Age-Related Macular Degeneration in Newly Diagnosed Type 2 Diabetic Patients and Control Subjects

A 10-year follow-up on evolution, risk factors, and prognostic significance

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OBJECTIVE — To investigate the evolution of visual acuity, age-related macular degeneration (AMD), and its relation to 10-year cardiovascular mortality and risk factors in patients with newly diagnosed type 2 diabetes and control subjects.

RESEARCH DESIGN AND METHODS — A 10-year prospective study consisting of a representative group of 133 (70 men, 63 women) newly diagnosed type 2 diabetic patients diagnosed at health centers between 1979 and 1981 and 144 (62 men, 82 women) nondiabetic control subjects recruited from the population register was performed. The frequency of AMD was determined by grading of 45° stereoscopic fundus photographs. The subjects were studied at baseline and after 5 and 10 years.

RESULTS — By the 10-year follow-up, visual acuity had declined more markedly in the diabetic patients than in the control subjects. Although the frequency of AMD was nearly the same in both groups (11–19%), it decreased visual acuity earlier in the diabetic patients than in the control group. AMD at baseline predicted 10-year cardiovascular mortality independently of adjustment for other risk factors in the diabetic patients (odds ratio [95% CI] 4.7 [1.1–19.3], $P = 0.033$).

CONCLUSIONS — Visual acuity deteriorated earlier in newly diagnosed type 2 diabetic patients than in the control group although the cross-sectional frequency of AMD was nearly the same in both groups. Interestingly, AMD was an independent risk factor for cardiovascular mortality in type 2 diabetic patients, but the background mechanism(s) behind this association is unknown.

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The etiology of age-related macular degeneration (AMD) is poorly understood although it is the most common cause of permanent visual impairment among the elderly, especially among diabetic elderly. The natural history of AMD has been poorly documented (1), a fact that precludes rational planning for the health care needs of a growing population of elderly people who are at risk of visual impairment from AMD. Genetic factors (2–4), oxidative stress with long-term exposure to light or low levels of antioxidants (5), tobacco smoking (6,7), and atherosclerotic vascular disease (8) have been hypothesized as possible pathogenetic factors for the development of AMD. The effect of hyperglycemia on development of AMD is unknown. Although some reports have suggested a positive association of elevated blood glucose values with AMD (9,10), a number of case-control studies (11–13) and the population-based Framingham Eye Study (14) have failed to find an association between AMD and diabetes. Type 2 diabetic patients have markedly increased cardiovascular mortality and morbidity. Thus, it can be hypothesized that AMD in the diabetic population may be associated with atherothrombotic vascular disease.

There are few long-term prospective studies on the development of and risk factors for AMD (1,15) and, to our knowledge, none included newly diagnosed type 2 diabetic patients and nondiabetic control subjects. In the present study, we followed a representative group of middle-aged patients with newly diagnosed type 2 diabetes and a comparable group of nondiabetic control subjects for 10 years and assessed the evolution of visual acuity, AMD, and cardiovascular mortality; their predictors; and the effect of aging per se on the ocular manifestations.

RESEARCH DESIGN AND METHODS

Study population

The formation and representativeness of the baseline, 5-year, and 10-year study populations have been described previously in detail (16–18). Briefly, the original study population consisted of 133 patients (70 men, 63 women) with newly diagnosed type 2 diabetes, aged 45–64 years, and 144 control subjects (62 men, 82 women) randomly selected from the population register of the same age-group. The selection of both groups was carried out between May 1979 and December 1981, with the subjects recruited from a defined area of 180,000 inhabitants in the county of Kuopio in Eastern Finland. Approval for

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Abbreviations: AMD, age-related macular degeneration; Mc, Minnesota code; WHO, World Health Organization.

