

# High Cardiovascular Disease Mortality in Subjects With Visual Impairment Caused by Diabetic Retinopathy

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**OBJECTIVE** — The aim of this study was to assess mortality and causes of death in subjects with visual impairment caused by diabetic retinopathy (DR). Only limited data are available concerning the mortality of subjects with DR, and to our knowledge, no data so far have been published on the mortality of subjects with visual impairment caused by DR.

**RESEARCH DESIGN AND METHODS** — We identified 34 men and 73 women living in northern Finland with visual impairment caused by DR on 31 December 1993. The median age of the subjects was 71 years (range 27–88). The mortality of these 107 diabetic subjects was followed up for 4 years, until 31 December 1997, and compared with the mortality rates of 3 age- and sex-matched control groups. The first control group consisted of subjects treated for DR by laser coagulation from 1990 to 1993. The second control group consisted of diabetic subjects who had had fundus photographs taken from 1991 to 1992. The third control group comprised nondiabetic subjects selected from the population register. Information on deaths was obtained from official death certificates.

**RESULTS** — A total of 91 diabetic and 10 nondiabetic subjects died during the follow-up. Of the deaths, 51 occurred in the subjects with visual impairment caused by DR, with a 4-year mortality rate of 477/1,000 (95% CI 382–571/1,000). Mortality rates were 224/1,000 (145–303/1,000) for the diabetic subjects with retinopathy treated by laser coagulation; 150/1,000 (82–217/1,000) for the diabetic subjects who had undergone fundus photography; and 94/1,000 (46–165/1,000) for the nondiabetic subjects. Cardiovascular diseases were the underlying cause of death in 55% of the subjects with visual impairment. Nephropathy was mentioned as the immediate cause of death for only 10% of the subjects. Compared with the nondiabetic control subjects, the odds ratios (ORs) for all-cause mortality were 5.1 (2.6–11) in the diabetic subjects with visual impairment caused by DR, and 5.6 (2.1–19) for mortality caused by diseases of the circulatory system. The ORs for all-cause mortality were 2.4 (1.1–5.6) in the diabetic subjects with retinopathy treated by laser coagulation and 1.6 (0.68–4.0) in the diabetic subjects with fundus photographs taken.

**CONCLUSIONS** — The survival of diabetic subjects with visual impairment caused by DR was poor. The high mortality rate was attributed mainly to cardiovascular diseases. Therefore, severe retinopathy proves to be a risk marker of cardiovascular death in diabetic patients.

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Subjects with both type 1 and type 2 diabetes have an increased risk of dying prematurely (1–18). Excess mortality associated with type 2 diabetes has been attributed mainly to cardiovascular diseases (1–6,9,10,12,15,19–24), whereas in patients with type 1 diabetes it has been the result of acute diabetes-related complications (25), kidney disease, and cardiovascular diseases (24–26).

Only limited data are available concerning mortality in subjects with diabetic retinopathy (DR). Davis et al. (27) reported the survival of diabetic subjects to be inversely related to the severity of retinopathy. The prognosis for survival in subjects with mild retinopathy (background retinopathy with only microaneurysms) has been only slightly poorer than that of the general population, and poor survival has been observed in subjects with more severe degrees of retinopathy. In 2 cohorts of subjects with type 2 diabetes, baseline retinopathy was identified as an important predictor of subsequent mortality (28,29). Mortality was also significantly elevated in subjects with nonproliferative retinopathy and even further elevated in those with proliferative disease (28). Diglas et al. (30) observed high mortality among diabetic subjects with retinopathy treated by laser coagulation. Within the first 5 years after laser coagulation, 11% of the subjects with type 1 and 24% of subjects with type 2 diabetes died.

Visual impairment has been associated with poor survival (31), but to our knowledge, no data have yet been published on mortality in subjects with visual impairment caused by DR. The aim of this study was to compare the mortality of subjects with visual impairment caused by DR to that of 3 age- and sex-matched control groups.

