Retinopathy in Older Type II Diabetics
Association With Glucose Control

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SUMMARY

Non-insulin-dependent (type II) diabetics over the age of 55 comprise most of the diabetic population and are at considerable risk for the development of both macrovascular and microvascular complications. We studied the prevalence of retinopathy and its association with putative risk factors for its development in an elderly (55- to 75-yr-old) population of type II diabetics. Our cross-sectional analysis revealed that duration of diabetes and hemoglobin A_{1c} (HbA_{1c}) concentration were the two major predictors of the presence of retinopathy. Duration effect was seen after 10 yr of diabetes, whereas HbA_{1c} effect was linear over its entire range. Hypertension, which has been reported to be a risk factor for microvascular disease in younger diabetic patients, was not associated with retinopathy in the older type II population. Multiple logistic regression analysis revealed that both the duration of diabetes and HbA_{1c} remained significant independent determinants of retinopathy even after taking age and blood pressure into account. Our results support an etiologic role for metabolic control in the development of retinopathy in the elderly type II population. DIABETES 1986; 35:797–801.

The relationship between glucose control and the development of diabetic complications remains an area of active investigation. Although previous[1–3] and ongoing[4] studies have examined the relationship between glucose control and retinopathy in insulin-dependent (type I) diabetic subjects, relatively few studies have attempted to examine the relationship in non-insulin-dependent (type II) diabetics.[5–7] The putative relationship between control and complications in the type II population is as important as in the type I population because type II diabetic patients represent >80% of the total diabetic population[8] and develop retinopathy with a frequency similar to type I patients with equal duration of diabetes.[9,10]

We examined the relationship between diabetic control as measured by glycosylated hemoglobin concentration and the prevalence of diabetic retinopathy in 185 type II diabetics between 55 and 75 yr of age. The balanced recruitment design of the study provided large subgroups of subjects of varying age, duration of disease, and type of therapy and allowed the careful evaluation of concurrent risk factors. The results of our study identify chronic glucose control as an independent risk factor for the development of retinopathy in the elderly type II population.

MATERIALS AND METHODS

This study was part of a larger prospective study of type II diabetes in the elderly. The recruitment methods used in this trial have been described previously.[11] In brief, type II diabetics and age-matched controls between the ages of 55 and 75 yr were recruited from the outpatient population of the Massachusetts General Hospital. Patients with the diagnosis of type II diabetes were identified by a computer search of major diagnoses. Medical records were then reviewed to confirm the diagnosis of type II diabetes according to the criteria of the National Diabetes Data Group.[12] The recruitment plan was a balanced one, designed to achieve a similar number of subjects in the 55–61, 61–68, and 69–75 yr age ranges and a similar distribution of therapies (diet, insulin, and oral agent) and duration of disease (0–5, 6–10, and >10 yr) in each of the age categories. Subjects were recruited consecutively until a particular patient category (e.g., 55–61 yr of age, treated with insulin and with a duration of 0–5 yr) was filled. In addition, ~50% of the subjects were female.

Baseline studies included a history that obtained detailed information regarding the duration of diabetes, type of therapy, presence of other known or putative risk factors for

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complications such as hypertension and smoking, and medication use. The physical examination included measurements of height, weight, supine and standing blood pressure, deep tendon reflexes, and sensory vibration threshold with a biothesiometer (Bio Medical, Newbury, OH).[13] Direct ophthalmoscopy was performed in a darkened room by two experienced diabetologists (D.M.N. and J.E.G.) who were masked to the hemoglobin A_{1c} (HbA_{1c}) value and as to whether the subjects were diabetic or nondiabetic. The eye examination was graded as showing the presence of nonproliferative retinopathy (>1 microaneurysm, hemorrhages, or exudates) or proliferative vascular changes in either eye. Visual acuity was examined with a Snellen eye chart.

