Glycemic Control and Prevention of Retinopathy in Japanese NIDDM Patients

A 10-year follow-up study

TOMOKO NAKAGAMI, MD
REIKO KAWAHARA, MD
SADAO HORI, MD
YASUE OMORI, MD

OBJECTIVE — To examine glycemic control for the prevention of retinopathy in early diagnosed Japanese NIDDM patients.

RESEARCH DESIGN AND METHODS — There were 137 patients with NIDDM but without retinopathy who first visited our facility from 1983–1985. Their age at diagnosis ranged from 30–65 years, with a disease duration of <3 years. The optic fundi were examined at least annually. The prevalence of retinopathy in the 10th year after registration in the study was compared in four groups stratified by mean HbA_{1c} values for 10 years. Multiple logistic regression analysis was used to assess the relationship between retinopathy and covariates.

RESULTS — None of the patients with a mean HbA_{1c} <6% had retinopathy. The prevalence of retinopathy was 17.2% in the group with a mean HbA_{1c} of 6–6.9%, 14.3% in the group with a mean HbA_{1c} of 7–7.9%, 41.9% at a mean HbA_{1c} of 8–8.9%, and 54.8% when the mean HbA_{1c} exceeded 9%. The prevalence of retinopathy increased with the increase in the mean HbA_{1c} values over 10 years (trend, $P < 0.005$). Multiple logistic regression analysis revealed that mean HbA_{1c} was the only significant risk factor for the development of retinopathy.

CONCLUSIONS — Our results support the concept that an early diagnosis and better control lessen the risk for the development of retinopathy in Japanese NIDDM patients.

The importance of achieving HbA_{1c} values <7% to prevent diabetic microangiopathy in patients with IDDM has been emphasized by the Diabetes Control and Complications Trial (DCCT) (1). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (2), as well as the U.K. Prospective Diabetes Study (UKPDS) (3), also emphasized the importance of glycemic control for preventing microangiopathy in patients with NIDDM. To examine the importance of glycemic control for minimizing the development of retinopathy, we have followed early diagnosed Japanese NIDDM patients for 10 years.

RESEARCH DESIGN AND METHODS

— The subjects of this study were diabetics who were admitted to the Diabetes Center of Tokyo Women's Medical College and who met the following criteria: *1*) the first visit to the Diabetes Center was between 1 January 1983 and 31 December 1985, *2*) age of the NIDDM patients at the initial diagnosis of diabetes was between 30 and 65 years, *3*) the duration of diabetes was <3 years, *4*) there was no retinopathy at the first visit, *5*) the patient attended the Diabetes Center for 10 years, and *6*) optic fundi was examined by an ophthalmologist at least annually. The diagnosis of NIDDM was made according to World Health Organization criteria (4). The duration of diabetes was estimated from the time between the first diagnosis and registration in this study. A total of 1,255 patients met the first four criteria. Only 137 patients (61 men, 76 women) met all six criteria and were included in the data analysis. Their mean age at registration was 49.9 ± 8.3 years. The HbA_{1c} value was measured at every visit using high-performance liquid chromatography (HA8110, Kyoto Daiichi Kagaku, Japan). The normal range was 4.8–6.4%. The mean HbA_{1c} value, BMI, and blood pressure for each patient were calculated from data obtained each month. The mean HbA_{1c} value of the subjects was 9.6 ± 3.0%, mean systolic blood pressure was 131.0 ± 21.3 mmHg, mean diastolic blood pressure was 81.0 ± 12.2 mmHg, and mean BMI was 23.5 ± 7.2 kg/m^2. The grade of retinopathy was judged from the results of ophthalmological examinations. Simple retinopathy corresponded to levels 21–53 and proliferative retinopathy to levels 60–80 of the modified Airlie House System (5).

Statistical analyses were carried out using SAS/STAT software version 6 (SAS Institute, Cary, NC). The Mantel-Haenszel χ^2 test (6) was used to evaluate the trend toward the prevalence of retinopathy within five groups, divided according to the mean HbA_{1c} value over 10 years. To assess the relationship between the covariates and retinopathy, we used multiple logistic regression analysis (7). A P value of <0.05 was considered as statistically significant.

RESULTS

— The prevalence of retinopathy in the group with a mean HbA_{1c} value <6% was 0% (0/11). The prevalence of retinopathy was 17.2% (5/29) in the group with a mean HbA_{1c} of 6–6.9%, 14.3% (5/35) in the group with a mean HbA_{1c} of 7–7.9%, 41.9% (13/31) at a mean HbA_{1c} of 8–8.9%, and 54.8% (17/31) when the mean HbA_{1c} exceeded 9%. The prevalence of retinopathy increased with the increase in the mean HbA_{1c} value over 10 years (trend, $P < 0.005$) (Fig. 1).

Multiple logistic regression analysis revealed that the only significant risk factor for the development of retinopathy in the 10th year was the mean HbA_{1c} value over 10 years ($P = 0.0149$). No statistically significant relationship was found between retinopathy and sex, age at onset of diabetes, mean systolic blood pressure during

From the Department of Internal Medicine and Ophthalmology of the Diabetes Center, Tokyo Women's Medical College, Tokyo, Japan.

Address correspondence and reprint requests to Tomoko Nakagami, MD, Diabetes Center, Tokyo Women's Medical College, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162, Japan.

Received for publication 22 July 1996 and accepted in revised form 30 October 1996.

ΔBMI, maximum BMI − BMI at registration; DCCT, Diabetes Control and Complications Trial.

