



## Incidence of Complications in Insulin-dependent Diabetes Mellitus: A Survival Analysis

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The authors used 4-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study to investigate the wider applicability of recent research findings that demonstrate an association between glycemic control and insulin-dependent diabetes mellitus (IDDM) complications. EDC subjects participated in a clinical examination at baseline (1986–1988) and were followed up every 2 years. Results demonstrated that, during the first 4 years of follow-up, subjects who were in “poor” control (glycosylated hemoglobin (GHb)  $\geq 11\%$ ) at baseline were significantly ( $p < 0.001$ ) more likely to develop microalbuminuria, proliferative retinopathy, and distal symmetrical polyneuropathy (DSP), compared with subjects who were in “fair” control (GHb  $< 11\%$ ). Subjects who were in poor control were somewhat more likely to develop overt nephropathy ( $p = 0.08$ ) and renal failure ( $p = 0.085$ ) during follow-up; however, no associations were observed with either coronary heart disease or lower extremity arterial disease (LEAD). These results confirm the strong association between prior glycemic control and the onset of microalbuminuria, proliferative retinopathy, and DSP observed in the Diabetes Control and Complications Trial study. However, the results of the study suggest weaker associations for the later stages of renal disease, and little relation was seen between glycemic control and LEAD or coronary disease. Other risk factors may be more important for the development of the later complications of IDDM. Further follow-up is necessary in order to rule out type II error. *Am J Epidemiol* 1996;143:431–41.

coronary disease; diabetes mellitus, insulin-dependent; diabetic nephropathies; diabetic neuropathies; diabetic retinopathy; survival analysis

The long-term effects of insulin-dependent diabetes mellitus (IDDM) are known to be wide ranging and often devastating, in both morbid and economic terms (1, 2). Diabetes complications include both microvascular disease (diabetic retinopathy, nephropathy, and distal symmetrical polyneuropathy) and macrovascular disease (lower extremity arterial and coronary heart disease). The risk of developing any of these complications increases with longer duration of the disease. It is particularly important to determine whether or not the development of complications can be delayed or

even prevented. Investigators have focused on blood glucose levels as a possible determinant of complication onset. Although early clinical trials reported inconsistent findings and suffered from small study sizes (3–6), a recent meta-analysis of these studies did suggest, that overall, long-term intensive blood glucose control reduces the risk of diabetic retinopathy and nephropathy (7). Subsequent data further support this conclusion (8, 9).

In 1993, a report from the largest clinical trial to date, the Diabetes Control and Complications Trial (DCCT), demonstrated that a marked reduction in risk of early complications (notably retinopathy, early nephropathy, and clinical neuropathy) could indeed be attained with intensive treatment of IDDM (10). This reduction was not without some cost, however, with increases in weight and in the risk of severe hypoglycemia being the most problematic side effects of treatment.

While the results of the DCCT are of great importance, questions remain in regard to their applicability to the general insulin-dependent diabetic population.

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Abbreviations: AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; DSP, distal symmetrical polyneuropathy; EDC Study, Epidemiology of Diabetes Complications Study; GHb, glycosylated hemoglobin; IDDM, insulin-dependent diabetes mellitus; LEAD, lower extremity arterial disease.

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Even more important, however, is the relation between glycemic control and the development of later diabetes complications (e.g., advanced renal disease and macrovascular disease). To address these twin issues of general applicability and later complications, 4-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, a representative incident-based cohort of childhood onset IDDM, were examined.

## MATERIALS AND METHODS

### Study population

All study participants had onset of IDDM at <17 years of age, and were diagnosed or seen within one year of diagnosis at the Children's Hospital of Pittsburgh, Pennsylvania, between January 1950 and May 1980. All were on insulin therapy at initial discharge. The registry of cases at Children's Hospital of Pittsburgh has been shown to have considerable overlap and similar epidemiologic characteristics to the population-based Allegheny County IDDM population (11). Recruitment for the EDC Study commenced in 1986. To be eligible, study participants had to live within 100 miles (160 km) of Pittsburgh and to have taken part in a prior morbidity survey, as previously described (12). All such subjects were invited to participate, and, on acceptance, were mailed a set of questionnaires for completion prior to attending the research center for a full clinical examination. These questionnaires included a medical history and the Rose questionnaire for angina and claudication. A 24-hour and an overnight urine sample were also collected before the subject came into the research center, and a further 4-hour sample was collected at the clinic. Death certificates were obtained for all study participants who subsequently died.

### Clinical examination

After arrival at the research center in a fasted state, subjects underwent sitting blood pressure measurements according to standardized procedures (13). Fasting blood samples were obtained for measurement of glycosylated hemoglobin (GHb), the methods for which have been described previously (12). The three timed urine samples (24-hour, overnight, and 4-hour) were assayed for albumin and creatinine to calculate the albumin excretion rate (AER), and estimated glomerular filtration rate. After receiving insulin and eating breakfast, subjects underwent a full clinical examination, including a 12-lead electrocardiogram, three-field stereoscopic fundus photography (pupils dilated), and an assessment of the presence of neuropathy (ac-

cording to DCCT clinical criteria), cardiovascular disease, and lower extremity arterial disease (LEAD). Complete details of all these measurements and the prevalence of complications at baseline have been published elsewhere (12). Subjects who did not attend clinical examinations completed a telephone interview with a research nurse and were also asked to complete the questionnaires.