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

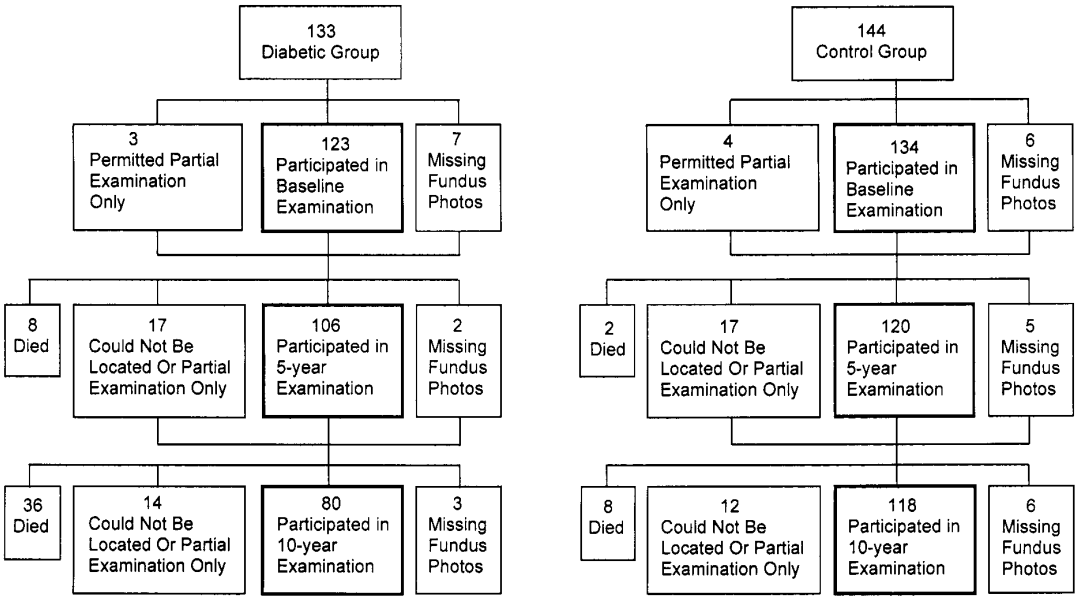

Figure 1—*Flow diagram of the formation of the follow-up study population.*

the study had been given by the Ethics Committee of Kuopio University and Kuopio University Hospital. Informed consent was obtained from all subjects studied.

The diabetic patients were referred to the study by general practitioners working in the community health centers of the survey area. The diagnosis of diabetes was primarily made in the clinical setting (16) and was confirmed by an oral glucose tolerance test using the diagnostic criteria recommended by the World Health Organization (WHO) Expert Committee on Diabetes Mellitus (19). All diabetic patients were nonketotic at the time of diagnosis, and none of them needed insulin treatment during the follow-up period of at least 3 months.

Patients were referred to the primary health care center after the baseline examination, with the exception of those who needed any kind of ophthalmic care, e.g., retinal photocoagulation. The same was true throughout follow-up.

Both diabetic and nondiabetic subjects were reexamined 5 and 10 years after the first examination, in the years 1985–1986 and 1991–1992, respectively. The number of diabetic patients and control subjects who participated and the reasons for nonparticipation in the 10-year follow-up are given in Fig. 1. During the 10-year follow-up, 36 (27.1%) diabetic patients and 8 (5.6%) control subjects died (20). The final 10-year study population consisted of 80 diabetic patients and 118 control subjects. Thus, 60.1 and 81.9% from the baseline diabetic and nondiabetic study groups, respectively, participated in the 10-year examination (Fig. 1). Those diabetic patients who were not available for 10-year analyses were initially older (58.3 ± 0.9 vs. 54.6 ± 1.1 years, $P < 0.05$), but no statistically significant differences were found at baseline in BMI, fasting plasma glucose, or insulin levels between the 10-year study participants and nonparticipants.

Methods

The clinical examination, detailed medical history, and use of drugs were registered at all examinations. The ophthalmic history included eventual inflammations and infections of the eyes that could deteriorate the visual acuity.

Morbidity and all-cause and cardiovascular mortality. A conventional 12-lead resting electrocardiogram was recorded from each subject at each examination and interpreted according to the Minnesota code (Mc) (21). The definite myocardial infarction class consisted of patients with major Q-QS abnormalities (Mc 1.1–2), those 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. Stroke was defined as a clinical syndrome consisting of neurological findings persisting >24 h and verified at a hospital (21). Data on the frequency of cardiovascular disease concern the following end points: total cardiovascular mortality and fatal and nonfatal myocardial infarction and stroke. Causes of deaths were ascertained from patient records and death certificates and nonfatal events from patient records, in addition to medical history and clinical examination at the 10-year examination.

