

Subclassification of Proliferative Diabetic Retinopathy and Glycemic Control: Relationship Between Mean Hemoglobin A_{1C} Value and Development of Proliferative Diabetic Retinopathy

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Purpose: We evaluated the relationship between long-term glycemic control and the proportion of patients developing proliferative diabetic retinopathy (PDR) among cases with mild type preproliferative diabetic retinopathy (PPDR).

Methods: The relationship was evaluated between the mean hemoglobin A_{1C} (HbA_{1C}) value during a period of at least 2 years and the proportion of patients developing PDR among cases with mild type PPDR, based on our previously proposed subclassification.

Results: During follow-up, 27% of the total PPDR cases developed PDR. The mean HbA_{1C} value in those patients who had developed PDR was 9.4% and was significantly higher than the 7.6% in those who had not developed PDR. The proportion developing PDR was 48% of the cases with a mean HbA_{1C} value of 8.6% or more. By comparison, the proportion developing PDR was 8% among those with a mean HbA_{1C} value below 8.6%. The proportion developing PDR was estimated to approximately double with each 1% increase in the mean HbA_{1C} value. The cumulative occurrence rates of PDR at 2, 5, and 10 years were estimated to be 5%, 28%, and 60% in cases with a mean HbA_{1C} value of 8.6% or more, and 0%, 7%, and 14% in those with a mean HbA_{1C} value below 8.6%, respectively.

Conclusion: Stricter systemic and ophthalmological control is indicated for cases with a mean HbA_{1C} value exceeding 8.6%. **Jpn J Ophthalmol 2001;45:523–527** © 2001 Japanese Ophthalmological Society

Key Words: Incidence of proliferative diabetic retinopathy, mean hemoglobin A_{1C} value, mild type, preproliferative diabetic retinopathy, subclassification.

Introduction

In a detailed study of systemic factors associated with the progression of retinopathy, Funatsu et al¹ found only glycemic control to be a significant factor. However, in their study, progression of retinopathy was evaluated in patients with simple diabetic retinopathy. To our knowledge, no study has as yet focused on the relationship between long-term glycemic control and the proportion of patients with

preproliferative diabetic retinopathy (PPDR) who go on to develop proliferative diabetic retinopathy (PDR).

We previously reported the results of a 1-year follow-up of PPDR cases subclassified as mild, moderate, or severe type according to our criteria.² We subsequently reported the results of long-term follow-up, ie, 2 or more years.³ In this study, in patients with mild type PPDR, the association between long-term glycemic control and the incidence of PDR development was evaluated.

Materials and Methods

Among patients with PPDR who in principle were followed up at our department for 2 years or more