### Definition of complication endpoints

**Proliferative retinopathy.** Stereoscopic fundus photographs were taken of fields 1, 2, and 4 with a Zeiss camera (Carl Zeiss, Germany), and were read by the Fundus Photography Reading Center, University of Wisconsin, Madison, Wisconsin. Readings were classified by the modified Airlie House System (14), with proliferative retinopathy defined as grade 60 or higher in at least one eye. Individuals without photographs were graded according to their medical history data with confirmation by their ophthalmologist if required. Those with panretinal photocoagulation scars and a grade <60 were recorded as having proliferative retinopathy if the medical history indicated that the laser therapy was for proliferative retinopathy.

**Diabetic nephropathy.** Microalbuminuria was defined as an AER between 20 and 200  $\mu\text{g}/\text{min}$  in two or three of the timed urine samples. Overt nephropathy was defined as an AER >200  $\mu\text{g}/\text{min}$  in two or three of the timed urine samples. Subjects who were on dialysis, or who were post-kidney transplant patients, or who had a serum creatinine >5 mg/dl were classified as having renal failure.

**Distal symmetrical polyneuropathy.** Distal symmetrical polyneuropathy (DSP) was determined according to the DCCT protocol (15) and considered present if, in the opinion of the examining physician, at least two of the following three criteria were present and not due to a nondiabetic cause: symptoms consistent with DSP, decreased (i.e., requiring reinforcement) or absent tendon reflexes, and signs of sensory loss.

**Coronary heart disease.** Coronary heart disease was considered present if subjects had a history of myocardial infarction that was confirmed by electrocardiographic changes at the time of examination, or after review of medical records that met standard criteria (16), or a history of angina obtained by the examining physician, or, in the case of follow-up, death due to coronary disease.

**Lower extremity arterial disease (LEAD).** LEAD was defined as an ankle-brachial pressure ratio <0.9 either at rest or after exercise, or a history of amputation for LEAD.

Study participants were invited to attend full clinical examinations approximately every 2 years after their baseline examination. The window for inclusion in each cycle of examinations was 12 months, i.e., subjects could attend clinic within one year of the date on which they were actually due to be examined. For certain endpoints (i.e., diabetic nephropathy, LEAD, and DSP), attendance at the clinic was required to determine the development of the complication. For others (i.e., coronary disease, proliferative retinopathy, and renal failure) information from the clinical examinations and from questionnaire and death certificate data were combined in order to determine their onset. This report is based on the first three cycles of data collection, which, although showing a wide range of actual follow-up time (12–60 months), gives a mean follow-up of 4 years (48.2 months).

### Statistical analysis

Crude incidence rates were calculated as the ratio of observed new cases of each complication to the total number of people at risk of developing that particular complication during the follow-up period. With the use of the life table method (17), the cumulative hazard was plotted for each complication endpoint, for subjects in “fair” and “poor” glycemic control at baseline for up to 60 months of follow-up. “Fair” and “poor” control were defined by the range of GHb for the total sample, “poor” (GHb  $\geq 11$  percent) being the top tertile of the distribution and “fair” being the lower two tertiles (GHb  $< 11$  percent). Although only one measure of GHb, at baseline, was used to indicate level of glycemic control, it has been demonstrated (18) that there is a strong correlation between a single measure of GHb and the mean of all GHb measurements taken during the previous 5 years, with the single measure thus acting as a proxy for longer term control. After stratifying the sample for duration ( $< 25$ , 25–30,  $> 30$  years), observed/expected ratios of new (incidence) cases were calculated for persons who were in poor control and those who were in fair control. The Mantel-Cox statistic (17) was used to test whether there were significant differences in the proportion of new cases in the poor versus fair control groups, after adjusting for duration. The relative risk for the two glycemic control groups (i.e., poor vs. fair control) for developing each complication was calculated using Cox proportional hazards modeling (19), adjusted for duration of diabetes. Life tables were also constructed to compare cumulative hazard rates for each complication endpoint by sex and by age at onset ( $< 10$  years and  $\geq 10$  years).

## RESULTS

Table 1 shows the demographic characteristics of the study population at entry into the study (baseline), by glycemic control (i.e., “fair” GHb  $< 11$  percent and “poor” GHb  $\geq 11$  percent). Age at and duration of diabetes at baseline did not differ according to glycemic control. Overall, age at baseline ranged from 8 to 48 years (mean, 27 years (standard deviation (SD), 8 years)), with duration of diabetes ranging from 8 to 37 years (mean, 19 years (SD, 8 years)). Glycemic control did not differ between the sexes. However, those in fair control were more likely to have a college (or higher) education.

### Diabetic nephropathy

By the third cycle of clinical examinations, 41 subjects developed microalbuminuria, giving a 4-year incidence rate of 14 percent. Over the same time period, 27 subjects developed overt nephropathy and 30 developed renal failure, giving crude incidence rates of 7 percent and 5 percent, respectively. The onset of these three stages of diabetic nephropathy did not differ significantly by either sex or by age at onset of diabetes.

As shown in the first life table or cumulative hazard graph (figure 1), subjects who were in poorer control at baseline (GHb  $\geq 11$  percent) were more likely to develop microalbuminuria during follow-up compared with subjects who were in fair control (GHb  $< 11$  percent) at baseline. The observed to expected ratios were calculated for the three duration groups ( $< 25$ , 25–30,  $> 30$  years) as shown in table 2. The results indicate a greater than expected number of new cases of microalbuminuria for subjects in poor control, with little difference shown across the duration groups. The association between baseline glycemic control and the development of microalbuminuria was statistically significant even when adjusted for duration of diabetes (see table 2). The relative risk for microalbuminuria for the poor versus fair glycemic control group was 3.5 ( $p < 0.001$ ).