Laboratory examinations. An oral glucose tolerance test was performed at all 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 afterward (19). HbA_{1c} was measured at the 5- and 10-year examinations by liquid cation exchange chromatography (normal range 4.0–6.0%). The methods concerning measurements of serum insulin, serum and lipoprotein lipids, and urinary albumin excretion have also been described earlier (20,22,23).

Ophthalmic examinations. The best corrected visual acuity of each eye was measured after retinoscopy and subjective refraction. AMD was assessed by grading of 45° color (at baseline and 5-year examinations) and red-free (at 10-year examination) fundus photographs taken through a dilated pupil. Fundus photography was performed at baseline using the Nikon 45 Retinapan fundus camera (Tokyo) and at the 5- and 10-year examinations by the Canon 60ZA fundus camera (Tokyo). At least one stereoscopic pair of photographs was taken from each eye. The central 45° field was photographed centered on the fovea. To confirm the difference between

AMD and diabetic maculopathy, fluorescein angiography was performed at baseline and 5-year examinations using the same fundus cameras used to obtaining the color fundus photographs with the built-in filter in place. Drusen, exudates, increased retinal pigment, retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal hemorrhages, fibrous scars, and geographic atrophy were criteria for AMD.

Grading of fundus photographs was conducted by the first author without knowledge of the metabolic status of the subjects and took place at least twice. If there was a discrepancy between the two gradings, a third grading was performed by another ophthalmologist (M.E.T.). The final record of each parameter was made on the basis of two identical gradings. At the baseline and 5-year examinations, the color fundus photographs were analyzed as stereoscopic pairs using magnification (22×) with two microfilm readers linked together. At the 10-year examination, the photographs were graded as 17 × 12 cm red-free positive prints, viewed stereoscopically.

Statistical methods

All the data were analyzed using the SPSS/PC+ program (SPSS, Chicago). Results are expressed as means ± SD. The differences between the two groups concerning continuous variables were analyzed by Student's *t* test for unpaired samples or the Mann-Whitney *U* test, when appropriate. Time-related changes within the group were analyzed by a paired Student's *t* test or Wilcoxon's test for paired samples. The χ^2 test or Fisher's test was used to analyze the differences between the groups for the frequency data. Logistic regression analysis was performed to assess the independent predictive effect of various selected variables. *P* values of <0.05 were considered statistically significant, but *P* values >0.05 are also shown. For technical reasons, complete data were not obtained from all subjects. Therefore, the number of subjects examined varied slightly from test to test.

RESULTS

Clinical characteristics

Clinical characteristics at the baseline and follow-up examinations are shown in Table 1. The type 2 diabetic patients were, on average, 2–3 years older at baseline than the control subjects, but there was no difference in age between the groups at the 10-year examination. At baseline, the diabetic patients were more obese and had lower LDL and HDL cholesterol, higher total serum triglycerides, a higher frequency of hypertension, and more microalbuminuria than the control subjects. With the exception of identical BMI at the 10-year examination, the same was true during the 10-year follow-up.

At baseline, all diabetic subjects were treated with diet only, and at the 5-year examination, 49 (35%) of 109 were treated with diet, 55 (58%) with oral hypoglycemic drugs, and 5 (7%) with insulin. The percentage of patients treated with diet only at the 10-year examination was 9%, whereas that of those treated with insulin alone or as a supplement to oral therapy, i.e., combination therapy, was 36%. By the 10-year follow-up, 30 (23.5%) control subjects had developed impaired glucose tolerance and 3 (2.1%) had diabetes treated with oral hypoglycemic drugs.

With the exception of the higher BMI of diabetic patients at the 5-year examination and the older age of diabetic and control

Table 1—*Clinical characteristics of type 2 diabetic patients and control subjects at baseline and at the 5- and 10-year examinations*

