# Longitudinal Measure of Glycemic Control and Diabetic Retinopathy

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In a population-based study, 5431 diabetic people in southern Wisconsin who were mature at onset of diabetes were identified, and their charts were reviewed. Recent glycemic control was evaluated from these charts. An index of recent glucose control with at least three glucose determinations abstracted from the doctor's chart was constructed. A sample of 1370 of the 5431 individuals was examined as part of this study. An index of glucose control could be derived for 568 of 674 people using insulin and for 565 of 696 nonusers of insulin. Correlation of the index with the glycosylated hemoglobin obtained at the time of study was significant in insulin users and nonusers. Patients with the poorest blood glucose control as described by index of past control or by current glycosylated hemoglobin had higher rates of retinopathy compared with patients who had the best control. When both the index of past control and current glycosylated hemoglobin values were combined, rate ratios for retinopathy for people with poorest control compared with those with best control were slightly better than when each measure was used alone. These analyses suggest that in planning programs, health-care impact may be increased if past and current data are considered. *Diabetes Care* 10:273–77, 1987

Epidemiologists prefer consistency of blood glucose measurement, both in technique of measurement and time with respect to food ingestion, when classifying patients by glycemic control (1). However, in clinical settings, fasting, casual, or postprandial blood glucose determinations may often be obtained by the physician when following patients with diabetes. In addition, some practitioners have begun to follow glycosylated hemoglobin rather than blood glucose. Although the use of different techniques often implies greater variability than is desirable in data accumulated for epidemiological studies, these techniques have the virtue of being frequently obtained and are readily accessible to chart reviewers.

We developed an index for characterizing blood glucose control as documented in medical records of a large population of diabetic people. We describe the relationship of this index to glycosylated hemoglobin, which was obtained during a population-based survey, and the associations between the index, current glycosylated hemoglobin, and a chronic complication of diabetes, retinopathy, in a group of people who developed diabetes as adults.

## PATIENTS AND METHODS

*Sample.* The population has been described in detail in previous reports (2–4). Briefly, 452 of the 457 physicians who provided primary care to diabetic patients in an 11-county area in southern Wisconsin [Health Service Area 1 (HSA-1)] participated in the study. Participation involved keeping lists of all diabetic patients for whom they provided primary care from 1 July 1979 to 30 June 1980. Over this 1-yr period, 10,135 diabetic patients were identified. Charts of 9841 of these patients were reviewed.

There were 5431 patients who were diagnosed at ≥30 yr of age and who had their diagnoses confirmed by a random or a postprandial serum glucose of at least 200 mg/dl or a fasting serum glucose of ≥140 mg/dl on at least two occasions. A probability sample of this group was selected for evaluation ($n$ = 1780). Seventy-seven percent (1370 of 1780) of these people actually participated.

*Index of glucose control.* At the time of the initial survey, glycosylated hemoglobin levels to measure glycemic control were not widely used by physicians; therefore, an index of

TABLE 1
Comparison of characteristics between diabetic individuals who had 3 or 4 and those with <3 blood glucose determinations