As shown in the second life table (figure 2), over the first 40–50 months of follow-up, a similar number of new cases of overt nephropathy developed in the two glycemic control groups. However, after this, those who were in poor control at baseline were somewhat more likely to develop overt nephropathy compared with subjects in fair control. Calculation of the observed to expected ratios demonstrated a greater than expected number of new cases of overt nephropathy in the poor control group (see table 2), especially in subjects with durations of  $\geq 30$  years. The relative risk for fair versus poor control, adjusted for duration of diabetes, was 1.8 ( $p = 0.08$ ).

**TABLE 1. Demographic details of study participants by level of glycemic control (fair (glycosylated hemoglobin (GHb) <11%) vs. poor (GHb ≥11%)), Pittsburgh Epidemiology of Diabetes Complications Study (baseline 1986–1988)**

Baseline characteristic	Glycemic control (GHb)	
	"Fair" (<11%) (n = 438)	"Poor" (≥11%) (n = 220)
Age (years), mean (SD)†	27.9 (7.7)	27.1 (8.3)
Duration (years) of diabetes, mean (SD)	19.6 (7.5)	18.9 (7.5)
Males, no. (%)	221 (50)	109 (50)
Education (≥college), no. (%)	246 (62)	104 (52)*
Income (>\$20,000), no. (%)	209 (60)	86 (52)

\*  $p < 0.05$ .

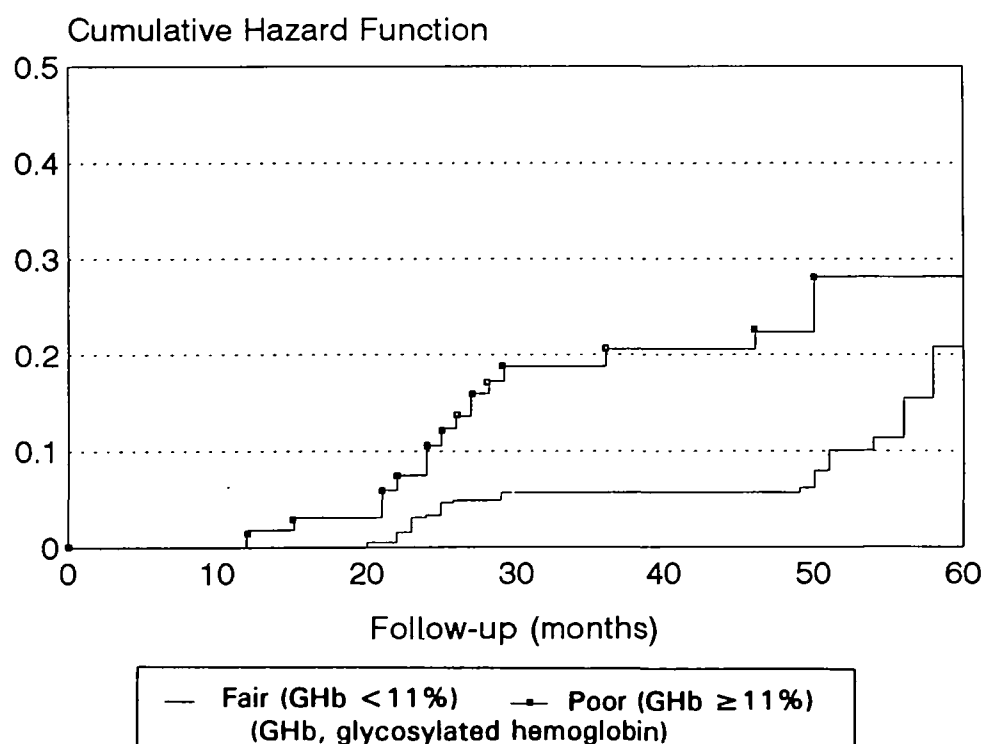
† SD, standard deviation.

As shown in the third life table (figure 3), subjects in poorer control at baseline were also more likely to develop renal failure compared with those who had been in fair control, although this difference was small. As indicated in table 2, the ratio of observed to expected new cases of renal failure for those in poor control was greatest in the shortest duration group (<25 years), with little difference in the longer duration strata. When adjusted for duration, the association between glycemic control and renal failure only approached statistical significance (see table 2). The relative risk for developing renal failure for the poor

versus fair control groups was calculated to be 1.97 ( $p = 0.085$ ).

### Proliferative retinopathy

A total of 69 new cases of proliferative retinopathy were observed during the first two follow-up cycles of the study, giving a 4-year incidence rate of 16 percent. Development of proliferative retinopathy was unrelated to both sex and age at onset of diabetes. The life table in figure 4 shows a clear difference in the development of proliferative retinopathy by glycemic con-



**FIGURE 1.** Life table: microalbuminuria by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.

**TABLE 2. Four-year incidence of insulin-dependent diabetes mellitus (IDDM) complications: observed/expected ratios for those in poor control (glycosylated hemoglobin (GHb)  $\geq 11\%$ ), stratified by duration of IDDM, for each complication, Pittsburgh Epidemiology of Diabetes Complications Study (baseline 1986–1988 with follow-up every 2 years)**

Complication	4-year incidence (%)	Ratio of observed vs. expected cases,* by duration (years)			<i>p</i> value†
		<25	25–30	>30	
Microalbuminuria	14	2.24	2.21	3.33	<0.001
Overt nephropathy	6	1.51	1.45	2.25	0.06
Renal failure	5	4.36	1.83	1.02	0.06
Proliferative retinopathy	16	1.44	2.15	3.31	<0.001
Distal symmetrical/polyneuropathy	13	2.38	1.86	2.14	<0.001
Lower extremity arterial disease	6	0.82	1.48	2.19	0.15
Coronary heart disease	5	1.18	0.46	0.93	0.81

\* Ratios are given for the poor control group. Corresponding data for the fair control group follows a similar but inverse pattern. "Expected" cases were obtained based on the overall study population distribution.