## RESEARCH DESIGN AND

**METHODS** — Finland maintains a register of subjects with visual impairment. On 31 December 1993, 120 subjects living in Northern Ostrobothnia, an area near the city of Oulu with ~350,000 inhabitants, were registered as being visually impaired because of DR (32). The mortality of these diabetic subjects was followed for 4 years,

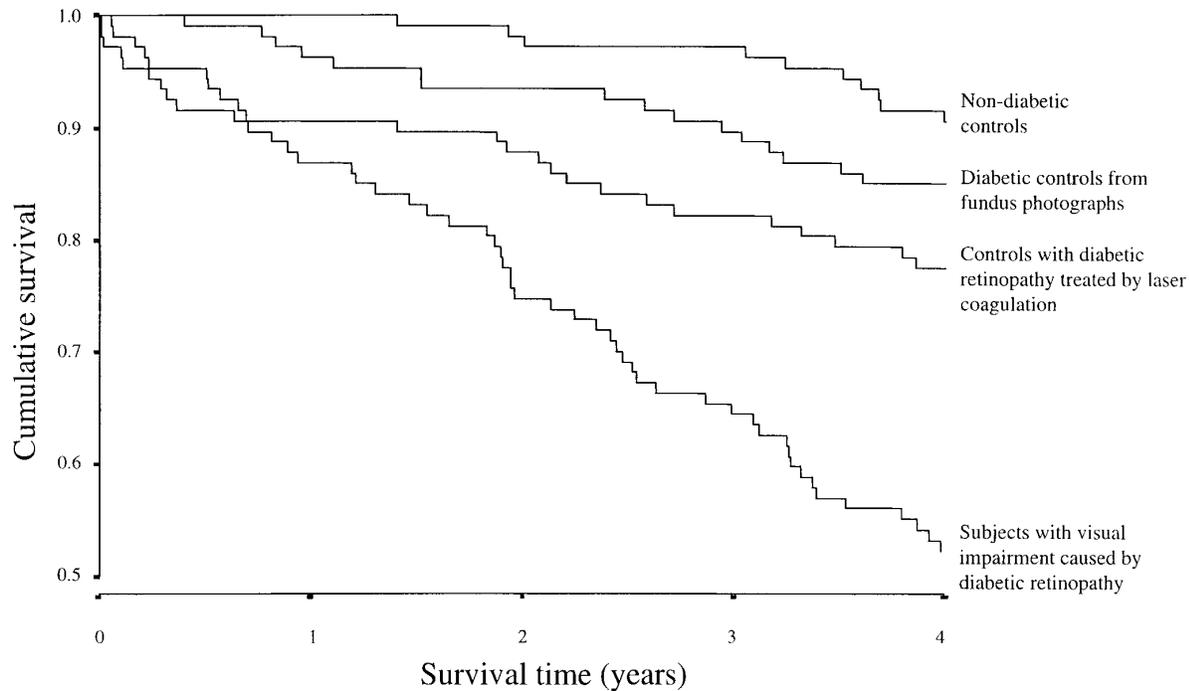
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**Abbreviations:** DR, diabetic retinopathy; ICD, International Classification of Diseases; OR, odds ratio; WHO, World Health Organization.

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



**Figure 1**—Survival curves for subjects with visual impairment caused by diabetic retinopathy and for 3 groups of control subjects.

until 31 December 1997, and compared with 3 age- and sex-matched control groups. The first of the control groups comprised subjects treated for DR by laser coagulation in the Department of Ophthalmology at the Oulu University Hospital from 1990 to 1993. The second control group comprised diabetic subjects who had had fundus photographs taken in the diabetes clinic of the Oulu Health Centre from 1991 to 1992. The third control group comprised nondiabetic subjects selected from the population register.

There were 107 subjects from each of the 3 control groups who were matched for age and sex with the study subjects. The median age of the subjects in the 4 groups was 71 years (range 27–88) at the baseline. Each group consisted of 34 (32%) men and 73 (68%) women.