| | 3 or 4 blood glucose determinations | | | <3 blood glucose determinations | | | |
|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | P |
| Insulin users* | | | | | | | |
| Age (yr) | 568 | 64.9 | 11.3 | 106 | 66.4 | 11.5 | <.25 |
| Duration of diabetes (yr) | 568 | 14.7 | 8.1 | 106 | 16.8 | 9.1 | <.05 |
| Age at diagnosis (yr) | 568 | 50.2 | 11.7 | 106 | 49.6 | 12.5 | <.75 |
| Systolic blood pressure (mmHg) | 567 | 147 | 25 | 105 | 145 | 24 | <.50 |
| Diastolic blood pressure (mmHg) | 567 | 78 | 12 | 105 | 78 | 13 | >.90 |
| Body mass index (lb/inch² × 100) | 562 | 4.04 | 0.83 | 106 | 3.98 | 0.82 | <.50 |
| Glycosylated hemoglobin (%) | 519 | 11.9 | 2.3 | 96 | 12.1 | 2.2 | <.50 |
| No insulin used† | | | | | | | |
| Age (yr) | 565 | 68.3 | 11.1 | 131 | 66.8 | 11.5 | <.20 |
| Duration of diabetes (yr) | 565 | 9.0 | 6.7 | 131 | 7.8 | 6.6 | <.10 |
| Age at diagnosis (yr) | 565 | 59.3 | 11.2 | 131 | 59.0 | 11.5 | <.90 |
| Systolic blood pressure (mmHg) | 564 | 148 | 23 | 130 | 149 | 22 | <.75 |
| Diastolic blood pressure (mmHg) | 561 | 80 | 12 | 128 | 82 | 10 | <.10 |
| Body mass index (lb/inch² × 100) | 563 | 4.13 | 0.79 | 131 | 4.13 | 0.72 | >.90 |
| Glycosylated hemoglobin (%) | 521 | 10.4 | 2.4 | 129 | 9.9 | 2.2 | <.05 |

*P* value was based on 2-tailed Student's *t* test.
*Percentages of men with 3 or 4 blood glucose determinations and <3 blood glucose determinations were 46.1% (n = 568) and 55.6% (n = 106), respectively ($P < .1$; $\chi^2$-test with 1 df).
†Percentages of men with 3 or 4 blood glucose determinations and <3 blood glucose determinations were 44.4% (n = 565) and 47.3% (n = 131), respectively ($P < .75$; $\chi^2$-test with 1 df).

recent control of glucose was constructed. The most recent three or four blood glucose levels measured a minimum of 1 mo apart but within 3 yr of the last visit were recorded; it was noted whether the values were taken after fasting or were casual. A fasting blood glucose level ≥140 mg/dl or a casual blood glucose level ≥200 mg/dl was considered to be higher than desirable and was assigned a value of 1; blood glucose values lower than these were assigned a value of 0. This index allowed classification of five levels of glucose control: 0, best control, in which none of the three or four glucose levels was above the specified values; 1, good control, in which one of the three or four glucose levels was above the specified values; 2, moderate control, in which two of the four glucose levels were above the specified values; 3, poor control, in which two of three or three of the four glucose levels were above the specified values; and 4, poorest control, in which all of the three or four glucose levels were above the specified values.

*Grading procedure for diabetic retinopathy.* The grading protocol has been described in detail in previous reports and is based on the modified Airlie House Classification of Diabetic Retinopathy (3). Gradings are based on seven standard stereophotographic fields of each eye. The grading was performed at the Fundus Photography Reading Center at the University of Wisconsin at Madison. Participants were classified by the more severely involved eye. Although 11 levels of increasing severity were possible, levels were combined for our analyses. For some analyses, individuals were classified