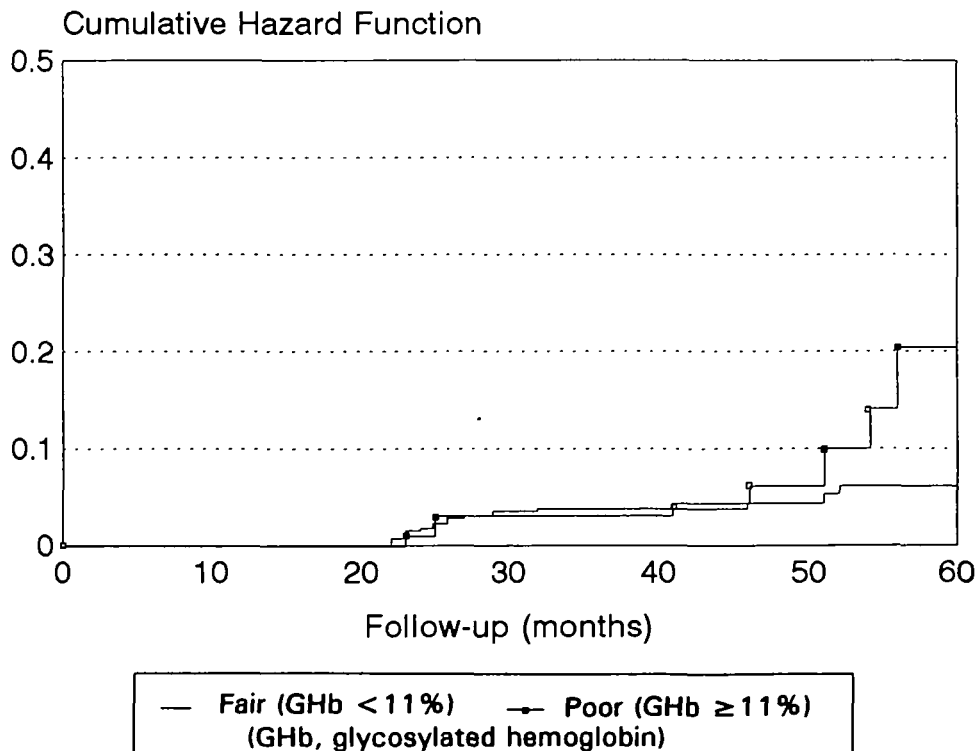
† Mantel-Cox test statistic to test the overall association between each complication and glycemic control (poor (GHb  $\geq 11\%$ ) vs. fair (GHb  $< 11\%$ )), adjusted for duration of diabetes.

trol group, with subjects in poor control at baseline being more likely to develop proliferative retinopathy compared with subjects who had been in fair control at baseline. The difference between those in fair and poor control remained significant when adjusted for duration of diabetes, with the observed to expected ratios for the poor control group increasing with longer durations (table 2). The relative risk for proliferative

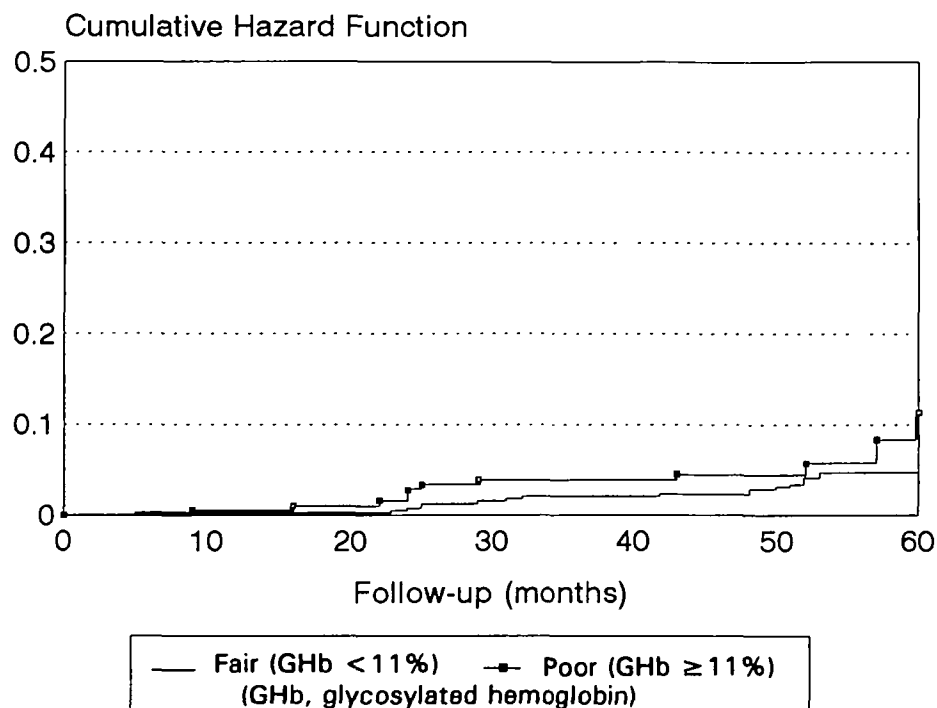
retinopathy for the poor versus fair control group was 3.9 ( $p < 0.001$ ).