	Diabetic patients	Control subjects	*P*
Baseline examination			
n	133	144	—
Male sex	70 (52.6)	62 (43.1)	0.112
Age (years)	55.7 ± 9.7	54.3 ± 5.6	0.134
BMI (kg/m^2)	30.4 ± 5.2	27.0 ± 4.3	<0.001
Fasting blood glucose (mmol/l)	12.0 ± 4.0	5.6 ± 0.8	<0.001
1-h blood glucose (mmol/l)	20.1 ± 5.3	7.6 ± 2.5	<0.001
2-h blood glucose (mmol/l)	19.6 ± 6.3	6.6 ± 2.0	<0.001
Fasting insulin (mU/l)	24.8 ± 16.1	15.4 ± 8.7	<0.001
Serum cholesterol (mmol/l)	6.43 ± 1.36	6.69 ± 1.17	0.085
LDL cholesterol (mmol/l)	4.17 ± 1.10	4.49 ± 1.04	0.013
HDL cholesterol (mmol/l)	1.07 ± 0.29	1.34 ± 0.34	<0.001
Total serum triglycerides (mmol/l)	2.41 ± 1.62	1.60 ± 1.16	<0.001
VLDL triglycerides (mmol/l)	1.75 ± 1.41	1.08 ± 1.06	<0.001
LDL triglycerides (mmol/l)	0.47 ± 0.25	0.37 ± 0.16	<0.001
Systolic blood pressure (mmHg)	150 ± 18	147 ± 19	0.165
Diastolic blood pressure (mmHg)	93 ± 10	91 ± 9	0.067
Drug treatment for hypertension (%)	51.9	20.8	<0.001
Prevalence of ischemic electrocardiogram changes	24 (18.0)	9 (6.3)	0.002
Smoking history (>1 year)	62 (46.6)	36 (25.0)	<0.001
History of myocardial infarction	24 (18.0)	9 (6.3)	0.002
Microalbuminuria (>30 mg/24 h) (%)	20.7	1.5	<0.001
5-year examination			
n	109	129	—
BMI (kg/m^2)	28.7 ± 4.5	27.1 ± 4.2	0.006
Fasting plasma glucose (mmol/l)	11.5 ± 3.7	5.8 ± 1.3	<0.001
HbA_{1c} (%)	9.1 ± 2.5	5.8 ± 1.5	<0.001
Fasting insulin (mU/l)	21.6 ± 21.8	18.2 ± 20.6	<0.001
10-year examination			
n	92	128	—
BMI (kg/m^2)	29.0 ± 4.9	28.3 ± 4.8	0.315
Fasting plasma glucose (mmol/l)	12.2 ± 3.5	6.0 ± 1.3	<0.001
HbA_{1c} (%)	9.0 ± 2.0	5.5 ± 1.4	<0.001
Fasting insulin (mU/l)	14.9 ± 7.1	11.9 ± 6.9	0.003
Serum cholesterol (mmol/l)	6.36 ± 1.34	6.37 ± 1.15	0.095
HDL cholesterol (mmol/l)	1.11 ± 0.29	1.31 ± 0.32	<0.001
Total serum triglycerides (mmol/l)	2.51 ± 1.70	1.78 ± 1.04	<0.001
Microalbuminuria (>20 μg/min) (%)	43.2	12.7	<0.001

Data are *n* (%) or means ± SD unless otherwise indicated.

Table 2—*Mean visual acuity of the better eye in type 2 diabetic patients and control subjects with and without AMD and cumulative percentage of subjects with visual acuity <20/25 at the 10-year follow-up*

	Visual acuity			Visual acuity <20/25 (%)	
	AMD$^+$	AMD$^-$	*P*	AMD$^+$	AMD$^-$
Diabetic patients					
Baseline examination (logMar)	20/21 (+0.02)	20/20 (+0.01)	0.038	16.7	2.2
5-year examination (logMar)	20/24 (+0.09)	20/22 (+0.03)	0.023	27.3	5.6
10-year examination (logMar)	20/21 (+0.02)	20/21 (+0.03)	NS	0	5.9
Control subjects					
Baseline examination (logMar)	20/21 (+0.01)	20/20 (+0.01)	NS	4.3	3.8
5-year examination (logMar)	20/21 (+0.02)	20/21 (+0.02)	NS	0	0
10-year examination (logMar)	20/22 (+0.05)	20/21 (+0.03)	NS	9.5	3.2

logMar, logarithm of minimal angle of resolution.

subjects at the 10-year examination, the baseline characteristics of those diabetic patients and control subjects who did not participate in the follow-up examination were not significantly different from the participants in terms of age, sex distribution, blood pressure, glucose and insulin levels, or frequency of cardiovascular diseases.

AMD and visual acuity

The type 2 diabetic patients with AMD had markedly lower visual acuity at the baseline and 5-year, but not at the 10-year, examinations than those without, but the number of patients with markedly impaired visual acuity (<20/25) was nonexistent, mainly because of selective mortality. The visual acuities of the control subjects with and without AMD were almost the same during the entire follow-up (Table 2).