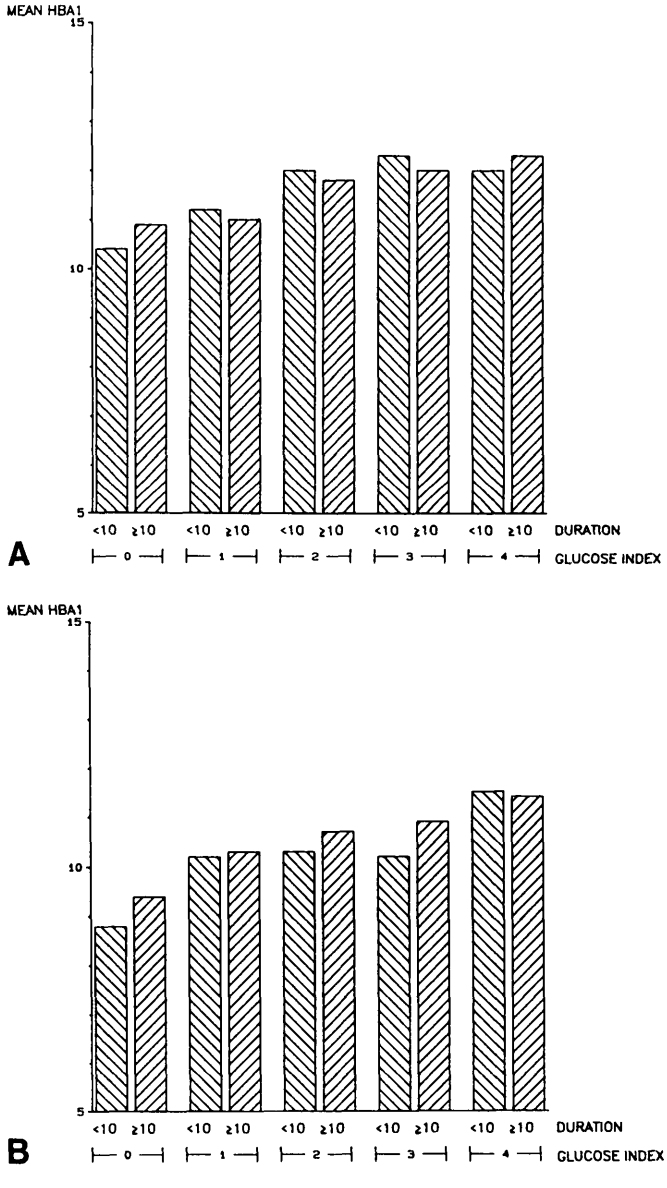


**FIG. 1. Mean glycosylated hemoglobin vs. index of glucose control by duration of diabetes. A: onset after maturity, insulin used; B: onset after maturity, no insulin used.**

TABLE 2
Spearman correlations (ρ) between index of glucose control and glycosylated hemoglobin by duration of diabetes

| Group | ρ | P |
|---|---|---|
| Insulin user | | |
| Duration 0–9 yr | .16 | <.05 |
| Duration ≥10 yr | .24 | <.001 |
| No insulin used | | |
| Duration 0–9 yr | .39 | <.001 |
| Duration ≥10 yr | .34 | <.001 |

as having retinopathy or not; for others, patients were classified as having proliferative retinopathy (levels 6–8) or not (levels 1–5).

*Laboratory measures.* Glycosylated hemoglobin was performed on a specimen of fingerstick capillary blood by the Isolab method (5).

Wisconsin Storage and Retrieval, an information-processing software system, was used for processing all subject files and for calculating $\chi^2$-statistics and analysis of variance (6). A one-sided test for trend was used for comparing rates of retinopathy by index of glucose control and glycosylated hemoglobin (7). This procedure tests for the tendency of a rate to increase or decrease with an increase in another variable. The rate ratio or relative risk is the ratio of the rate of occurrence of an outcome in one group to that rate in a reference group. A rate ratio of 1 indicates that there is no difference in rate between the two groups. A rate ratio >1 indicates the rate in the first group is greater than the rate in the second group. We used the rate ratio to compare the rate of diabetic retinopathy in the group with the highest index of glucose control or quartile of glycosylated hemoglobin with the lowest group.

## RESULTS

Of the population surveyed, three or four glucose determinations, which were necessary to derive an index of glucose control, were available for 568 of 674 (84%) patients who used insulin and 565 of 696 (81%) who did not use insulin. In addition, a glycosylated hemoglobin determination was obtained for 614 of 674 (91%) individuals who used insulin and for 646 of 696 (93%) who did not use insulin; 518 of 674 (77%) individuals who used insulin and 518 of 696 (74%) who did not use insulin had an index of glucose control and a glycosylated hemoglobin. A comparison of patients who had three or four blood glucose determinations as defined in

