levels were not predictive of CVD warrants some comments. This finding should not be interpreted to mean that hypertension is of little significance. First, the frequency of hypertension was already high at the time of diagnosis of type 2 diabetes, and when a risk factor becomes the "norm" in some population, it is highly unlikely that a relatively small sample size has enough power to reveal these associations. Furthermore, the hypertension, as judged from the mean blood pressure levels and the frequent use of antihypertensive drugs, was rather well controlled, unlike lipid disorders.

To conclude, the results of this 15-year follow-up study strongly support the idea that both hyperglycemia and diabetic dyslipidemia among patients with type 2 diabetes are determinants of markedly increased cardiovascular mortality. Therefore, type 2 diabetes should be considered as a serious disease that necessitates more intensive treatment of both cardiovascular risk factors and hyperglycemia from its early phases.

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