Occurrence of AMD and its predictive factors

The frequency of AMD was about the same in type 2 diabetic patients as in the control subjects during the entire follow-up (at baseline, 17.1 vs. 18.7%, NS; at 5 years, 11.3 vs. 14.2%, NS; and at 10 years, 11.3 vs. 17.8%, NS, respectively; Fig. 2). At the baseline examination, type 2 diabetic women had AMD more often than men (24.1 vs. 10.8%, $P = 0.049$), but this difference between the sexes was not significant at the 5- and 10-year examinations. In the control group, the frequency of AMD was nearly the same in both sexes in every examination. In all type 2 diabetic patients and control subjects, AMD was of dry or nonexudative form manifested by drusen and retinal pigment epithelial changes (i.e., hypo- or hyperpigmentation).

By the 10-year follow-up, 14 (6 diabetic and 8 control subjects without AMD at baseline) had developed AMD, giving an incidence rate of 4.9% in the diabetic group and 6.0% in the control group. The diabetic patients with AMD were initially older in every examination than those without, but the difference was significant only at the 10-year examination (59.4 ± 4.4 vs. 55.7 ± 5.4 years of age, $P = 0.034$). The same was true in the control group at the 10-year examination (57.0 ± 5.2 vs. 52.4 ± 5.0 years, subjects with vs. without AMD, $P < 0.001$).

In the control group, but not in type 2 diabetic patients, age at the baseline examination was the only predictive factor for the development of AMD during the 10-year follow-up (57.6 ± 4.1 vs. 52.9 ± 4.9 years, subjects with vs. without AMD, $P = 0.010$). Smoking, BMI, resting blood pressure, serum total and HDL cholesterol, or total triglycerides were not associated with the development of AMD in the control group. Type 2 diabetic patients with AMD at the 10-year examination were not more hyperglycemic or more obese than those without AMD. Also, there were no consistent differences in smoking, systolic or diastolic blood pressure levels, or serum lipids (data not shown).

AMD as a predictor of mortality, myocardial infarction, and stroke

Diabetic patients with AMD at baseline died more often from cardiovascular disease than those without (38.1 [8 of 21] vs. 18.6% [19 of 102], $P < 0.05$]. The frequency of myocardial infarction and stroke tended to be higher in diabetic patients with AMD than in those without (myocardial infarction 50.0% [9 of 18] vs. 28.6% [24 of 84], $P = 0.078$; stroke: 21.1% [4 of 19] vs. 14.0% [14 of 100], NS) (Fig. 3). In the logistic regression analysis, after controlling for age, sex, fasting glucose level, and conventional risk factors (smoking,

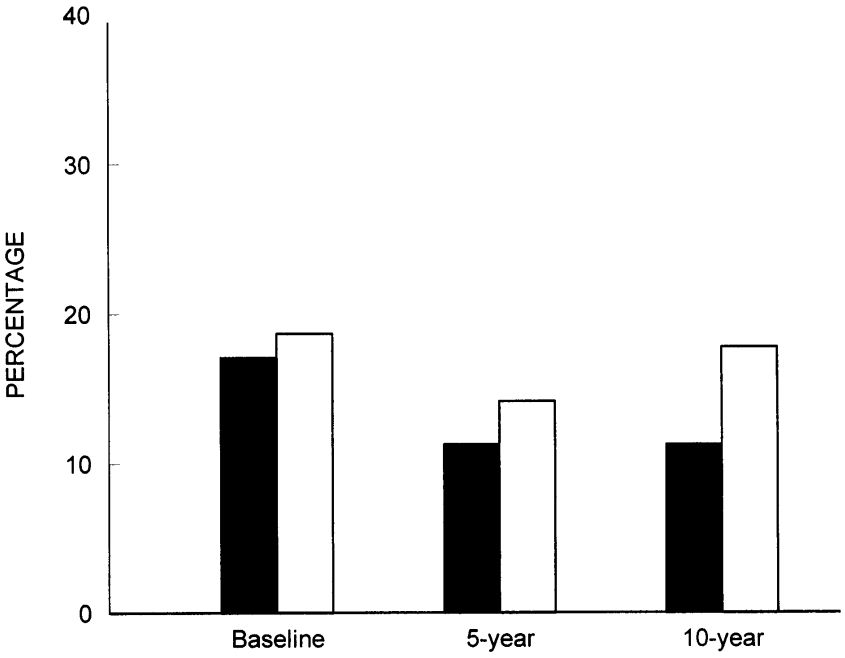

Figure 2—*Frequency of age-related macular degeneration in type 2 diabetic patients (■) and control subjects (□) at the 10-year follow-up.* P = *NS in every examination. Type 2 diabetic patients versus control subjects,* χ^2 *test.*