#### Distal symmetrical polyneuropathy

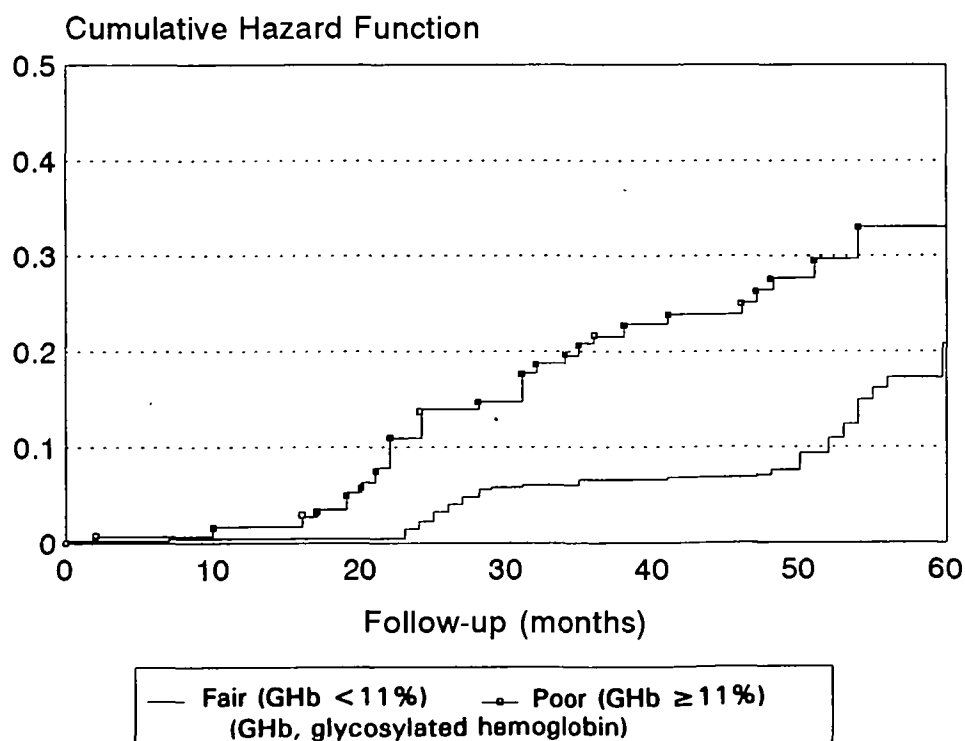
By 4-year follow-up, 58 new cases of distal symmetrical polyneuropathy (DSP) were observed, an incidence rate of 13 percent. The development of DSP



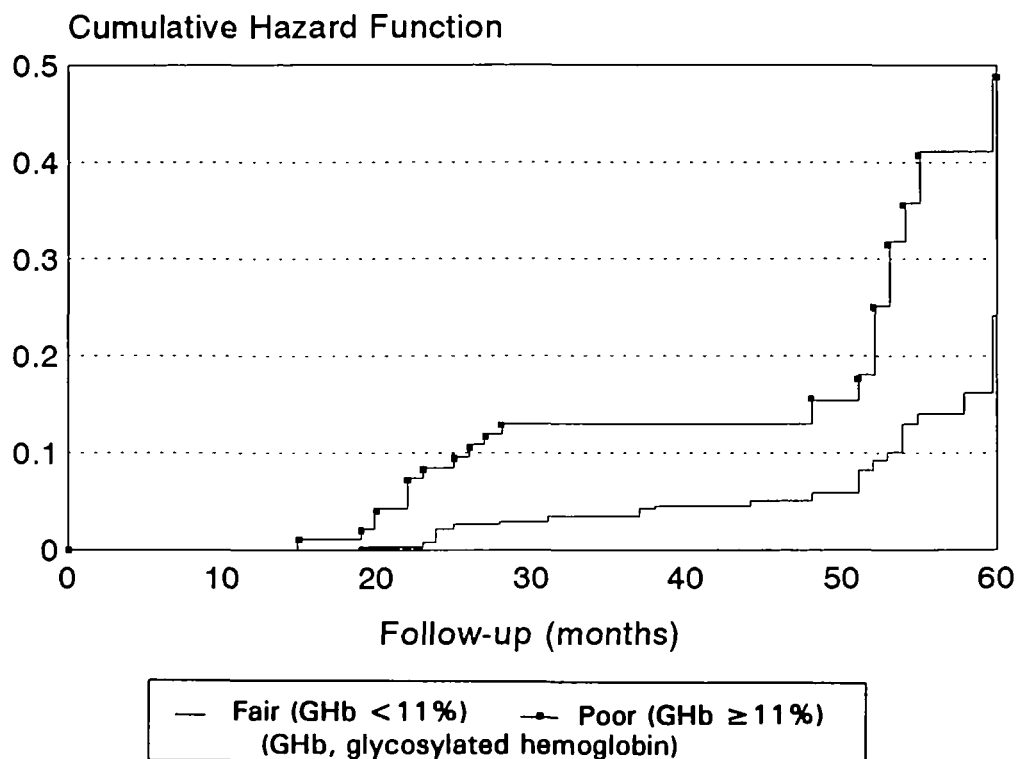
**FIGURE 2.** Life table: overt nephropathy by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.