One of the control groups consisted of diabetic patients subjected to fundus photography in the diabetes clinic of the Oulu Health Centre from 1991 to 1992. Altogether, 1,844 diabetic patients were outpatients in this clinic at that time, and 1,701 (92%) of them were scheduled for fundus photography. The majority (87%) of the participants had type 2 diabetes, and the median duration of the disease was 10 years. For 39% of the diabetic subjects, the only treatment was diet, while 35% were

taking oral antidiabetic drugs, 7% were taking oral antidiabetic drugs and insulin, and 19% were taking insulin. In the control group, 75% of the subjects had type 2 diabetes, and the median duration of disease was 15 years. For 5% of the diabetic subjects in the control group, the only treatment was diet, while 21% were taking antidiabetic drugs, 27% were taking oral antidiabetic drugs and insulin, and 47% were taking insulin. The classification of retinopathy used in this diabetic clinic was the same as that used in the Department of Ophthalmology of the Oulu University Hospital, based on the classification proposed by Davis et al. (33). Reference photographs were used, and retinopathy was graded as follows: grade 1, no retinopathic changes; grade 2, fewer background retinopathic changes than in the control photographs; grade 3, more background retinopathic changes than in the control photographs (preproliferative retinopathy); and grade 4, proliferative retinopathy. Retinopathic changes were found in 23% of all participants, and the majority of subjects had only slight retinopathic changes (grade 2). Retinopathy was classified as grade 3 in 4% of the subjects and as grade 4 in only 1% of the subjects. In the control group, the prevalence of retinopathy was 47%, and retinopathy was classified as grade 3 in 9%

of the subjects and as grade 4 in 1% of the subjects.

The official register of subjects with visual impairment in Finland is categorized according to World Health Organization (WHO) criteria, and includes subjects who are blind (WHO 1–3, visual acuity  $\geq 0.05$ ) or partially sighted (WHO 4–5, visual acuity  $>0.05$ , but  $<0.3$ ). At the time of this study, 90% of the subjects included in the register were partially sighted and 10% were blind (32). We had data about the visual acuity of 99 control subjects (93%) who were treated for DR with laser coagulation. Visual acuity was  $>0.9$  in 38 subjects, 0.6–0.9 in 30 subjects, 0.3–0.5 in 24 subjects, and  $<0.3$  in 7 subjects. Approximately two-thirds of the subjects treated with laser coagulation had received pan-retinal treatment and one-third had received macular laser coagulation.

Mortality rates and their 95% CIs were calculated for the study group and the 3 control groups. The underlying causes of death were coded according to the International Classification of Diseases (ICD). The ninth revision (ICD-9) was used until 31 December 1995, after which the tenth revision (ICD-10) was used. The ICD-9 classification was used in presenting the results because it has fewer classes than ICD-10. When the cause of death was coded in the

**Table 1—Causes of death after 4 years of follow-up in the 428 subjects classified according to the presence of diabetes, diabetic retinopathy treated by laser coagulation, and visual impairment caused by diabetic retinopathy**

Cause of death	Nondiabetic control subjects (n = 107) n of deaths (%)	Diabetic control subjects from fundus photographs (n = 107) n of deaths (%)	Control subjects with DR treated by laser coagulation (n = 107) n of deaths (%)	Subjects with visual impairment caused by DR (n = 107) n of deaths (%)	Total n of deaths
Neoplasms	3 (30)	2 (13)	3 (13)	4 (8)	12
Endocrine, nutritional, and metabolic diseases	0	0	2 (8)	14 (27)	16
Mental disorders	0	0	1 (4)	1 (2)	2
Diseases of the nervous system and sense organs	0	1 (6)	0	1 (2)	2
Diseases of the circulatory system					
Ischemic heart disease	3	12	11	20	
Cerebrovascular disease	2	1	0	6	
Other cardiovascular diseases	0	0	1	2	
Total	5 (50)	13 (81)	12 (50)	28 (55)	58
Diseases of the respiratory system	2 (20)	0	3 (13)	3 (6)	8
Diseases of the digestive system	0	0	1 (4)	0	1
Diseases of the genitourinary system	0	0	2 (8)	0	2
Total	10 (100)	16 (100)	24 (100)	51 (100)	101

Data are n (%) or n.

death certificate according to ICD-10, it was adapted to ICD-9 classification. The odds ratios (ORs) of death by cause, with the nondiabetic control group as the reference group, were calculated with their 95% CIs.

The Kaplan-Meier method was used to describe the cumulative survival of the subjects with visual impairment caused by DR and the 3 control groups (35). The differences between the survival curves for the 4 groups were tested by the Mantel-Cox test. BMPD statistical software was used to calculate the survival curves and to test the difference between the groups.

