Decreasing the Risk of Diabetic Retinopathy in a Study of Case Management

The California Medi-Cal Type 2 Diabetes Study

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OBJECTIVE — Diabetic retinopathy affects >60% of people with type 2 diabetes during the first 2 decades of the disease and is ameliorated by good glycemic control. This study tested whether intensive diabetes case management could prevent or delay diabetic retinopathy in patients with established type 2 diabetes.

RESEARCH DESIGN AND METHODS — This study was part of a randomized, controlled clinical trial of diabetes case management in type 2 diabetes in southern California counties serving low income ethnic minority populations. Subjects were randomized to intervention (diabetes case management) or control (traditional treatment) groups. Subjects with at least two retinal photographs (n = 149) were included in this analysis to assess the effect of intervention on development or progression of diabetic retinopathy.

RESULTS — Progression of retinopathy in the intervention group was not significantly less than in the control group (P = 0.226). However, those in the intervention group with no evidence of retinopathy at baseline were less likely to develop diabetic retinal changes (5/48) during a mean follow-up of 23.1 months than those in the control group (10/34, $\chi^2 = 4.805$, P = 0.028). This difference remained significant in a logistic regression model that controlled for potential confounders (odds ratio 5.35 [95% CI 1.14–25.12]).

CONCLUSIONS — This study shows that a relatively short duration of case management instituted before the onset of clinically identifiable retinopathy significantly diminished the risk of developing retinopathy in patients with type 2 diabetes. The findings also emphasized the retinal disease burden in this population, with development and progression of retinopathy occurring in <2 years.

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Diabetic retinopathy, the most frequent cause of blindness among adults in the U.S., affects >60% of people with type 2 diabetes during the first 2 decades of the disease (1). This devastating complication can be prevented and its progression slowed if glycemia is improved under the rigorous conditions of surveillance in controlled clinical trials (2–5). Benefits have been reported both in individuals with type 1 (2,3) and in those with type 2 (4,5) diabetes. The purpose of this study was to test whether diabetes case management, when added to standard primary care, was sufficient to prevent or delay diabetic retinopathy.

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Abbreviations: NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

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

RESEARCH DESIGN AND METHODS

— Between 1 July 1995 and 30 June 1999, a randomized, controlled study of subjects aged ≥18 years who had type 2 diabetes of at least 1-year duration was conducted in southern California. Detailed information about the methods used in this study was presented in an earlier publication (6) and will be briefly summarized here. Subjects with type 2 diabetes, as defined by the American Diabetes Association (7), were recruited at clinical sites in Santa Barbara, Los Angeles, and San Diego counties, three California counties serving predominantly ethnic minority, low-income Medicaid (called Medi-Cal in California) populations. Although specific income data were not collected as part of this study, overall 93.9% of the Medi-Cal–eligible population is classified as medically indigent or needy or is eligible for public assistance. Two of these sites, in Santa Barbara and Los Angeles counties, had access to fundus cameras and participated in the retinal photograph component of the study, and the data provided in this manuscript are limited to those two sites. Signed, witnessed, informed consent was obtained from all prospective participants using forms approved by local institutional review boards.

As previously described (6), the main trial recruited participants with HbA_{1c} (A1C) levels >7.5%. At the two participating sites, 121 subjects were randomized to the intervention group and 119 to the control group. Intensive diabetes case management was provided to the intervention group in addition to the standard care (8) that was received by both groups from a primary physician not connected with the trial. In the intervention group, subjects were seen or contacted by the case management staff at varying intervals according to the need (at least monthly) to lower A1C. In the control group, blood for A1C determination was collected at 6-month intervals, and contact between study staff and participants was generally limited to that needed to assure collection