TABLE 3
Relationship of index of glucose control and glycosylated hemoglobin to diabetic retinopathy

| | Duration <10 yr | | | Duration >10 yr | | |
|---|---|---|---|---|---|---|
| | n | With any retinopathy (%) | P | n | With proliferative retinopathy (%) | P |
| Insulin users | | | | | | |
| Glucose control index | | | | | | |
| 0 | 17 | 35.3 | | 31 | 6.5 | |
| 1 | 26 | 30.8 | | 57 | 17.5 | |
| 2 | 25 | 48.0 | <.25 | 66 | 13.6 | <.50 |
| 3 | 43 | 58.1 | | 90 | 27.8 | |
| 4 | 71 | 45.1 | | 141 | 15.6 | |
| $HbA_1$ quartile | | | | | | |
| 1 | 45 | 42.2 | | 104 | 9.6 | |
| 2 | 53 | 43.4 | | 105 | 19.0 | |
| 3 | 53 | 50.9 | >.90 | 108 | 19.4 | <.01 |
| 4 | 48 | 41.7 | | 98 | 23.5 | |
| No insulin used | | | | | | |
| Glucose control index | | | | | With any retinopathy | |
| 0 | 80 | 26.2 | | 33 | 45.5 | |
| 1 | 65 | 20.0 | | 20 | 50.0 | |
| 2 | 64 | 34.4 | <.01 | 27 | 51.9 | <.01 |
| 3 | 76 | 38.2 | | 38 | 57.9 | |
| 4 | 97 | 39.2 | | 62 | 67.8 | |
| $HbA_1$ quartile | | | | | | |
| 1 | 122 | 25.4 | | 48 | 39.6 | |
| 2 | 114 | 31.6 | | 50 | 50.0 | |
| 3 | 109 | 31.2 | <.025 | 49 | 55.1 | <.001 |
| 4 | 106 | 39.6 | | 48 | 72.9 | |

*P* values were determined by 1-sided test for trend.

TABLE 4
Rates of retinopathy by combined measure of glucose control

| | Duration <10 yr | | | Duration >10 yr | | |
|---|---|---|---|---|---|---|
| | n | With any retinopathy (%) | P | n | With proliferative retinopathy (%) | P |
| Insulin used | | | | | | |
| L-L | 27 | 29.6 | | 53 | 7.5 | |
| Varying | 87 | 48.3 | <.25 | 174 | 17.8 | <.25 |
| H-H | 57 | 47.4 | | 120 | 20.8 | |
| No insulin used | | | | | With any retinopathy | |
| L-L | 89 | 22.5 | | 32 | 40.6 | |
| Varying | 168 | 33.9 | <.05 | 71 | 50.7 | <.01 |
| H-H | 100 | 40.0 | | 58 | 72.4 | |

L-L, low levels; varying, inconsistent levels; H-H, high levels.
*P* values based on $\chi^2$-test with 2 df.

PATIENTS AND METHODS with those who had fewer than three blood glucose measurements is shown in Table 1. For patients who used insulin, there was little difference between the groups, except for a significant difference in duration of diabetes. Individuals who had fewer blood glucose measurements had slightly longer mean duration. For patients who did not use insulin, no significant differences were found between the groups, except for glycosylated hemoglobin.

The relationship of mean glycosylated hemoglobin obtained from most participants to the index of glucose control for the two groups is shown in Fig. 1. Duration of diabetes appears to have little effect on this relationship. The Spearman correlation coefficient between these two parameters is significant in all cases and is slightly greater for patients who were not using insulin (Table 2).

Next we examined the relationship of antecedent glucose control to retinopathy status at time of examination in 1980–1982. For patients with <10 yr duration of diabetes, the rates of proliferative retinopathy were 4.9% for insulin users and 2.6% for nonusers. For people with >10 yr of diabetes, the rates of proliferative retinopathy were 17.7% for insulin users and 3.9% for nonusers. Because of these considerations, Tables 3–5 present data for only those groups with a sufficient number of subjects for meaningful comparisons. People with the poorest previous blood glucose control (a glucose control index of 4) had higher rates of any retinopathy and of proliferative retinopathy when compared with individuals who had the best control (Table 3). However, in most groups there was not a consistent systematic increase in rate of retinopathy as control worsened.

In parallel analyses, we evaluated the relationship of glycosylated hemoglobin to diabetic retinopathy (Table 3). The pattern was similar to that found for the index of control and retinopathy.