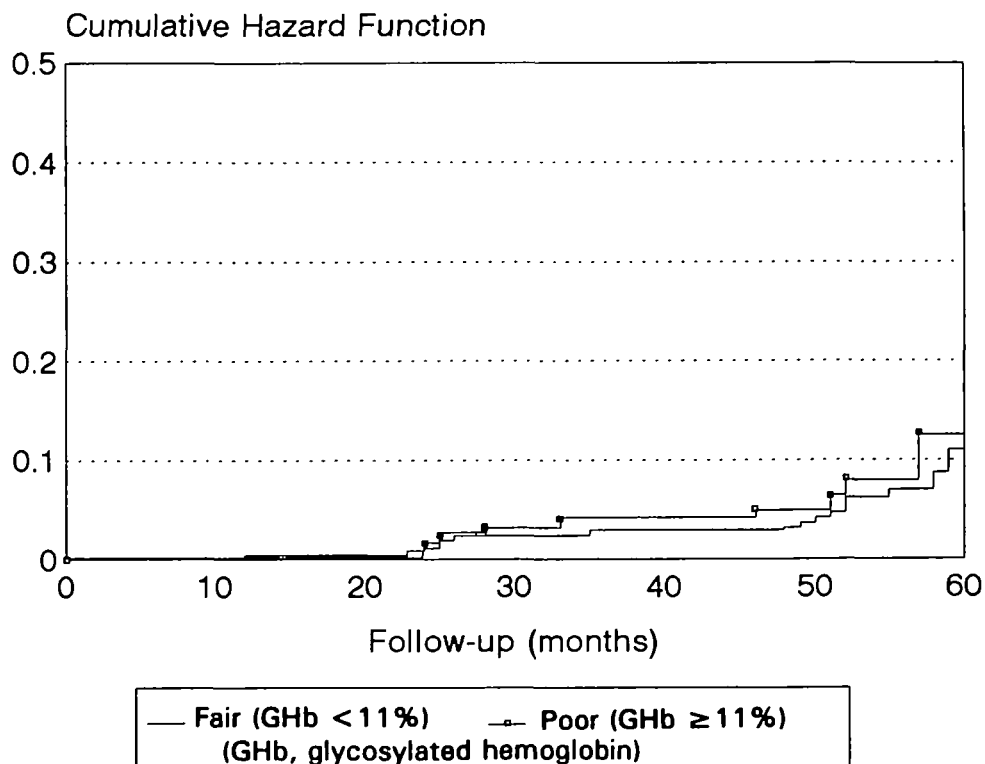
**FIGURE 3.** Life table: renal failure by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.



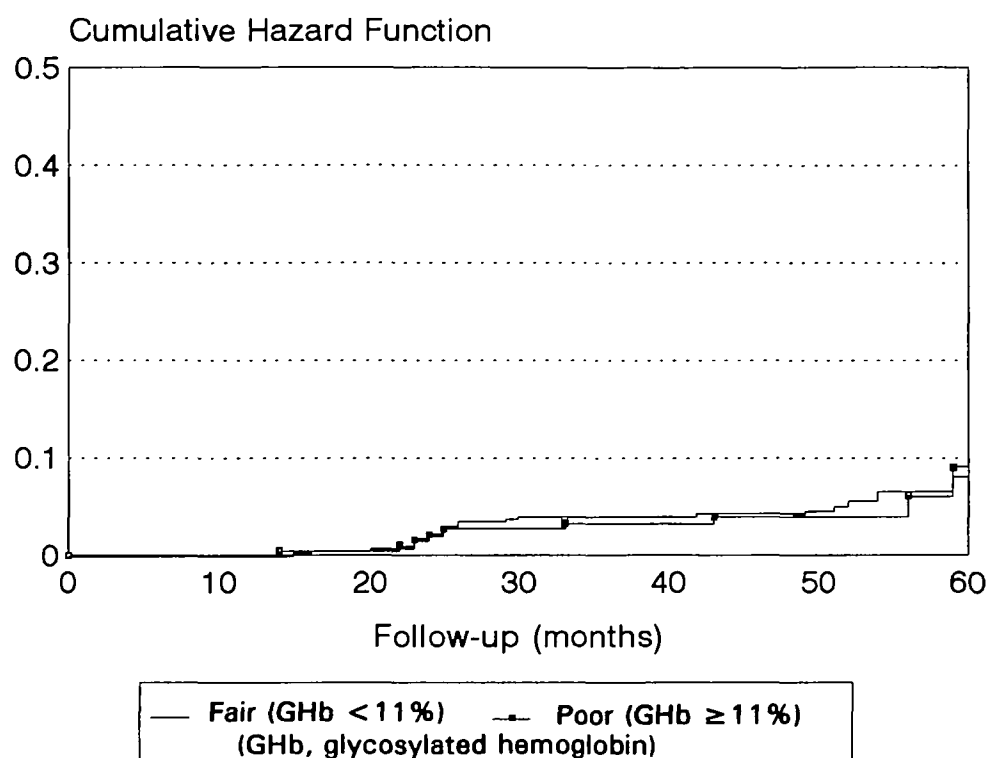
**FIGURE 4.** Life table: proliferative retinopathy by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.



**FIGURE 5.** Life table: distal symmetrical polyneuropathy by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.



**FIGURE 6.** Life table: lower extremity arterial disease by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.



**FIGURE 7.** Life table: coronary heart disease by glycemic control among Pittsburgh Epidemiology of Diabetes Complications Study subjects who participated in a clinical examination at baseline (1986–1988) and who were followed up every 2 years.

was again unrelated to both sex and age at onset of diabetes. As the life table in figure 5 shows, subjects in poor control at baseline were more likely to develop DSP during follow-up compared with those in fair control. The observed to expected ratios indicated a greater than expected number of new cases for those in poor control, the association between glycemic control and DSP remaining significant when adjusted for duration of diabetes ( $p < 0.001$ ). The relative risk for DSP for poor versus fair control was 3.2 ( $p < 0.001$ ).

#### Lower extremity arterial disease

A total of 31 new cases of lower extremity arterial disease (LEAD) were detected during the follow-up period, a 4-year incidence rate of 6 percent. Both sex and age at onset of diabetes were unrelated to the development of this complication. There was some difference seen in the onset of LEAD according to glycemic control group, as shown in the life table in figure 6. Table 2 shows that the observed to expected ratios for those in poor control indicated a higher than expected number of new cases in the longer duration groups. The association between GHb and LEAD did not remain statistically significant when adjusted for duration of diabetes. However, when an interaction term for GHb  $\times$  duration was entered into the multi-

variate model, results showed a significant (positive) association with LEAD.