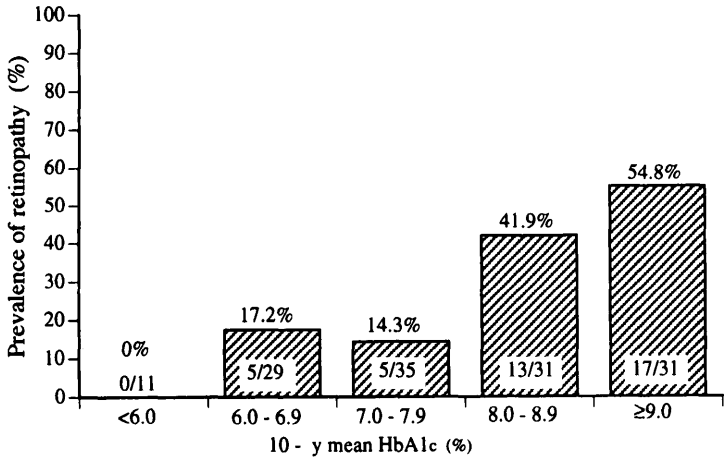

Figure 1—*Prevalence of retinopathy in relation to the mean HbA_{1c} value for 10 years. In the group with a mean HbA_{1c} value of <6%, no patients had retinopathy. The prevalence of retinopathy increased with the increase in the mean HbA_{1c} over 10 years (χ^2 test for trend, P < 0.005).*

the 10-year period, ΔBMI (maximum BMI − BMI at registration in study), or the HbA_{1c} value at registration (Table 1).

Eleven patients with a mean HbA_{1c} value <6% had been treated by diet only. In the patient group with a mean HbA_{1c} value ≥9%, 1 had been treated by diet, 15 with an oral hypoglycemic agent, and 16 with insulin. In the group with a mean HbA_{1c} value between 6 and 6.9%, five patients had simple retinopathy, and none had proliferative retinopathy. Of 31 patients with a mean HbA_{1c} value ≥9%, 11 had simple retinopathy and 6 had proliferative retinopathy.

CONCLUSIONS — The DCCT research group recommended that the mean HbA_{1c} value should be kept below 7% to prevent retinopathy (1). They also acknowledged that this did not completely prevent retinopathy and that to do so would require the HbA_{1c} value to be kept at 5–6%, i.e., the normal level. The present study showed that 17.2% of patients with a mean HbA_{1c} value between 6 and 6.9% had retinopathy in the 10th year, but none of those with a mean HbA_{1c} value below 6% had retinopathy. In the present study, patients with a mean HbA_{1c} value <6% were confirmed as actually having diabetes by undergoing the standard 75-g oral glucose tolerance test annually. Maintenance of the HbA_{1c} value <6% might be effective for the prevention of retinopathy. However, patients who maintained HbA_{1c} <6% succeeded in achieving glycemic control by diet therapy. These patients probably had a milder form of the disease, which would enable them to maintain a good HbA_{1c} value, which would lead to a decrease in the prevalence of retinopathy. Maximum BMI has been cited as an important factor for the prevalence of retinopathy (8), but the relationship between BMI or ΔBMI and retinopathy was not significant in this study. The mean maximum BMI of the subjects was 25.7 ± 3.2 kg/m², showing that they were not obese. Blood pressure is also said to be an important factor in the development of retinopathy (9). The blood pressure of the subjects was well controlled so that no such relationship was observed in this study. One study showed a positive association between the genetic background of the subjects and retinopathy (10). Because we had not obtained any information of the genetic background of our subjects at the initial point of this study, we could not include the influence of genetic susceptibility to microvascular complications in our study. In conclusion, our results support the concept that an early diagnosis and better glycemic control lessen the risk for the development of retinopathy in Japanese patients with NIDDM.

Table 1—*Multiple logistic regression analysis of retinopathy in the 10th year of follow-up*

Variable	β	SE	χ^2	*P* value
Sex (male = 0, female = 1)	1.0986	0.6185	3.1548	0.0757
Age at onset (years)	0.0636	0.0393	2.6148	0.1059
HbA_{1c} at registration (%)	0.1967	0.1381	2.0271	0.1545
Mean HbA_{1c} for 10 years (%)	0.5568	0.2287	5.9225	0.0149*
Mean systolic blood pressure (mmHg)	0.0128	0.0253	0.2569	0.6122
ΔBMI (kg/m²)	0.2157	0.1571	1.8838	0.1699

*Mean HbA_{1c} for 10 years related to retinopathy ($P = 0.0149$).

References

1. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
2. Klein R, Klein BE, Moss SE: Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. *Ann Intern Med* 124:90–96, 1996
3. Turner R, Cull C, Holman R: United Kingdom prospective diabetes study 17: a 9-year update of a randomized controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 124:136–145, 1996
4. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
5. Diabetic Retinopathy Study Research Group: Report VII: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 21:210–226, 1981
6. Mantel N: Chi-square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *J Am Stat Assoc* 58:690–700, 1963
7. Hosmer DW, Lemeshow S: *Applied Logistic Regression*. New York, Wiley, 1989
8. Knuiman MW, Welborn TA, MacCann VJ, Stanton KG, Constable IJ: Prevalence of diabetic complications in relation to risk factors. *Diabetes* 35:1332–1339, 1986
9. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 102:527–532, 1984
10. Ko BCB, Lam KSL, Wat NMS, Chung SSM: An (A-C)n dinucleotide repeat polymorphic marker at the 5′ end of the aldose reductase gene is associated with early-onset diabetic retinopathy in NIDDM patients. *Diabetes* 44:727–732, 1995