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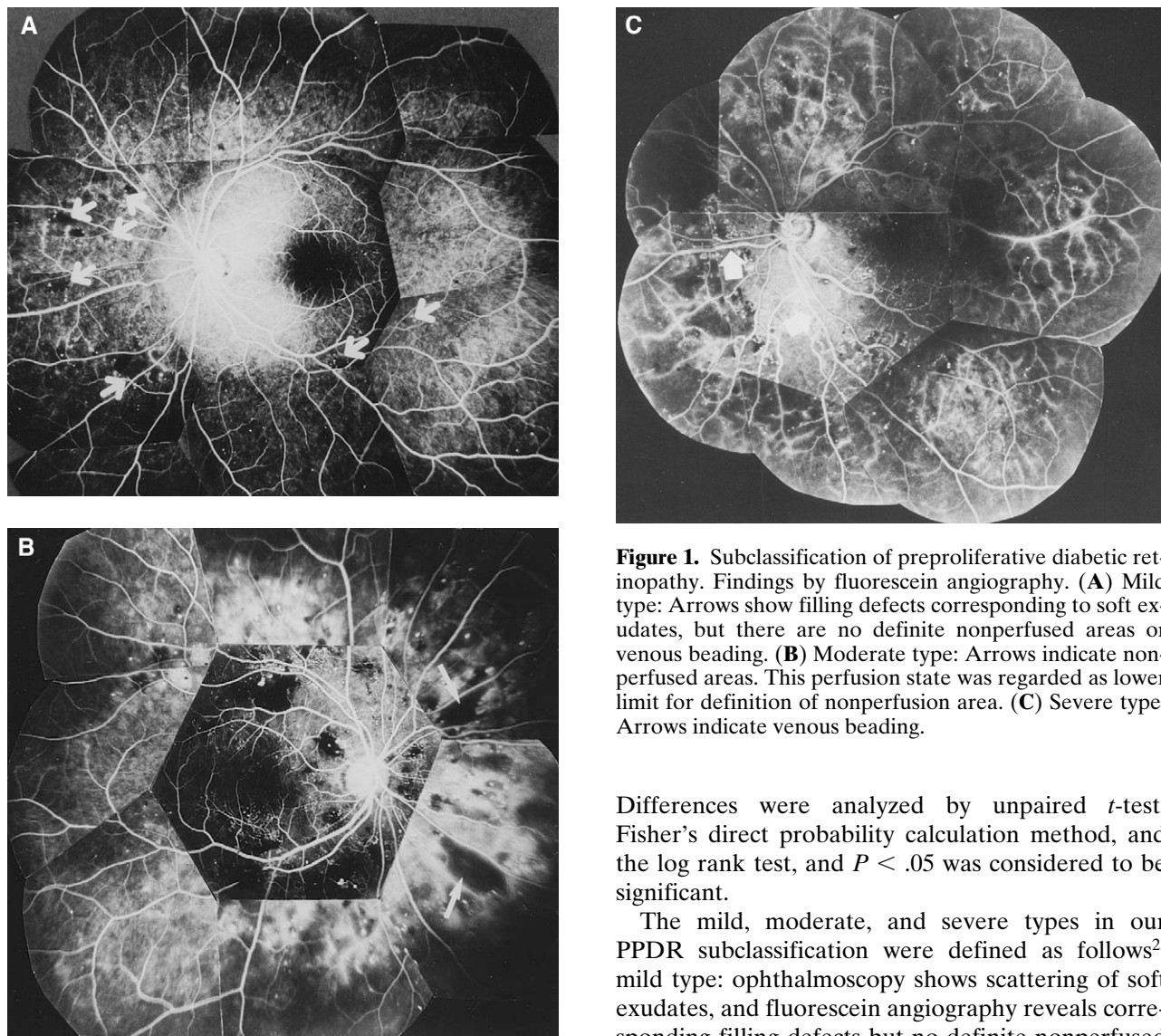


Figure 1. Subclassification of preproliferative diabetic retinopathy. Findings by fluorescein angiography. (A) Mild type: Arrows show filling defects corresponding to soft exudates, but there are no definite nonperfused areas or venous beading. (B) Moderate type: Arrows indicate nonperfused areas. This perfusion state was regarded as lower limit for definition of nonperfusion area. (C) Severe type: Arrows indicate venous beading.

by fluorescein angiography at 6-month intervals, 45 patients diagnosed as having the mild type at the first examination were enrolled in this study.

Ages of patients at the time mild type PPDR was diagnosed ranged from 37 to 75 years (55.9 ± 8.1 years: mean \pm SD). All patients had had type 2 diabetes mellitus for a duration of 1-30 years (10.8 ± 6.4 years). The follow-up period was 2-12 years (6 years and 10 months \pm 3 years and 6 months). During follow-up, 25 patients showed progression from the mild type to the moderate or severe type and underwent photocoagulation of nonperfused areas.

The association between glycemic control, using the hemoglobin A_{1C} (HbA_{1C}) value as a parameter, and the incidence of PDR development was evaluated by methods such as the Kaplan-Meier method.

Differences were analyzed by unpaired *t*-test, Fisher's direct probability calculation method, and the log rank test, and $P < .05$ was considered to be significant.

The mild, moderate, and severe types in our PPDR subclassification were defined as follows²: mild type: ophthalmoscopy shows scattering of soft exudates, and fluorescein angiography reveals corresponding filling defects but no definite nonperfused areas (Figure 1A); moderate type: soft exudates and definite nonperfused areas are observed, by fluorescein angiography, other than in filling defects corresponding to the soft exudates (Figure 1B); severe type: venous beading, in addition to soft exudates and definite nonperfused areas, are observed (Figure 1C). A standard photograph of minimal venous beading was used to assess the presence or absence of venous beading.²

Results

Incidence of PDR Development During Entire Follow-up Period

During the follow-up period, PDR developed in 12 (27%) of the 45 patients.

At the development of PDR, ages of patients

ranged from 42–84 years (61.3 ± 11.7 years), and the duration of diabetes mellitus was 5–25 years (16.3 ± 5.6 years). The interval between the diagnosis of mild type PPDR and PDR development ranged from 2 years and 3 months to 14 years and 10 months (6 years and 2 months \pm 3 years and 4 months). In patients with mild type PPDR in both eyes, progression to PDR in 1 eye was regarded as PDR development.