Table 1—*Baseline characteristics of all subjects in the retinopathy study*

	Intervention group	Control group	Significance
n (male/female)	102 (27/75)	98 (29/69)	$P = 0.738$
Age (years) (means ± SD)	55.0 ± 11.6	55.5 ± 12.9	$P = 0.758$
Ethnicity			
Non-Hispaninc white	41	42	$P = 0.866$
Hispanic	41	35	
Black	14	13	
Other	6	8	
A1C (%)	9.5 ± 1.8	9.4 ± 1.5	$P = 0.512$
Diabetes duration (years)	8.8 ± 6.8	10.6 ± 8.5	$P = 0.104$
Follow-up time (months)	21.1 ± 8.8	23.3 ± 8.8	$P = 0.091$
Retinopathy			
None	61	49	$P = 0.055$
Mild	38	38	
Severe	3	11	
Dropouts (total)	23	28	$P = 0.415$
Withdraw/move	8	8	$P = 0.699$
Loss of benefit	1	3	
Death	2	1	
Loss to follow-up	4	8	
No second photo	8	8	

Data are means ± SD, unless otherwise indicated.

of A1C samples or to obtain retinal photographs. All subjects, in both the intervention and control groups, were referred for retinal photographs at baseline and then at least yearly. Two hundred subjects (98 control and 102 intervention subjects) had at least one photograph and 149 (70 control and 79 intervention subjects) had least two sets of retinal photographs that could be analyzed in this study. For subjects with more than two sets of photographs, only the first and last were used in this analysis. Only the main study (6) had sufficient power to see differences in metabolic variables. Thus, for this small ancillary study of retinopathy, which utilized only two of three original participating centers, follow-up analyses of A1C, blood pressure, and lipids were not planned. Photographs were obtained at a separate case management visit, and, after baseline, photographs were not necessarily scheduled to coincide with the laboratory tests or physical examinations.

The study staff at each site, consisting of registered nurses and registered dietitians working in close collaboration with an endocrinologist, provided diabetes case management to the intervention group only. Evidence-based practice guidelines and algorithms for oral medicines and insulin initiation and adjustment were used in a collaborative practice model with the primary care provider (6). Treatment goals and targets for therapy were uniform across sites, with flexibility to utilize individualized treatment algorithms and strategies at each site. Interactions between the participant and study staff occurred in person at the clinic site and via telephone between visits as needed. The need for ancillary medical evaluations and/or services such as ophthalmologic examinations was monitored, with subsequent follow-up to ensure receipt of services, results retrieval, and communication of results to the primary care provider.

One photograph was taken of each eye with a Canon CR4-45° nonmydriatic camera. Photographs were taken in a dark room to facilitate dilatation of the pupils and improve the quality of the photographs. Additionally, at the Los Angeles site, pupils were dilated before taking the photos. The retinal field photographed was identical at both sites and consisted of the area nasal to the disc and temporal to the macula and the superior and inferior arcades. All photographs were labeled with only the patient's identification number and were sent for reading in Santa Barbara. Polaroid prints from the Canon camera were examined and graded by an experienced endocrinologist (L.J.) who, before this study, had readings verified by an ophthalmologist until agreement was virtually 100% (9). An overall grading was assigned for each eye at each examination using the Wisconsin Epidemiologic Study of Diabetic Retinopathy II/III–modified diabetic retinopathy levels, which used a modification of the Airlie House Criteria (10). This scale has nine levels per eye, ranging from no retinopathy to total vitreous hemorrhage. The scale was used as follows: no retinopathy (grade 10), very-mild nonproliferative diabetic retinopathy (NPDR) (grade 20), mild NPDR (grade 35), moderate NPDR (grade 43), severe NPDR (grade 53), mild proliferative diabetic retinopathy (PDR) (grade 61), moderate PDR (grade 65), high-risk PDR (grade 71), and advanced PDR and/or fundus partially obscured by disease (grade 85). Photograph quality was deemed adequate for accurate assignment of retinopathy grade in all of the graded photographs included for analysis. The primary outcome measures are the development of retinopathy of any degree in subjects without retinopathy at baseline and the progression of retinopathy in subjects with nonproliferative retinopathy at baseline.