Two hundred fifty type II diabetics and 48 age-matched nondiabetic subjects were identified and recruited for the study. Satisfactory eye examinations were performed through a nondilated pupil in all 48 nondiabetics and in 185 diabetic subjects. Of the 65 subjects recruited who did not receive satisfactory eye examinations, 55 were not examined because of scheduling difficulties, and 10 were examined, but the fundus was not adequately visualized. There was no known relation between retinopathy or its determinants and the completion of satisfactory eye exams. Mean HbA_{1c} concentrations in the subjects who had complete eye exams was not significantly different than the mean HbA_{1c} for those who did not have a completed eye exam (8.43 ± 2.08 vs. 8.60 ± 2.21%, $P > .5$).

Laboratory evaluation performed on the day of the history and physical examination included fasting cholesterol and triglycerides, measured by autoanalyzer (Boehringer-Mannheim, Indianapolis, IN). Hemoglobin A_{1c} was measured on the day of the examination as well as every 3 mo prospectively by a high-performance liquid chromatography method with saline preincubation to remove the labile component.[14] The nondiabetic range for this assay was 3.80–6.40%, and the interassay and intra-assay coefficients of variation were <3%.

An age-matched population with no history of diabetes and with normal fasting and 2-h postprandial blood glucose concentrations and normal HbA_{1c} concentrations was drawn from the outpatient population of the Massachusetts General Hospital.

TABLE 1
Univariate correlates of retinopathy

	Retinopathy		
	Present (N = 46)	Absent (N = 139)	Significance (one tailed)
Duration (yr)*	12.2 ± 7.3	7.5 ± 7.4	$P < .001$
Hemoglobin A_{1c}* (%)	9.61 ± 2.1	8.30 ± 2.1	$P < .001$
Insulin therapy (%)	55	35	$P < .02$
Age (yr)	65.3 ± 5.5	63.7 ± 5.4	NS
Hypertension			
by history (%)	62	57	NS
by exam (%)	24	17	NS
Systolic BP > 155			
by history or exam (%)	70	62	NS
Cholesterol* (mg/dl)	236 ± 43	242 ± 57	NS
Cigarette smoking (%)			
Ever	68	59	NS
Current	13	24	NS

NS, not significant.
*Mean ± 1 SD.

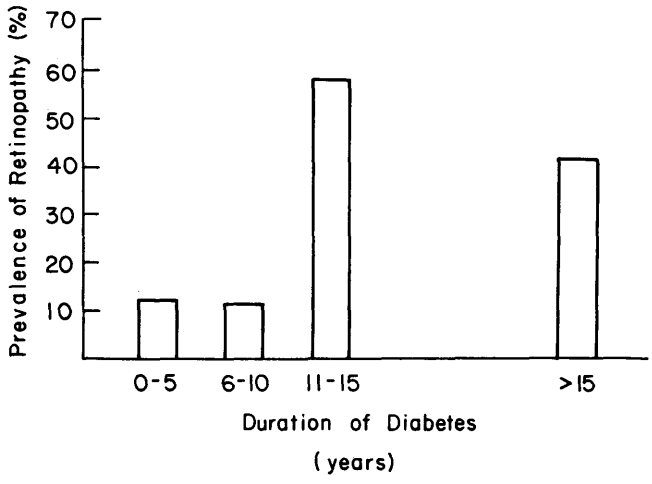

FIGURE 1. Prevalence of retinopathy for subjects according to duration of diabetes; 11 of 81 patients with 0–5 yr duration, 5 of 47 with 6–10 yr, 19 of 33 with 11–15 yr, and 11 of 24 patients with >15 yr duration had retinopathy. χ^2 for deviation from linear trend (24) was 17.1, $P < .001$, making hypothesis of simple linear trend untenable.

STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS-X statistical package on a Digital Equipment Corporation VAX/VMS computer.[15] Analyses of variance, χ^2-analysis, Student's two-tailed t test, and correlation coefficients were performed as indicated. Stratified analysis illustrated in Figure 3 was by the Mantel-Haenszel technique.[16] Multiple logistic regression models were developed with BMDP Program LR.[17]

RESULTS

The analyses include 185 type II diabetics and 48 age-matched nondiabetic subjects. The prevalence of retinopathy in the diabetics was 25%, most with background retinopathy but including three subjects (1.6%) with proliferative retinopathy. Most (>95%) subjects with retinopathy had both eyes affected. In the nondiabetic group, one subject with hypertension was noted to have exudates and microaneurysms thought to be consistent with retinopathy for a prevalence of 2.4%. The difference between the groups was highly signficant ($P < .005$).

UNIVARIATE CORRELATES OF RETINOPATHY

The remainder of this analysis focuses exclusively on the diabetic group. Among the possible clinical correlates of retinopathy, there were several significant relationships. Increasing duration of diabetes was strongly associated with an increasing prevalence of retinopathy (Table 1). Subjects with a duration of diabetes >10 yr had a prevalence more than fourfold higher than those with a duration <10 yr (53 vs. 12%, Figure 1). The risk imparted by increasing duration appeared to follow a step function, with the most dramatic change in retinopathy prevalence occurring after 10 yr.

Glucose control as measured by the initial study HbA_{1c} was also significantly related to the prevalence of retinopathy. In contrast to the step-function appearance of the plot of reti-

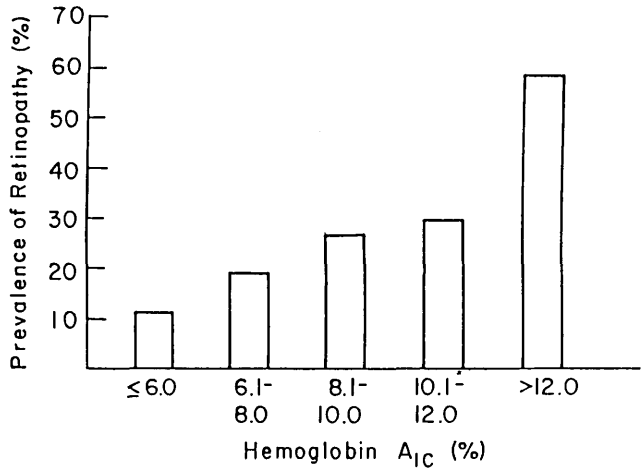

FIGURE 2. Prevalence of retinopathy for subjects according to hemoglobin A_{1c} (HbA_{1c}) concentration; 2 of 19 patients with HbA_{1c} < 6.0%, 12 of 62 with HbA_{1c} 6.1–8.0%, 15 of 56 with HbA_{1c} 8.1–10%, 10 of 36 with HbA_{1c} 10.1–12%, and 7 of 12 patients with HbA_{1c} > 12.0% had retinopathy. χ^2 for linear trend was 8.24, $P = .002$; χ^2 for deviation from linear trend was 2.46 $P > .10$.

nopathy versus duration of diabetes, retinopathy appears in our data as a simple linear function of HbA_{1c} (Figure 2). The slope from the linear test of trend suggests a 12.4% increase in retinopathy for every 3% change in HbA_{1c} (a 3% change in HbA_{1c} is equivalent to a 100 mg/dl change in mean blood glucose).[18] Therapy for diabetes was also associated, but less strongly, with retinopathy, with the greatest prevalence of retinopathy in insulin-treated subjects. Note the type of therapy was associated with disease duration as well as HbA_{1c}, with insulin-treated subjects having longer duration and higher HbA_{1c} levels than the oral-agent– and diet-treated subjects (data not shown). Age, gender, hypertension, serum cholesterol, and smoking status were not significantly associated with retinopathy (Table 1).

REMOVAL OF CONFOUNDING FROM RELATIONSHIP BETWEEN HEMOGLOBIN A_{1c} AND RETINOPATHY

Accounting for individual potential confounders. The relationship between HbA_{1c} and retinopathy may be confounded because HbA_{1c} is associated with other determinants of retinopathy. An initial approach to remove this potential confounding is to examine the effect of HbA_{1c} on prevalence of retinopathy within strata of the possible confounders. This approach is illustrated in Figure 3. The analysis was simplified by dichotomizing the range of HbA_{1c} at its median value of 8.34%. The qualitative effect of HbA_{1c} on prevalence of retinopathy is preserved across the entire series of potential confounders.