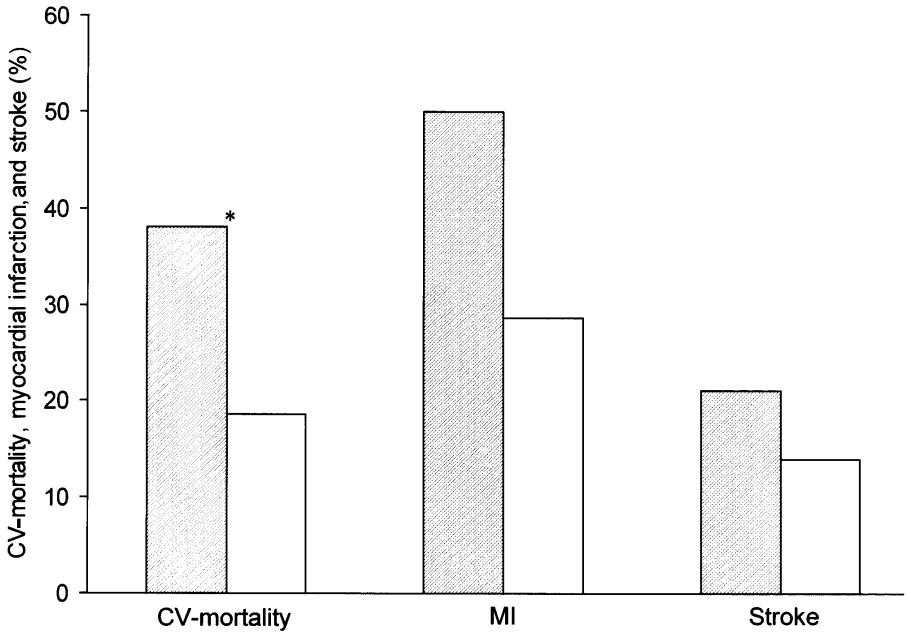

Figure 3—*The 10-year cardiovascular (CV) mortality, myocardial infarction (MI), and stroke in newly diagnosed type 2 diabetic patients with (▨) or without (□) AMD. *P < 0.05 for cardiovascular mortality in diabetic patients with vs. without AMD, χ^2 test.*

systolic blood pressure, LDL and HDL cholesterol, and total serum triglycerides), the relative risk for cardiovascular mortality in diabetic patients with AMD at baseline was 4.7 times higher than in diabetic patients without AMD (95% CI 1.1–19.3, *P* = 0.033; Table 3). In the control group, the relationship of AMD and cardiovascular mortality or morbidity could not be seen because of the small number of subjects.

CONCLUSIONS — This long-term study of well-characterized type 2 diabetic patients indicates that the increase in AMD with time was, if anything, somewhat lower in diabetic patients than in control subjects, but this can be largely explained by selective mortality. Interestingly, AMD predicted cardiovascular mortality independently of other risk factors in the diabetic group. Moreover, AMD deteriorated visual acuity earlier and more markedly in diabetic patients than in nondiabetic control subjects.

The essential question in the interpretation of the present results is the selection of the study population. At baseline, all of the diabetic patients fulfilled the WHO criteria for diabetes (19). At baseline and at the 5-year examination, most patients were treated with diet and/or oral hypoglycemic drugs. It should be noted that we similarly followed up the nondiabetic control population as the reference group, strengthening the present data.

Mean visual acuity was recorded using the best possible optical correction. It is known that visual acuity declines with advancing age because of the development of involutional changes in the crystalline lens and the macula, especially in type 2 diabetic patients with macular changes. In the Framingham Eye Study, 95.4% of nondiabetic subjects aged <65 years had 20/30 or better visual acuity (24). In our study, AMD was the main reason for the impairment of visual acuity in the diabetic group at the first two examinations, but AMD did not become evident in the control group.