**RESULTS** — A total of 101 of the 428 subjects died during the follow-up of 4 years. Ten deaths occurred in the group of nondiabetic subjects, yielding a 4-year mortality rate of 94/1,000 (95% CI 46–165/1,000), whereas 91 deaths occurred in the diabetic subjects, resulting in a mortality rate of 283/1,000 (234–399/1,000). A total of 51 of the deaths occurred in the subjects with visual impairment caused by DR, and the 4-year mortality rate was 477/1,000 (382–571/1,000). The number of deaths was 24 in the diabetic subjects with retinopathy treated by laser coagulation, and 16 in diabetic subjects scheduled for fundus photography, and the mortality rates were 224/1,000 (145–303/1,000) and 150/1,000 (82–217/1,000), respectively. The difference between the Kaplan-Meier survival curves of the groups was statistically significant ( $P < 0.0001$ ) (Fig. 1).

The underlying cause of death was a disease of the circulatory system in the majority of cases (58 subjects) (Table 1). In 16 subjects, diabetes (classified into the category of endocrine, nutritional, and metabolic diseases) was mentioned as the underlying cause of death. Neoplasms were coded as the cause of death in 12 subjects, and diseases of the respiratory system in 8 subjects. The numbers in the other categories were small.

In all except 1 of the death certificates of the 16 subjects whose underlying cause of death was coded as diabetes, microvascular and macrovascular complications were mentioned as factors contributing to death. The most common complications were nephropathy, gangrene in the lower extremities, and coronary heart disease. Renal insufficiency, pneumonia, and septicemia were most commonly mentioned as the immediate cause of death. Fourteen of the 16 deaths occurred in subjects with visual impairment and 2 in the control group of subjects with DR treated with laser coagulation; the OR for death due to diabetes was 7.0 (95% CI 1.6–63) in the former group compared with the latter. In 9 of the 16 subjects, the presence of nephropathy was mentioned in the death certificate. Nevertheless, nephropathy was coded as the immediate cause of death in only 5 of these death certificates, and all of these 5 subjects were visually impaired. In addition, in 1 subject with DR treated by laser coagulation, whose underlying cause of death was nephropathy, the cause of death

was coded into the category of diseases of the genitourinary system.

Compared with the nondiabetic control subjects, the OR for death from all causes was 5.1 (95% CI 2.6–11) in the subjects with visual impairment caused by DR (Table 2), 2.4 (1.1–5.6) in the diabetic subjects with retinopathy treated by laser coagulation, and 1.6 (0.68–4.0) in the diabetic subjects with fundus photographs taken. When we look at the specific causes of death, the OR for death due to diseases of the circulatory system was 5.6 (2.1–19) in the diabetic subjects with visual impairment caused by DR compared with the nondiabetic control subjects. The corresponding OR of the control group of subjects with DR treated by laser coagulation (2.4; 0.79–8.7) and that of the control group of diabetic subjects with fundus photographs taken (2.6; 0.87–9.3) did not reach statistical significance.

**CONCLUSIONS** — Almost half of the subjects with visual impairment caused by DR died during the follow-up of 4 years, and their risk for death was 5-fold compared with the age- and sex-matched nondiabetic control subjects. The excess mortality was attributed to diseases of the circulatory system, mainly to ischemic heart disease.

To our knowledge, there are no previous reports of the mortality and the causes of death in subjects with visual impairment caused by DR. In this study population, the survival of subjects with visual impairment

## Mortality in subjects with visual impairment

**Table 2—ORs (95% CI) for death caused by neoplasms, diseases of the circulatory system, diseases of the respiratory system, and all causes in the 428 subjects classified according to the presence of diabetes, diabetic retinopathy treated by laser coagulation, and visual impairment caused by diabetic retinopathy**

Cause of death	Nondiabetic control subjects (n = 107)		Diabetic control subjects from fundus photographs (n = 107)		Control subjects with DR treated by laser coagulation (n = 107)		Subjects with visual impairment caused by DR (n = 107)	
	Deaths (n)	OR (95% CI)	Deaths (n)	OR (95% CI)	Deaths (n)	OR (95% CI)	Deaths (n)	OR (95% CI)
Neoplasms	3	Reference group	2	0.67 (0.56–5.8)	3	1.0 (0.13–7.5)	4	1.3 (0.23–9.1)
Diseases of the circulatory system	5	Reference group	13	2.6 (0.87–9.3)	12	2.4 (0.79–8.7)	28	5.6 (2.1–19)
Diseases of the respiratory system	2	Reference group	0	0	3	1.5 (0.17–18)	3	1.5 (0.17–18)
All causes	10	Reference group	16	1.6 (0.68–4.0)	24	2.4 (1.1–5.6)	51	5.1 (2.6–11)

Data are n or OR (95% CI).

caused by DR was extremely poor. Nevertheless, visual impairment had already been diagnosed an average of 5 years before the baseline of the follow-up (32).