The most important confounder is disease duration because it is strongly associated with retinopathy and is also associated with HbA_{1c} (Pearson $r = 0.251$, $P < .001$; HbA_{1c} and duration coded continuously). The apparent effect of HbA_{1c} is indeed reduced when disease duration is accounted for: the difference in prevalence of retinopathy in the two hemoglobin categories dropping from 16.5% in the unstratified analysis to 8.7% (maximum likelihood estimate[16]) in the duration stratified analysis. This residual effect of HbA_{1c} remains significant ($P = .037$, one tail). The level of significance increases when a more optimal coding of HbA_{1c}, i.e., as a continuous variable, is included in a multiple logistic regression model.

Accounting for confounding via multiple logistic regression analysis. The occurrence of retinopathy can be modeled by multiple logistic regression analysis,[17] which allows for simultaneous accounting of multiple confounders. Table 2 lists three models that demonstrate a persistent significant effect of HbA_{1c} despite inclusion of many possible confounders. The models listed are simple additive models; two-way interaction (product) terms including HbA_{1c} were not significant. Note that HbA_{1c} was continuous, whereas the other terms were dichotomous. History of hypertension and measured blood pressure were aggregated into a single dichotomous variable.

The effect of HbA_{1c} on occurrence of retinopathy is provided by the coefficient of HbA_{1c}.[19] There is a substantial decrease in this coefficient when duration is included but little further change when the other variables are added. The effect of HbA_{1c} remains statistically significant. For this study's population, the adjusted prevalence of retinopathy for HbA_{1c} of 10% was 24% compared with 15% for an HbA_{1c} of 7%.

HEMOGLOBIN A_{1c} AS MEASURE OF CHRONIC GLUCOSE CONTROL

The validity of HbA_{1c} as a measure of glucose control over a preceding 8- to 12-wk period is well established.[18] In our

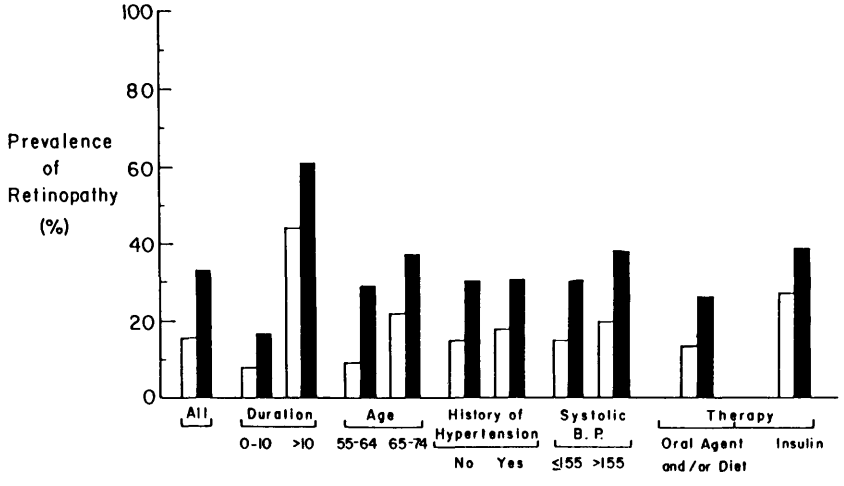

FIGURE 3. Stratified analysis of the prevalence of retinopathy for diabetic subjects with hemoglobin A_{1c} (HbA_{1c}) ≤ 8.34% compared with prevalence in subjects with HbA_{1c} > 8.34% (*solid bars*). One-tailed *P* value for association of HbA_{1c} and retinopathy from Mantel-Haenszel χ: unstratified ("all"), $P = .005$; duration, $P = .037$; age, $P = .003$; history of hypertension, $P = .005$; systolic BP, $P = .006$; insulin use, $P = .017$.

