Glycemic Control and the Risk of Multiple Microvascular Diabetic Complications
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Background and Objectives: Tight glycemic control in type 2 diabetes reduces risk of certain end-organ complications. However, among patients with one complication already, it is unknown whether tight glycemic control reduces the risk of subsequent complications in another organ. We sought to determine if glycemic control is associated with the risk of a second, distinct, end-organ diabetic complication.

Methods: Subjects were a retrospective cohort of 250 patients with type 2 diabetes, at least one microvascular diabetic complication, and at least one hemoglobin A1c (HbA1c) measurement after that complication. Proportional hazard models estimated the relative hazard of developing another diabetic complication in a second organ system, as predicted by either (1) mean HbA1c level over the study period or (2) first HbA1c after the initial complication. Results: Thirty-eight patients had a second complication; the average follow-up duration was 3.7 years. The mean HbA1c model showed an adjusted relative hazard of 1.25 (95% confidence interval [CI]=1.04, 1.51) per percentage-point elevation in mean HbA1c. The first HbA1c model showed an adjusted relative hazard of 1.23 (95% CI=1.08, 1.40) per percentage-point elevation in first HbA1c. Conclusions: Among these type 2 diabetes patients with an initial complication, tight glycemic control was associated with reduced risk of additional complications in other organs.

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Type 2 diabetes mellitus is a common disease that often leads to debilitating and costly complications. From the population-based National Health and Nutrition Examination Survey, it is estimated that there are about 14 million persons with type 2 diabetes in the United States; prevalence increases significantly with age, and incidence among younger adults has risen sharply over the last decade. Microvascular complications from type 2 diabetes are common and include retinopathy, leading to various degrees of visual impairment, including blindness; neuropathy, leading to pain and numbness; chronic and recurrent infected skin ulcers in the extremities, which can lead to amputation; and nephropathy, ultimately leading to renal failure.

While it has not always been clear that aggressive glycemic control can reduce the end-organ complications of diabetes, recent evidence indicates that aggressive glycemic control in type 2 diabetes is associated with a 25% lower incidence of microvascular complication endpoints. However, aggressive glycemic control also increases the risk of treatment complications such as hypoglycemia.

Studies to date have assessed the relationship of glycemic control and the development of any type 2 diabetes complication but have not distinguished between single and multiple complications in the same individual. Among patients who have already developed one end-organ complication, it is not known whether tight glycemic control still matters in reducing the incidence of complications in another, distinct organ system. Given the risks of aggressive glycemic control and the uncertain benefit in patients with a prior complication, we sought to determine whether tight glycemic control in patients with type 2 diabetes is associated with reduced risk of a second, distinct, microvascular complication.

Methods
Design
This was a retrospective cohort study. Subjects for the study were drawn from those in a parent case-control study, undertaken to determine whether screening asymptomatic individuals for the presence of type 2
diabetes was associated with a reduced risk of serious diabetic complications. Cases in the parent study were patients with type 2 diabetes and at least one end-organ complication.

Setting

Study subjects were drawn from the enrollment of a well-established health maintenance organization (HMO) in the Pacific Northwest, with a total enrollment of more than 500,000 patients and a unified system of medical records. This HMO has computerized laboratory, pharmacy, administrative, and enrollment data and a population-based registry of its diabetic patients.

Study Subjects

Subjects were taken from the parent study, in which 303 participants were initially randomly selected from the HMO’s Diabetes Registry, which is a computerized database drawing on enrollment data, diagnostic codes, and laboratory and pharmacy data used to identify the population of diabetics in the health plan. Cases selected for the current study were the 250 subjects from the parent study who (1) had developed at least one of the complications of interest for this study (defined below) and (2) had at least one recorded glycosylated hemoglobin measurement after their initial complication. Subjects had to be continuously enrolled in the HMO for the duration of follow-up.

Definitions

Complications were defined as symptomatic microvascular end-organ manifestations that were attributable to diabetes. No macrovascular endpoints were chosen owing to the lack of evidence linking glycemic control with reduced rates of macrovascular complications. There were four categories of eligible complications.

Neurologic complications were any diabetic peripheral or autonomic neuropathy or Charcot arthropathy. Ophthalmologic complications were diabetic retinopathy, retinal detachment or macular edema that required laser treatment, blindness, or any other visual impairment resulting from diabetes. Renal complications were end-stage renal disease, including dialysis or transplant, or persistent average serum creatinine over 3.5 mg/dl, as measured over the duration of available data. Foot ulcers/amputations were diabetic foot ulcers and non-traumatic lower-extremity amputations. The occurrence of a complication was confirmed through billing data and review of physicians’ notes in the medical record. In all instances, complications were considered attributable to type 2 diabetes only if this attribution was explicit in the medical record.