The mortality rate of the subjects with visual impairment caused by DR was higher than that of the diabetic control groups, and the mortality rate of the subjects treated for DR by laser coagulation tended to be higher than that of the diabetic subjects scheduled for fundus photography, who were drawn from an unselected group of diabetic subjects. Nevertheless, the disease was more serious and the prevalence of retinopathy higher in the control group used in this study compared with the whole diabetic population treated in the diabetes clinic of the Oulu Health Centre. Laser coagulation was used in the treatment of proliferative and preproliferative retinopathy and maculopathy. The prevalence of proliferative and preproliferative retinopathy was only 10% in the diabetic patients in the control group selected from the patients treated in the diabetes clinic of the Oulu Health Centre. Therefore, the results of this study can be interpreted as showing that the poor survival was predicted by severe retinopathy, which is consistent with the results of some previous studies (27–29). The higher overall mortality of diabetic subjects compared with nondiabetic subjects is consistent with the results of many previous studies (1–18).

The basic disease was most severe in the diabetic subjects with visual impairment caused by retinopathy, and these subjects suffered most often from mortality-causing complications. Cardiovascular diseases were mentioned as the cause of death for 55% of the subjects with visual

impairment, whereas only 10% of the subjects had nephropathy as the immediate cause of death. Thus, the principal cause of death in the diabetic subjects with severe microvascular complications was not end-stage renal disease, but macrovascular disease. Mortality due to cardiovascular diseases tended to be higher in the 2 diabetic control groups than in the nondiabetic control group. Surprisingly, there was no significant difference between the 2 diabetic control groups in this respect. This may be due to the small number of subjects in the groups. In our opinion, the results of this study are consistent with the assumption that microvascular and macrovascular diseases are mutually interdependent events (28,29,36,37). Baseline retinopathy (28,29) and albuminuria (24,26,29,36) have predicted mortality in cohorts of diabetic subjects, and cardiovascular diseases have been the most common causes of death in these cohorts (24,26,28,29). The coincidence of albuminuria, proliferative retinopathy, and cardiovascular diseases in diabetic subjects has been explained by the Steno hypothesis (37). According to this hypothesis, albuminuria, proliferative retinopathy, and cardiovascular diseases reflect generalized vascular leakage, which is caused by genetically determined alterations in the basement membrane metabolism associated with hyperglycemia. In the arterial wall, these alterations increase the accumulation of lipids, thus promoting arteriosclerosis.

The current study had some limitations. First, we lacked exact information about the type and duration of diabetes, glycemic control, and treatment for the subjects with visual impairment and the subjects treated with laser coagulation. Because there is an association between the duration

of diabetes and the severity of glycemia and retinopathy (38), it is likely that the diabetic groups of this study were different in these respects. Instead, the duration of diabetes was not related to the risk of coronary heart disease in patients with type 2 diabetes (4,22). Therefore, the high prevalence of and mortality from coronary heart disease among subjects with visual impairment cannot be explained by a long duration of diabetes. Instead, this high mortality may reflect a common pathogenetic mechanism underlying microvascular and macrovascular complications, as suggested by the Steno hypothesis (37). Second, another limitation of this study might be that some possible confounders were not measured. We had no data about smoking, hypertension, and lipid levels in all of the groups, but it is unlikely that these variables would explain the results.

In conclusion, the results of this study showed that the 4-year mortality of diabetic subjects with visual impairment was 5-fold compared with age- and sex-matched nondiabetic control subjects. Excess mortality was attributed mainly to cardiovascular diseases. In the subjects treated for DR by laser coagulation, mortality from all causes was higher and mortality due to cardiovascular diseases tended to be higher than that of the nondiabetic control subjects. Therefore, severe retinopathy proves to be a risk marker for cardiovascular death in diabetic subjects.

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