Statistical analyses were performed using SAS statistical software for Windows version 9.1 (SAS Institute, Cary, NC). Continuous data were compared between groups with an unpaired *t* test, and categorical data were compared with a χ^2 test. Odds ratio (OR) for progression of retinopathy in each group was estimated using the PROC GENMOD procedure while accounting for duration of follow-up and controlling for confounders. A repeated statement was used to specify within-subject effect. The first-order Taylor expansion approximation was used to estimate the variance of difference in the ORs between the two groups (11). Logistic regression with the development of any degree of retinopathy as the binary outcome variable was used to control for covariates in the subset of subjects who had no retinopathy in the baseline photograph.

RESULTS — There were 200 subjects (56 male and 144 female subjects) from the two centers who were included in the retinal photographic studies. The baseline characteristics of the subjects included in the retinopathy study are shown in Table 1. Subjects randomized to the intervention ($n = 102$) and control ($n = 98$) groups were of similar age and diabetes duration, had similar A1C concentrations, had similar follow-up periods dur-

Table 2—*Baseline characteristics of subjects with no retinopathy at baseline*

	Intervention group	Control group	Significance
Number (male/female)	61 (15/46)	49 (15/34)	$P = 0.841$
Age (years)	53.5 (12.4)	53.5 (13.9)	$P = 0.997$
Ethnicity			
Non-Hispanic white	22	20	$P = 0.930$
Hispanic	26	19	
Black	8	7	
Other	5	3	
A1C (%)	9.6 ± 1.6	9.7 ± 1.8	$P = 0.638$
Diabetes duration (years)	7.3 ± 5.4	7.5 ± 8.3	$P = 0.921$
Follow-up time (months)	19.9 ± 8.4	24.0 ± 8.9	$P = 0.019$*
Dropouts (total)	13	15	$P = 0.372$
Withdraw/move	6	3	$P = 0.384$
Loss of benefit	1	1	
Death	1	0	
Loss to follow-up	2	5	
No second photo	3	6	

Data are means ± SD, unless otherwise indicated.

ing this study, and had similar drop-out rates.

The progression or development of retinopathy was noted in both the intervention and control group, and the difference in the ORs for progression between the two groups (−0.65) was not statistically significant ($P = 0.226$). Subjects without evidence of retinal disease at baseline were evaluated separately. As with the total sample, the intervention and control groups were similar (Table 2), with the exception of follow-up time. However, among 82 subjects who remained in the study through at least a second photograph and could therefore be used to assess the development of retinopathy, the follow-up was similar in the intervention (22.0 months) and the control groups (24.6 months, $P = 0.136$, data not shown). Those in the intervention group who had no evidence of retinopathy at baseline (Airlie House score = 10 in each eye) were less likely to develop diabetic retinal changes during a mean of 23.1 months of follow-up (5/48) than were those in the control group (10/34, $\chi^2 = 4.805$, df = 1, $P = 0.028$). This difference remained significant in a logistic regression model that controlled for age at diagnosis, duration of diabetes at baseline, duration of follow-up, A1C, ethnicity, and sex (OR 5.35 [95% CI 1.14–2.12], $P = 0.034$, Table 3). In a stepwise logistic model, only randomization group, baseline A1C concentration, and age were significant predictors of developing retinopathy (data not shown).

CONCLUSIONS — This report is the first evidence that intensive case management reduces risk of new-onset retinopathy in people with established type 2 diabetes. The U.K. Prospective Diabetes Study (4,5) first demonstrated the effects of improved glycemic control on retinopathy in type 2 diabetes, but the subjects who participated in that landmark study were all newly diagnosed, whereas the patients without retinopathy in this study had a mean duration of diabetes of 7.5 years by the time the case management intervention was begun. Although the number of subjects with established retinopathy in this study was not sufficient to draw conclusions about progression of retinopathy compared with those who had none at baseline, the response observed in the latter suggests that early intervention with case management is an effective approach to reducing the burden of retinopathy in patients with type 2 diabetes. This conclusion is reinforced by the finding that even when case management is maintained for a short duration (mean <2 years), it is sufficient to diminish the risk of retinopathy.