TABLE 2
Hemoglobin A_{1c} and retinopathy: multiple logistic regression models

Variables in model*	Coefficient	*P* value (one tailed)
Model 1		
Hemoglobin A_{1c}†	0.2594	<.001
Model 2		
Hemoglobin A_{1c}	0.1983	.013
Duration	1.0386	<.0001
Model 3		
Hemoglobin A_{1c}	0.2023	.013
Duration	1.0366	<.0001
Age	0.0415	.129
Hypertension	0.1763	.203

*Models are of the form

$$\ln \frac{\text{prevalence of retinopathy}}{1 - \text{prevalence of retinopathy}} = \alpha + \sum_i \beta_i X_i$$

where α is a constant, X_i is the variables listed, and β_i their coefficients.
†Coding of variables: *1*) hemoglobin A_{1c}, continuous; *2*) duration, dichotomous split at ≤10 yr; 3) age, continuous; *4*) hypertension, yes or no, where "yes" is applied if an individual had a history of hypertension or if his/her measured systolic blood pressure was >155. Note that the coding in the model for dichotomous categories was +1, −1.

analysis we assume that a single HbA_{1c} is a useful index of glucose control over a much longer period of years. One hundred seventy-eight study subjects subsequently had from 1 to 15 additional HbA_{1c} measurements performed prospectively every 3 mo. The Spearman correlation coefficient between the original hemoglobin and the mean of all subsequent assessments for each subject was 0.83 ($P < .001$), indicating a strong "tracking" of HbA_{1c} values. The stability of glucose control in type II diabetes has been suggested by others.[20]

DISCUSSION

The occurrence of retinopathy in the type II diabetic population appears to occur with a frequency similar to retinopathy in the type I population with similar duration of diabetes.[9,10] The overall prevalence of 25% in our population with an average duration of 8 yr is similar to the prevalence documented in studies of type I subjects with a similar duration.[21] The clinical significance of this finding is considerable because the type II population includes most of the diabetic population. Our ophthalmologic exam was not as sensitive as in other studies with stereoscopic fundus photography[10,21] and fluorescein angiography.[21] However, errors in assessment of retinopathy would not have led to the observed associations because the examining physicians were unaware of the patient's diabetes status, duration of diabetes, or the HbA_{1c} result.[23]

We identified three univariate correlates of retinopathy: duration of diabetes, HbA_{1c}, and insulin use. Duration was the most powerful determinant, with a fourfold increase in prevalence of retinopathy in those whose duration of disease exceeded 10 yr. Although we recognize the difficulty in accurately dating the time of onset of type II diabetes because patients may have a variable asymptomatic period before diagnosis, the durations obtained were the best estimates available. The relationship between retinopathy and disease duration was remarkable for the apparent sudden increase in retinal abnormalities occurring at the 10-yr mark. Whether this step function with regard to duration has implications for the pathophysiology of retinopathy or its treatment is conjectural.

Glucose control as measured by the initial study HbA_{1c} was also a powerful univariate correlate of retinopathy, their relationship revealing a smooth linear increase in retinopathy with HbA_{1c}. The apparent relationship of insulin use with retinopathy was probably spuriously inflated. The "natural history" of our type II diabetics was to develop worse control (higher HbA_{1c} levels) over time, leading to a higher proportion treated with insulin. As a result, insulin use was highly related to HbA_{1c} and to duration. When the latter two determinants of retinopathy were included in a multivariate model, insulin use was no longer significant. A history of hypertension, a risk factor for retinopathy in type I subjects,[22] was not a risk factor in our type II population. Perhaps this is a result of the aggressive antihypertensive therapy used in our elderly diabetic population. The mean systolic and diastolic pressures were not significantly different between our subjects with a positive and negative history of hypertension.