For the purposes of this study, “symptomatic” was taken to mean a disease manifestation that was almost certainly noticeable to patients. For example, early diabetic retinopathy may not cause any visual impairment. Thus, even if retinopathy in a given patient may have been attributed to diabetes, it was not counted as a complication unless the patient had to undergo laser therapy treatment or had resulting visual impairment. Similarly, microalbuminuria and mild degrees of renal impairment are usually asymptomatic and thus did not count as complications in this study. However, the substantial renal impairment represented by chronic serum creatinine over 3.5 mg/dl typically results in protein wasting and at minimum has an effect on diet and lifestyle. Neuropathy complications were considered inherently symptomatic, as were foot ulcers and amputations.

The rationale for choosing symptomatic endpoints was twofold. First, the true incidence of symptomatic complications for which patients present for medical care is more reliably measured than asymptomatic complications, which if detected at all would be found incidentally or by screening. We preferred the use of symptomatic complications because we could be more certain about the ascertainment of these complications, since patients would presumably seek care for them, and this would be reflected in the medical records we reviewed. Ascertainment of early, asymptomatic complications is less certain in a retrospective, observational study such as ours. Second, because these complications are noticeable to patients, these are outcomes that matter to patients because of effects on quality of life or functioning.

Data Collection

Each HMO member had a single outpatient chart that contained all ambulatory care encounters as well as discharge summaries from hospitalizations. The principal investigator and three trained research assistants performed chart reviews. Prior to including a subject in the study, chart review verified that the subject had type 2 diabetes and at least one of the indicated complications attributable to type 2 diabetes. Using the series of International Classification of Diseases, Ninth Edition (ICD-9) and Current Procedural Terminology (CPT) codes derived from the complications as defined above, computerized records were searched, and a list of presumptively valid complications was generated for each subject. Based on chart review, the existence and date of each complication was confirmed and recorded. For the purposes of analysis, complications were grouped as described above into four organ system categories. Additional complication diagnoses within the same category (eg, foot ulcer and below-the-knee amputation or peripheral neuropathy and autonomic neuropathy) were counted as a single event. Computerized HMO laboratory data were queried, and all glycosylated hemoglobin test dates and results were obtained for each subject after the initial complication.
Computerized enrollment data were also obtained. We used the period of time containing the continuous enrollment period during which the first complication occurred, structured as shown in Figure 1. Subjects were enrolled, and follow-up data were gathered starting with the first diabetic microvascular complication. Subjects were then followed until either they developed a microvascular diabetic complication in a second organ system (in terms of survival analysis methods, this is known as “failure”) or until no further follow-up data were available. This could be due to the subject’s death, disenrollment from the health plan, or because the subject reached the end of our study data, which was June 14, 1999.

In addition, data were gathered on each subject about factors that were potential confounders. These included age at the time of the first complication, gender, and comorbid states, such as hypertension and hyperlipidemia, that might be associated with increased likelihood of developing microvascular complications. We were able to ascertain the presence or absence of hypertension and hyperlipidemia at the time of diabetes diagnosis (as judged by an explicit diagnosis of hypertension or hyperlipidemia in the medical record) but did not have data indicating whether these conditions were controlled or not, nor whether some subjects may have developed these conditions subsequent to the diagnosis of diabetes. Data regarding smoking status were not reliable and thus not recorded.

Statistical Analysis
Analyses were performed with STATA Version 8.0 (Stata Corporation, College Station, Tex). Two different multivariate Cox proportional hazards models were used to estimate the relative hazard of a second end-organ complication. Because there was variation in the duration of follow-up time for our cohort, survival analysis methods were chosen to permit us to maximize the use of all available data; Cox regression modeling in particular was used since this allows for adjustment for multiple covariates in the context of survival analysis.

The predictor variable for the first model was mean glycosylated hemoglobin (HbA1c) level over each person’s study period (ie, beginning after the initial complication and continuing until the end of available surveillance data). This measure was used to summarize the glucose control over each person’s period at risk for a second complication. However, its precision varied depending on how many HbA1c tests a person received during this period.

For the second model, the predictor variable was first HbA1c after the initial complication. Both models adjusted for age, gender, type of initial complication, and the presence of hypertension and hyperlipidemia as comorbid states. The proportional hazards assumption was evaluated and accepted based on a test for zero slope of Schoenfeld regression residuals, which tests whether the log hazard ratio function is constant over time. Subjects were considered to have a second complication if they developed a diabetes-related complication in a category other than the category of the original complication, for example neurologic and then renal, but not, for example, if they developed two different neurologic complications.