#### Coronary heart disease

The number of new cases of coronary disease during the first 4 years of follow-up reached 34, an incidence rate of 5 percent. The onset of coronary disease was not associated with sex or age at diabetes onset. As shown in the life table in figure 7, there was also little difference according to glycemic control group. When adjusted for duration of diabetes, the observed to expected ratio of new cases of coronary disease was not significant in the poor versus fair control groups (see table 2).

#### DISCUSSION

The EDC Study shows a clear relation between prior glycemic control and the onset of certain diabetes complications, in particular microvascular diseases that develop early on (i.e., proliferative retinopathy, DSP, and microalbuminuria). A much weaker association was observed, however, between GHb and the later stages of diabetic nephropathy, i.e., overt ne-



phropathy and renal failure. Our results thus suggest that the effect of glycemic control is modified by duration of diabetes and becomes less important than duration as a risk factor for developing renal failure at the longer durations. However, a significant interaction term for GHb  $\times$  duration was not observed for renal failure with multivariate analysis, which showed duration of diabetes to be the major factor. When adjusted for duration of diabetes, prior GHb levels were not significantly and independently associated with either coronary disease or LEAD in our study. For LEAD, however, an effect modification was observed such that the interaction term duration  $\times$  GHb entered the multivariate model, demonstrating that as duration increases, so does the effect of GHb. In a previous analysis (20), we demonstrated a borderline effect for GHb on the development of LEAD, once other risk factors are entered into the multivariate model. In contrast, for coronary disease, the interaction term does not enter the multivariate model, and neither does GHb alone.

Until recently, most investigations of the association between glycemic control and complications have suffered from small study populations or have been retrospective in design (7, 21–23). In more recent years, there have been several prospective studies that have sought to assess the role of glycemic control in the development and progression of complications (9, 10, 24, 25). Particularly notable has been the Diabetes Control and Complications Trial (DCCT) study (10), which, with the use of a definitive experimental design, has found a strong association between GHb and microvascular complications. Overall, the EDC Study reports similar incidence rates of the major complications of IDDM, although comparisons with the DCCT data may be problematic because of some differences in both the study population and definitions of complication endpoints. Comparisons are more appropriate with the DCCT secondary (conventional therapy) cohort, who on entry to the study were required to have had IDDM for 1–15 years, to have very mild-to-moderate non-proliferative retinopathy, and to have an AER of less than 200 mg/24 hours. Microalbuminuria was defined as an AER of 40–299 mg/24 hours (28–207  $\mu$ g/min), and albuminuria as  $\geq$ 300 mg/24 hours ( $\geq$ 208  $\mu$ g/min) based on a single collection. In contrast, in the EDC Study, AER endpoints are based on the use of multiple urine collections, which may provide a better characterization of renal status than a single sample. The EDC Study 4-year incidence rates of microalbuminuria (14 percent), overt nephropathy (6 percent), and DSP (13 percent) compare closely to the DCCT approximate 4-year cumulative incidence rates of 13 percent for microalbuminuria, 4 percent for

overt nephropathy, and 16 percent for DSP. The event rate/100 patient-years of 3.9 for proliferative retinopathy in the EDC Study is also comparable to the combined rate for severe non-proliferative retinopathy and proliferative retinopathy in the DCCT study (2.4/100 patient-years). Both studies used stereo fundus photographs that were read at the same center (Fundus Photography Reading Center, University of Wisconsin, Madison, Wisconsin).

Although the EDC Study population has a similar mean age to the DCCT secondary cohort, duration of diabetes is longer in the EDC Study population (19 vs. 8 years), which might logically suggest a greatly increased risk of complications for EDC subjects. However, the similar age but longer duration of IDDM in the EDC Study also infers a greater number of prepubertal years of diabetes in EDC participants, years which may not increase risk for the development of complications (26), so comparable rates might be expected. In summary, although there are minor study differences in the definition of complications, we have shown the EDC Study to have broadly comparable rates of microalbuminuria, overt nephropathy, DSP, and proliferative retinopathy.

There is little evidence to date, in either direction, linking prior GHb levels to the onset of either coronary disease or LEAD. In the DCCT study, when all major cardiovascular and peripheral vascular events were combined, a non-significant link between intensive therapy (i.e., improved glycemic control) and this endpoint was observed (10). However, even after 5 years, the number of events was extremely small, due to the young age of the study population. We report here a weak association between LEAD and prior glycemic control, and no relation between glycemic control and coronary disease. Although it is possible that this finding may be due to type II error, we have shown a strong association between glycemic control and microalbuminuria, for which there are only seven more cases compared with coronary disease. There may be a stronger link between GHb and other risk factors for cardiovascular disease, for example, serum triglycerides and cholesterol levels (10, 27, 28). These findings require further investigation. A recent study of 476 IDDM patients has shown that while glycemic control was not predictive of subsequent cardiovascular disease, GHb levels were associated with increased urinary albumin concentrations (found to be a strong prognostic marker for cardiovascular disease) during follow-up (29). Our results indicate a stronger role for glycemic control in LEAD as duration increases. It is possible that we will be able to more effectively explore this question in the future because further follow-up (up to 10 years) is planned. Interestingly, the

technical problem associated with measuring LEAD, e.g., possible interference by medial-wall calcification leading to spuriously high ABI values, does not seem to have arisen in this population. As calcification also increases with duration, this problem would have masked any association, particularly in those who have had IDDM the longest. Clearly, this is not the case.