The demonstration of a relationship between the initial study hemoglobin and retinopathy was particularly interesting. This effect was decreased but still substantial and statistically significant after accounting for potential confounders, particularly disease duration. Defining the relationship between metabolic control and diabetic vascular complications has been difficult because of unreliable indices of control. Although HbA_{1c} is a major improvement over other single blood or urine measures, a single HbA_{1c} only reflects the preceding 8–12 wk. It can be a measure of distant glucose control only insofar as long-term stability of glucose control prevails in type II diabtes. Our data suggest a strong tracking effect of HbA_{1c} measures and supports this notion. Random variation from such tracking should reduce the observed relationship between HbA_{1c} and retinopathy.[23] Nonetheless, a sizable significant effect was seen.

Our study was a cross-sectional observational survey. There are various pitfalls in using such data to suggest causation. We need to assume that the relationship of exposures and prevalence (here HbA_{1c} and retinopathy) is a fair estimate of the relationship of exposures and incidence. For this assumption to be valid, exposure cannot simply prolong the duration of disease either by preventing its cure or by enhancing the survival of diseased individuals. Neither of these possibilities seems likely for HbA_{1c} or retinopathy. An additional concern is that high HbA_{1c} might lead to preferential recruitment of patients with retinopathy. Our recruitment pattern, based simply on the diagnosis of diabetes in older ambulatory patients, would not lend itself to such a bias. A final concern is the obscuring of temporal relationships by a cross-sectional design. Could retinopathy cause poor control rather than vice versa? This too seems unlikely because most cases of retinopathy were asymptomatic, not affecting visual acuity. Perhaps retinopathy was associated with another diabetic complication that causes poor glucose control. In our group of relatively healthy diabetics the major concern might be some association with medications that worsen glucose control. The likely candidates here would be antihypertensives,

and this concern is indirectly addressed by the persistence of the HbA_{1c}-retinopathy relationship after accounting for hypertension. Thus, although there are several potential pitfalls, none seems to clearly apply to our results.

Our study can be compared and contrasted with three other studies that have examined the prevalence of retinopathy in type II diabetes and its association with diabetes control. Two of the studies were prospective and involved a younger population of type II diabetics,[5,7] and the third examined a genetically distinct type II population, i.e., the Pima Indians.[6] The University Group Diabetes Program (UGDP) accumulated much data on the occurrence of complications in type II diabetes, but the data were analyzed largely on the basis of treatment assignment rather than blood glucose outcome.[5] However, note that there was no significant difference in the development of retinopathy between the four treatment groups despite the significantly lower mean fasting blood glucose level achieved by the variable-insulin treatment group. A direct comparison between blood glucose and retinopathy was not performed. Although the randomized design of the UGDP should have balanced any confounding variables, the actual impact of such variables was not examined. A study by Howard-Williams and colleagues[7] examined outcome in diet-treated type II diabetics randomized to either a low-carbohydrate or low-fat diet.[24] Although the 149 of 250 subjects enrolled who had eye examinations were younger than the population examined here and appeared to be adversely affected with regard to retinopathy by the low-carbohydrate, high-fat diet, some of the findings can be compared with our study. The overall prevalence of retinopathy was 37% and appeared to increase as metabolic control worsened. It was difficult to determine the independent or joint effects of various risk factors such as duration, treatment mode, and hypertension on the occurrence of retinopathy from their report. However, glycemia seemed to remain a significant risk factor when some confounders were taken into account. The study of retinopathy in the Pima Indian population of Arizona, which has the highest reported prevalence of diabetes, revealed almost no retinopathy in subjects with a fasting blood glucose <140 or a 2-h post-GTT blood glucose <200 mg/dl.[6] The prevalence of retinopathy tended to increase with higher blood glucose levels. The impact of other possible confounders was not analyzed in this study, and the applicability of the results in this genetically distinct population to other type II diabetics is unknown.

Our study suggests that the major predictors of retinopathy in the aging type II population are duration and HbA_{1c}. Whereas cross-sectional data such as these must be viewed cautiously, the relationship between metabolic control and complications provides more supportive evidence for the glucose hypothesis in humans.

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