Mean HbA_{1C} Value and PDR Development

The association between the mean HbA_{1C} value during follow-up and PDR development was evaluated. The mean HbA_{1C} value was $9.4\% \pm 1.3\%$ in 12 patients who developed PDR and $7.6\% \pm 1.4\%$ in the other 33 who did not develop PDR. This difference is significant (unpaired *t*-test, $P < .0004$; Table 1).

Mean HbA_{1C} Value and PDR Incidence

A significant difference was observed in the incidence of PDR between patients with a mean HbA_{1C} value of 8.6% or more and those with a mean HbA_{1C} value below 8.6%. PDR developed in 10 (48%) of the 21 patients with a mean HbA_{1C} value of 8.6% or more and in 2 (8%) of 24 patients with a mean HbA_{1C} value below 8.6%; the incidence of PDR was significantly higher in the former (Fisher’s direct probability calculation method, $P < .004$; Table 2).

As the mean HbA_{1C} value rose, the incidence of PDR increased; PDR developed in none of 3, 1 (8%) of 12, 1 (17%) of 6, 1 (10%) of 10, 4 (57%) of 7 and 5 (71%) of 7 patients with a mean HbA_{1C} value between 5% and 6%, 6% and 7%, 7% and 8%, 8% and 9%, 9% and 10% and 10% and 11%, respectively (Figure 2). Analysis using the Cox proportional hazards model showed a hazard ratio of 1.89, indicating an approximately twofold increase in the incidence of PDR with each 1% increase in the mean HbA_{1C} value.

Cumulative Incidence of PDR Development

The cumulative incidence of PDR at 2, 5, and 10 years estimated by the Kaplan-Meier method was

Table 1. Mean Hemoglobin A_{1C} (HbA_{1C}) Value and Whether or Not There is Proliferative Diabetic Retinopathy (PDR) Development

	PDR Development (+)	PDR Development (-)
Mean HbA _{1C} value	$9.4 \pm 1.3\%$	$7.6 \pm 1.4\%$
<i>P</i> value	$<.0004$	

Table 2. Mean Hemoglobin A_{1C} (HbA_{1C}) Value and Incidence of Proliferative Diabetic Retinopathy (PDR)

Mean HbA _{1C} Value	PDR Development
$\geq 8.6\%$	10/21 cases (48%)
$< 8.6\%$	2/24 cases (8%)
<i>P</i> value	$<.004$

*Comparison between mean HbA_{1C} > 8.6% and <8.6%.

5%, 28%, and 60%, respectively, in patients with a mean HbA_{1C} value of 8.6% or more and 0%, 7%, and 14%, respectively, in those with a mean HbA_{1C} value of below 8.6% (Figure 3) showing significant differences between the two groups (Log rank test, $P < .04$).

Discussion

Glycemic control, patient age at diagnosis of diabetes mellitus, disease duration, sex, and glycemic control methods have been suggested as systemic factors that are significantly associated with the development of diabetic retinopathy.⁴ On the other hand, Funatsu et al¹ evaluated in detail systemic factors associated with the progression of retinopathy and found only glycemic control to be significant. In this study, progression to PDR was evaluated in patients with PPDR. Glycemic control, using the HbA_{1C} value as a parameter, was assessed as a systemic factor.

We previously evaluated the long-term follow-up results of cases with mild and moderate type PPDR for 2 years or more (mean = 6 years and 3 months) and observed the mean interval between PPDR diagnosis and PDR development to be 6 years and 5 months for the mild type but only 2 years for the

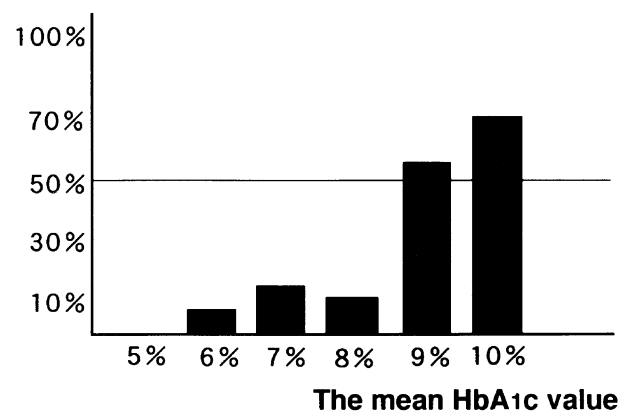


Figure 2. Incidence of proliferative diabetic retinopathy (PDR) development according to mean hemoglobin A_{1C} value.