While an HbA1c of less than 7% is considered the ultimate goal for diabetic therapy, the American Diabetes Association (ADA) recommends physician and patient consider making therapeutic changes when a patient’s HbA1c rises to greater than 8%. Thus we chose an HbA1c greater than 8% as the basis for dichotomizing patients for the purpose of incidence rate analyses. However, in the Cox regression models, mean HbA1c and first HbA1c were used as continuous variables.

Results
There were 250 subjects in this study. Almost half were female, and the average age was 71 (Table 1). More than 15% of the subjects had a second diabetic complication over the mean follow-up time of 3.7 years; this rate of complications is comparable to estimates from a recent population-based study in the United Kingdom. Thirty-three percent of subjects did not have follow-up through the end of data collection: 12% died before the end of the study period, and 21% disenrolled from the HMO. Data on cause of death were not available.

The mean HbA1c of the study group was 8.1%, 1.1 percentage points above the ADA goal of 7%. The mean number of HbA1c tests performed per subject over the study period was 7.9. Based on our mean follow-up time, this represents a testing frequency of roughly every 6 months. On average, patients had diabetes for 7.6
years, as determined by time from date of diagnosis until end of available follow-up data.

Table 2 shows the distribution of complication types among those with one versus more than one complication. Neurologic problems were the most common first complication, and for those patients who already had a complication in another organ system, neurologic problems were also the most common second type of complication. Symptomatic renal complications, as defined by our study, were relatively rare as either a first or a second complication.

### Table 1

**Study Subject Characteristics**

<table>
<thead>
<tr>
<th>Eligible subjects</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up days, [range]</td>
<td>1,350 (746) [17—5,126]</td>
</tr>
<tr>
<td>Mean age, [range]</td>
<td>71.3 (10.3) [38.8—94.3]</td>
</tr>
<tr>
<td>Gender—female</td>
<td>49%</td>
</tr>
<tr>
<td>Second complication (%)</td>
<td>38 (15.2)</td>
</tr>
<tr>
<td>Mean HbA1c% (SD)</td>
<td>8.1 (1.95)</td>
</tr>
<tr>
<td>Mean number of HbA1c tests (SD)</td>
<td>7.9 (5.3)</td>
</tr>
<tr>
<td>Mean duration of diabetes in years, [range]</td>
<td>7.6 (4.0) [0.2—22.4]</td>
</tr>
</tbody>
</table>

HbA1c—hemoglobin Alc
SD—standard deviation

The cumulative incidence of a second complication in the group with mean HbA1c < 8 was 11.9%; in the group with mean HbA1c ≥ 8 it was 21.1%. Table 3 shows the rate of developing multiple complications per 100 person years as a function of key exposure variables. In this unadjusted analysis, the effect of tight glycemic control in both the mean HbA1c model and the first HbA1c model was similar and consistent with multivariate analyses. There was little difference in second complication rates between men and women. Rates of second complications did differ by age, with older patients having lower rates than younger. None of these differences, however, were statistically significant.

Table 4 presents results from different adjusted and unadjusted Cox proportional hazards models. Proportional hazards regression with the mean HbA1c model showed an unadjusted or “crude” relative hazard ratio of 1.28 per each 1-point increase in mean HbA1c value. After adjusting for age, gender, type of initial complication, hypertension, and hyperlipidemia, and duration of diabetes, the relative hazard ratio increased to 1.49 (95% CI=1.21, 1.82). Of note, before adding duration of diabetes to the model, the otherwise fully adjusted hazard ratio was similar to the crude estimate at 1.25. Proportional hazards regression using the first HbA1c model showed a crude relative hazard of 1.16 and a relative hazard of 1.25 (95% CI=1.10, 1.43) after adjusting for the same covariates as the mean A1c model. In contrast to the mean A1c model, the introduction of duration of diabetes to the first A1c model did not have a substantial effect on results; the hazard ratio before adjusting for diabetes duration was 1.23 (95% CI=1.08, 1.40).