The frequency of AMD was slightly higher in the control group than in type 2 diabetic patients, and, although there is much evidence of the progressive nature of AMD, its frequency did not increase during the 10-year follow-up (being even lower at the 5- and 10-year examinations), but this was due to selective cardiovascular mortality associated with AMD among diabetic patients (see below). The prevalence estimates of AMD vary considerably because of differences in diagnostic criteria. In the Framingham Eye Study, based on the ophthalmoscopical assessment of macular changes with the requirement of central vision loss, the total frequency of AMD in the population aged between 52 and 85 years was 8.8% (11% for subjects aged 65–74 years and 28% for subjects aged 75–85 years) (25). The Blue Mountains Eye Study, using diagnostic criteria similar to those proposed by the International Age-Related Maculopathy Study Group (26), provided an accurate estimate of the age-specific prevalence of AMD (0 and 18.5% among people aged <55 and ≥85 years, respectively) (27). In a population-based study of individuals ≥70 years of age, Hirvelä et al. (28) observed signs of AMD in up to 45% of subjects aged ≥70 years with no requirement of visual loss—a percentage much higher than that found in the present study. Whatever the definition or method of diagnosis, all estimates show a strong rise with age. A reasonable overall prevalence for any type of AMD is 20% in the 65–74

Table 3—*Adjusted odds ratios from logistic regression analysis on the impact of selected baseline predictors of cardiovascular death at the 10-year follow-up in patients with newly diagnosed type 2 diabetes*

	Odds ratio (95% CI)	*P*
Age (years)	1.11 (1.00–1.24)	0.054
Sex (0 = female, 1 = male)	0.82 (0.15–4.38)	0.820
Smoking history (0 = no, 1 = yes)	8.32 (1.32–52.34)	0.024
Systolic blood pressure (mmHg)	1.00 (0.97–1.03)	0.954
Fasting blood glucose (mmol/l)	1.13 (0.98–1.31)	0.087
Fasting serum insulin (mU/l)	1.04 (1.00–1.07)	0.027
LDL cholesterol (mmol/l)	1.151 (0.91–2.51)	0.107
HDL cholesterol (mmol/l)	1.47 (0.10–21.33)	0.779
Total serum triglycerides (mmol/l)	1.15 (0.81–1.63)	0.436
Microalbuminuria (≥30 mg/24 h)	1.00 (0.99–1.01)	0.777
AMD (0 = no, 1 = yes)	4.67 (1.13–19.3)	0.033

years age-group (corresponding to our results) and 35% in the 75–84 years age-group (29). Although there was no increase in the frequency of AMD during the 10-year follow-up, the control subjects and type 2 diabetic patients with AMD were older than those without AMD.

Conflicting reports have been published about the association between AMD and atherosclerotic diseases; many case-control studies found a positive association (8,9, 30–32), whereas others did not (33,34). In a recent study of type 2 diabetic patients with retinopathy, Lopes de Faria et al. (35) reported that patients with cardiovascular disease had a higher prevalence of macular edema. Hyman et al. (11) noticed that patients with macular degeneration had higher risk of stroke. It has been suggested that atherosclerosis plays a direct role in the development of macular degeneration by affecting the flow and permeability of choroidal vessels through thickening of Bruch's membrane and decreased perfusion of choroidal capillaries (36).

In the present study, the independent predictive value of AMD with cardiovascular disease in diabetic patients was an interesting finding. However, the mechanisms remain rather speculative. First, age-related macular degeneration, as the name implies, reflects age-related degeneration. Indeed, there was a quite consistent association with age, but in this regard, there was a discrepancy between diabetic and control subjects. Further, in diabetic patients, the association between cardiovascular mortality and AMD persisted after adjustment for age. Second, this association may be mediated by the effect of cardiovascular risk factors. However, despite extensive adjustment for known predictors of cardiovascular disease, the relationship between AMD and cardiovascular mortality persisted. Therefore, it is possible that AMD and atherosclerotic vascular disease in diabetes may have common, yet unidentified, determinants, as recently speculated (37).

To conclude, AMD deteriorated visual acuity earlier in type 2 diabetic patients than in control subjects although the frequency of AMD was almost the same in both groups. Interestingly, AMD was an independent risk factor for cardiovascular mortality in type 2 diabetic patients, but the mechanisms behind this association require further clarification.

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