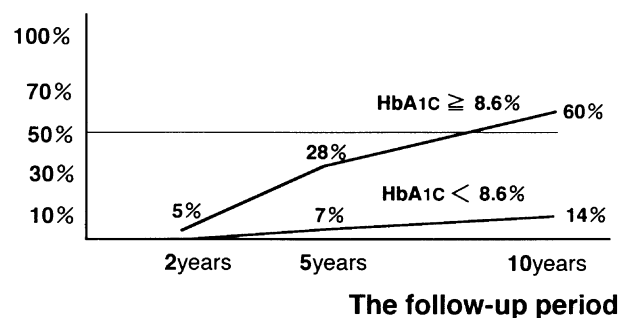


Figure 3. Cumulative incidence of proliferative diabetic retinopathy (PDR). Comparison between mean hemoglobin A_{1C} \geq 8.6% versus < 8.6%.

moderate type.³ The purpose of this study was to evaluate the association between long-term glycemic control, ie, for 2 years or more, and PDR development. Therefore, patients with the mild type showing slow progression were selected as subjects.

As described above, both the incidence and the cumulative incidence of PDR estimated by the Kaplan-Meier method differed markedly between patients with a mean HbA_{1C} value of 8.6% or more and those with a mean HbA_{1C} value below 8.6%. The overall incidence of PDR was 27%, with PDR developing in about 50% of the former but in less than 10% of the latter. The cumulative incidence at 2, 5, and 10 years was less than 10%, approximately 30%, and approximately 60%, respectively, in patients with a mean HbA_{1C} of value 8.6% or more; in patients with a mean HbA_{1C} below 8.6%, the cumulative incidence was 0%, less than 10%, and less than 20%, respectively.

In the field of ophthalmology in Japan, Funatsu et al⁵ evaluated the association between the mean HbA₁ value and changes in stage according to the Fukuda classification. They reported the stage of diabetic retinopathy to be closely associated with the mean HbA₁ value, showing aggravation of retinopathy above a mean HbA₁ value of 9.53%. Although direct comparison between HbA₁ and HbA_{1C} is difficult, the mean HbA₁ and HbA_{1C} values in normal subjects were reported to be $6.9\% \pm 0.7\%$ and $4.3\% \pm 0.6\%$, respectively.⁶

Therefore, the HbA₁ value of 9.53% reported by Funatsu et al⁵ is estimated to correspond to an HbA_{1C} value of approximately 7.0%.

A representative investigation in the medical field in Japan is the Kumamoto study^{7,8} in which the development and progression of complications including retinopathy in type 2 diabetes mellitus patients were prospectively investigated. In the Kumamoto study, the HbA_{1C} value predicting inhibition of the development and/or progression of retinopathy was

6.5% or less. Despite this low value, the observed HbA_{1C} value in the group showing aggravation of retinopathy was $8.1\% \pm 0.3\%$ ⁷ or $9.3\% \pm 1.1\%$.⁸

As described above, the subjects in both the Funatsu study⁵ and the Kumamoto study^{7,8} were diabetic patients without retinopathy or with simple diabetic retinopathy. Aggravation of retinopathy was diagnosed by the presence of changes in the Fukuda stage in Funatsu's study and changes of grade 2 or more in severity according to the modified Early Treatment Diabetic Retinopathy Study grading of diabetic retinopathy in the Kumamoto study. In our study, the subjects had mild type PPDR, and aggravation of retinopathy was determined based on whether or not there was progression to PDR. Therefore, it is difficult to compare the HbA_{1C} value of 8.6% observed in our study with the valuation of the group showing aggravation of retinopathy in the Kumamoto study.

As mentioned above, the association between long-term glycemic control and PDR development was evaluated in patients with mild type PPDR in the present study. The mean HbA_{1C} value was significantly higher in patients who developed PDR, and a marked difference in PDR incidence was observed when an HbA_{1C} value of 8.6% was used as the cut-off.

Therefore, physicians in charge of systemic control should understand that the incidence of PDR increases when the HbA_{1C} value exceeds 8.6% in patients with mild type PPDR. In patients persistently showing an HbA_{1C} value of 8.6% or more, stricter ophthalmological management, such as increasing the frequency of fluorescein angiography, may be necessary.

In this study, because the number of subjects was small, the effects of glycemic control in patients who showed progression from the mild type to the moderate or severe type could not be evaluated. We intend to evaluate these effects in additional cases.

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