In conclusion, the EDC Study has demonstrated a strong association between prior glycemic control and the onset of proliferative retinopathy, DSP, and microalbuminuria, consistent with the results of the DCCT study. Broadly comparable rates were seen compared with the secondary cohort of the DCCT study, suggesting considerable generalizability of the DCCT results. In addition, the participants of these two studies had similar levels of glycemic control at entry, indicating further generalizability of the DCCT results. As the EDC Study has previously been shown to have considerable overlap and similar epidemiologic characteristics to a population-based IDDM population (11), this further enhances the generalizability of both EDC and DCCT findings. However, our study shows only a weak association between GHb and the later stages of diabetic nephropathy (i.e., overt nephropathy and renal failure) and LEAD, and no significant relation between prior glycemic control and coronary disease. The latter findings suggest that other risk factors may be important for the later progression to advanced renal disease and macrovascular disease. These risk factors should be the subject of future analyses, and further follow-up should yield sufficient numbers of advanced renal disease and macrovascular events to address the issue of whether the lack of GHb association is due to type II error.

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## REFERENCES

1. Lloyd CE, Orchard TJ. Insulin dependent diabetes mellitus in young people: the epidemiology of physical and psychosocial complications. In: Marshall SM, Home PD, Alberti KGMM, et al, eds. *The diabetes annual*. Amsterdam: Elsevier Scientific Publications, 1993;7:211-44.
2. American Diabetes Association. *Direct and indirect costs of diabetes in the United States in 1992*. Alexandria, VA: American Diabetes Association, 1993.
3. Feldt-Rasmussen B, Mathiesen ER, Hegedus L, et al. Kidney function during 12 months of strict metabolic control in

- insulin-dependent diabetic patients with incipient nephropathy. *N Engl J Med* 1986;314:665-70.
4. Lauritzen T, Frost-Larsen K, Larsen HW, et al. Two-year subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 1985;34(suppl 3):74-9.
5. Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, et al. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps and conventional insulin therapy. *Arch Ophthalmol* 1988;106:1242-6.
6. Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. *N Engl J Med* 1984;311:365-72.
7. Wang PH, Law J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. *Lancet* 1993;341:1306-9.
8. Brinchmann-Hansen O, Dahl-Jorgensen K, Sandvik L, et al. Blood glucose concentrations and progression of diabetic retinopathy: the 7 year results of the Oslo study. *Br Med J* 1992;304:19-22.
9. Reichard P, Nilsson BY, Rosenquist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304-9.
10. The Diabetes Control and Complications Trial 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* 1993;329:977-86.
11. Wagener DK, Sacks JM, LaPorte RE, et al. The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. *Diabetes* 1982;31:136-44.
12. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;39:1116-24.
13. Borhani NO, Kass EH, Langford HG, et al. The Hypertension Detection and Follow-up Program. *Prev Med* 1976;5:207-15.
14. Early Treatment of Diabetic Retinopathy Study Coordinating Center. *Manual of operations*. Baltimore, MD: University of Maryland School of Medicine, 1980, chapter 5:18.
15. DCCT Research Group. *Manual of operations for the Diabetes Control and Complications Trial*. Washington DC: US Department of Commerce, 1987.
16. Orchard TJ, CCSP Investigators. Validation of coronary heart disease mortality data: the Community Cardiovascular Surveillance Project Pilot Experience. *Am Heart Assoc Cardiovasc Dis Epidemiol Newslett* 1985;157:46.
17. Dixon WJ, ed. *BMDP statistical software manual*. Vol 2. Berkeley, CA: California University Press, 1992:795-823.
18. Kingsley LA, Dorman JS, Doft BH, et al. An epidemiologic approach to the study of retinopathy: the Pittsburgh Diabetic Morbidity and Retinopathy Studies. *Diabetes Res Clin Pract* 1988; 4:99-109.
19. Kahn HA, Sempos CT. *Statistical methods in epidemiology*. New York: Oxford University Press, 1989:193-8.
20. Lloyd CE, Kuller L. Predictors of macrovascular complications in insulin-dependent diabetes mellitus (IDDM). (Abstract). *Diabetes* 1994;43(suppl 1):99A.
21. Gilbert RE, Tsalamandris C, Bach LA, et al. Long-term glycemic control and rate of progression of early diabetic kidney disease. *Kidney Int* 1993;44:855-9.
22. McCance DR, Atkinson AB, Hadden DR, et al. Long-term glycemic control and neurological function in IDDM patients. *Diabetes Care* 1993;16:1291-3.
23. Dahl-Jorgensen K, Bjoro T, Kierulf P, et al. Long-term glycemic control and kidney function in insulin-dependent diabetes mellitus. *Kidney Int* 1992;41:920-3.
24. Kullberg CE, Arnqvist HJ. Elevated long-term glycated haemoglobin precedes proliferative retinopathy and nephropathy in Type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1993;36:961-5.
25. Goldstein DE, Blinder KJ, Ide CH, et al. Glycemic control and

- development of retinopathy in youth-onset insulin-dependent diabetes mellitus. Results of a 12-year longitudinal study. *Ophthalmology* 1993;100:1125-32.
26. Kostraba JN, Dorman JS, Orchard TJ, et al. Contribution of diabetes duration before puberty to development of microvascular complications in Type 1 diabetes subjects. *Diabetes Care* 1989;12:686-93.
27. Cruickshanks KJ, Orchard TJ, Becker DJ. The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. *Diabetes Care* 1985;8:118-24.
28. D'Antonio JA, Ellis D, Doft BH, et al. Diabetes complications and glycemic control. The Pittsburgh Prospective Insulin-Dependent Diabetes Cohort Study status report after 5 yr of Type 1 diabetes. *Diabetes Care* 1989;12:694-700.
29. Torffvit O, Agardh CD. The predictive value of albuminuria for cardiovascular and renal disease. A 5-year follow-up study of 476 patients with type 1 diabetes mellitus. *J Diabetes Complications* 1993;7:49-56.