The mechanisms for the effect of case management on reduction in the development of new-onset retinopathy may be related to any of the different facets of the case management process, although the major factor is likely to be improved glycemic control. Although A1C concentrations were not consistently evaluated at the time the follow-up photographs were taken, in the main trial the case management group showed a persistent improvement in the A1C that was greater than in the standard care group (6), suggesting that the decreased risk of retinopathy is likely due to improvement in glycemia. This study, therefore, confirms the necessity of providing adequate education and follow-up support, as delivered in this trial that utilized case management and frequent intervention, in order to achieve and maintain an A1C improvement over and above the standard care given to this county clinic Medi-Cal population.

However, other elements of the case management approach may well have contributed to the reduction in development of new-onset retinopathy. With adequate surveillance and support, glycemia improves, but, as demonstrated in our primary report (6), this improvement was associated with significant decreases from baseline to end of study in diastolic blood pressure, LDL cholesterol, and total cholesterol and an increase in HDL cholesterol in the intervention group. Thus, case management not only resulted in im-

Table 3—*Logistic regression results in subjects with no retinopathy at baseline*

Parameter	OR (95% CI)	*P* value
Randomization group (control vs. intervention)	5.35 (1.14–25.12)	0.034
A1C	1.76 (1.07–2.90)	0.025
Age (years)	1.15 (1.05–1.25)	0.002
Female sex	1.19 (0.48–2.95)	0.704
Diabetes duration (years)	1.02 (0.94–1.10)	0.677
Follow-up (months)	0.94 (0.85–1.05)	0.287
Race		
Non-Hispanic white	—	—
Hispanic	1.07 (0.34–3.40)	—
Black	1.65 (0.33–8.11)	—
Other	1.18 (0.17–8.39)	0.739

Dependent variable = development of retinopathy ($n = 82$).

provement of glycemic control but also had an effect on diminishing the risk of microvascular disease, as measured by retinopathy.

Case management may also have played a role in attendance at sessions when the photographs were taken and the immediate feedback that nonmydriatic photography can give to the health care team and thus facilitate the follow-up of patients with documented retinopathy. Whether it is the support associated with case management and the resultant adherence to nonglycemic targets such as hypertension that led to the improved retinal status, independent of improved glycemic control, cannot be addressed by this study. However, perhaps because case management clearly improves glucose control in a Medi-Cal–type population and is associated with decreased risk of new-onset retinopathy, comprehensive case management may be justified in similar health care settings.

Limitations of this study include the fact that it was not of sufficient duration to address whether case management may have also prevented progression of previously recognized retinopathy, which may have required more time or larger numbers to see an effect. Another limitation is the fact that we only used a single field for evaluation of the retina rather than the seven fields used in other studies of retinopathy (1,10), although in previous reports, this technique for diabetic retinopathy screening has been shown to be effective (9). In this way, minimal retinopathy may have been missed in the periphery at baseline and at the follow-up study. However, since both baseline and follow-up retinal fields were identical, it is most likely that our findings reflect a clinically meaningful decrease in the development of retinopathy over the 2-year time span that was tested. Furthermore, seven-field photography was not practical in this case management setting. Although all participants were urged to visit an ophthalmologist, those subjects with evidence of any retinopathy on the photograph were personally followed by the case management team to facilitate the consultation (6).

Although other studies (2–5) show that improved glycemic control decreases the risk of retinopathy, this study is the first to show that even a relatively short duration of improved control (~2 years) instituted before the onset of clinically identifiable retinopathy can decrease the risk of developing new retinopathy. This study also underscores the risk of retinal disease in type 2 diabetes in that progression of retinopathy occurred within a relatively short time when glycemic control was not achieved. Further studies are necessary to determine whether early intervention to achieve glycemic control in established diabetes has a greater effect to reduce diabetic retinopathy than its introduction at a later stage of the disease.

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