To estimate an effect of poor, variable, and good diabetic control from the first-recorded glucose measurement until the survey, we evaluated the severity of diabetic retinopathy after grouping participants in the following way: patients with a glucose index of 0 or 1 were considered to have low blood glucose levels (L), those with an index of 2 were considered to have intermediate levels (M), and those with an index of 3 or 4 were considered to have high levels (H). The same patients were classified by their glycosylated hemoglobin levels at the time of survey. People with values below the median were classified as having low glycosylated hemoglobin (L), and those with values above the median were classified as having high values (H). Participants were then grouped into three strata: those with low levels for both measures (L-L), those with high levels for both measures (H-H), and those with less consistent levels (varying) (Table 4). The rates of retinopathy or proliferative retinopathy are consistently lowest in people in the L-L (best control) categories in all groups

TABLE 5
Rate ratios for the effect of poorest glucose control and diabetic retinopathy

| | Insulin used | | No insulin used | |
|---|---|---|---|---|
| | Any retinopathy (<10 yr) | Proliferative retinopathy (≥10 yr) | Any retinopathy (<10 yr) | Any retinopathy (≥10 yr) |
| Index of glucose control | 1.28 | 2.40 | 1.50 | 1.49 |
| Glycosylated hemoglobin | 0.95 | 2.15 | 1.28 | 1.61 |
| Combined | 1.60 | 2.77 | 1.78 | 1.78 |

and highest in the H-H (poorest control) groups. Furthermore, there is a gradient of increasing rates of proliferative retinopathy with poorer control of blood glucose as defined herein.

Rate ratios comparing patients with poorest levels of control with those with best control were calculated for all groups (Table 5). The rate ratios for those with poorest control, as defined by high values for the index of glucose control and glycosylated hemoglobin, were higher than when either the index or the glycosylated hemoglobin alone were considered. The rate ratios for the groups with any retinopathy are similar for the three groups; rate ratios for proliferative retinopathy are distinctly higher.

## DISCUSSION

There are several characteristics of patients with diabetes that are associated with the development of chronic complications. Of these, the causal role of elevated blood glucose itself, although pathognomonic of diabetes, has been difficult to define. This difficulty may be due to varying management strategies and follow-up procedures that are in practice in the community and possibly to differences in the inherent severity of the condition. The analyses reported herein suggest that regardless of the etiologic role of poor glucose control in the development of complications, it can be considered a risk indicator for retinopathy. The methods used to evaluate the relationship were chosen because of the varied nature of the information on previous blood glucose levels. Thus, for some patients we used blood glucose levels recorded as long as 4 yr before the survey; for others, blood glucose was measured 2 yr before; casual or fasting values were used. Laboratory methods may not have been standard or uniform; because the data were abstracted from charts of 452 doctors' offices, the laboratories and techniques used are not known.

In the field survey, glycosylated hemoglobin, a test currently employed to assess diabetes control, was used. This test, although performed according to protocol in a standardized fashion, is a different laboratory determination, and therefore using it in these analyses adds another source of variation when attempting to combine the data. These factors may be partly responsible for the lack of a consistent dose-response relationship between past glycemic control and prevalence of any or of proliferative diabetic retinopathy. The individuals for whom we had fewer than three blood glucose determinations were similar to those for whom we had complete data. Although it is possible that, were their data complete, the relationship found would be altered, it appears unlikely that the differences would result in a significant bias in our finding of the correlation of glycosylated hemoglobin to the index or to the severity of retinopathy.

These analyses should not be construed as supporting an etiologic relationship. However, there are important public health implications of these data for planning programs for secondary prevention of complications of diabetes. Relatively poor glycemic control in the past, ascertained in various ways, is usually associated with an increased rate of retinopathy (and possibly other chronic complications of diabetes); higher glycosylated hemoglobin is also associated with an increased rate of retinopathy, and combining these data, presumably due to more evidence that glycemic control is poor, further increases the strength of the association. Therefore, when planning health-care programs for diabetic patients, the impact of the program may be improved if all past data are considered.

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