### Discussion

The burden of diabetic complications is significant. In the United States, diabetes is the leading cause of end-stage renal disease, polyneuropathy, non-traumatic amputations, and in adults age 20—74 it is the most common cause of new blindness. In one study, nearly 10% of subjects with type 2 diabetes had experienced a microvascular complication by 9 years after diabetes diagnosis. Nearly half the cost of treating type 2 diabetes complications has been attributed to microvascular complications. Direct medical costs for all diabetes care in the United States in 2002 were estimated to be $92 billion, of which costs for chronic complications comprised 25%. The United Kingdom Prospective Diabetes Study (UKPDS) was the first clear evidence linking tight glycemic control with the risk of microvascular complications in type 2 diabetes. Of note, the UKPDS and other randomized studies have not shown that tight diabetic control was associated with reduced incidence of macrovascular endpoints such as cerebrovascular, coro-
Patients with type 2 diabetes are typically older than those studied in the UKPDS (in which mean age was 53, compared to 64 in the United States overall,8 and 71 in our study) and thus more likely to have multiple medical issues that demand attention and make aggressive glycemic control particularly challenging. Moreover, tight glycemic control is not without attendant risks and costs.15-17 These include the increased risk of hypoglycemic events and their associated sequelae and costs, plus the additional cost of increased intensity of medical intervention (professional services, pharmaceuticals, equipment) to achieve tight control.

To our knowledge, this is the first study to have examined the relationship between glycemic control and the risk of subsequent complications in a cohort of type 2 diabetics with an initial microvascular complication. We found an association between glycemic control (measured either as mean HbA1c or first HbA1c after an initial complication) and the risk of a second complication in this cohort with an initial symptomatic end-organ diabetic complication. This association persisted after controlling for age and gender, as well as for hypertension and hyperlipidemia, none of which were important confounders.

These results support the idea that the course of type 2 diabetes may be modifiable even after the first complication. Thus, not only can tight glycemic control reduce the risk of progression to severe endpoints in patients with early or mild complications, as shown in the UKPDS trial,5,6,8 but it appears to be associated with reduced risk of symptomatic complications in a second organ system. The hazard ratio of 1.49 found in the mean HbA1c model implies that each 1-percentage point increase in mean HbA1c, eg, going from 8 to 9, is associated with a 49% increase in the relative risk of developing a second complication. In this model, there was a strong effect of adjusting for diabetes duration, increasing the hazard ratio from 1.26 to 1.49, likely representing significant confounding from duration of exposure to diabetes. In the first HbA1c model analysis, we found a 25% increased risk of a second complication associated with each 1-percentage point increase in HbA1c. There was minimal effect of adjusting for diabetes duration in this model, possibly because the predictor variable in this model represents only a single measurement event (the first HbA1c after the initial complication) and thus is less sensitive to the effects of time. Overall, these findings are consistent with the 25% risk reduction seen for microvascular endpoints in the UKPDS study.5

**Table 3**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th># With Second Complication</th>
<th>Person Years</th>
<th>Rate Per 100 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤65 (n=73)</td>
<td>15</td>
<td>197.7</td>
<td>7.6</td>
</tr>
<tr>
<td>66–79 (n=124)</td>
<td>19</td>
<td>361.8</td>
<td>5.3</td>
</tr>
<tr>
<td>≥80 (n=53)</td>
<td>4</td>
<td>137.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Gender Male (n=128)</td>
<td>21</td>
<td>359.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Female (n=122)</td>
<td>17</td>
<td>337.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Mean HbA1c &lt;8 (n=160)</td>
<td>19</td>
<td>413.9</td>
<td>4.6</td>
</tr>
<tr>
<td>≥8 (n=90)</td>
<td>19</td>
<td>283.3</td>
<td>6.7</td>
</tr>
<tr>
<td>First HbA1c &lt;8 (n=146)</td>
<td>18</td>
<td>378.3</td>
<td>4.8</td>
</tr>
<tr>
<td>≥8 (n=104)</td>
<td>20</td>
<td>318.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

HbA1c—hemoglobin A1c

**Table 4**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c—crude</td>
<td>1.28</td>
<td>1.06–1.54</td>
</tr>
<tr>
<td>Mean HbA1c—adjusted*</td>
<td>1.49</td>
<td>1.21–1.82</td>
</tr>
<tr>
<td>First HbA1c—crude</td>
<td>1.16</td>
<td>1.02–1.32</td>
</tr>
<tr>
<td>First HbA1c—adjusted*</td>
<td>1.25</td>
<td>1.10–1.43</td>
</tr>
</tbody>
</table>

* Covariates in adjusted models: age, gender, hyperlipidemia, hypertension, initial complication type, duration of diabetes (from diagnosis to end of study data)

HbA1c—hemoglobin A1c CI—confidence interval

**Limitations**

This study has limitations. First, this is an observational study and thus cannot demonstrate causation between good glycemic control and the risk of second end-organ complications. Further, because of the non-randomized design, there may be residual or unmeasured confounding that could affect our results. However, given UKPDS data demonstrating the general value of tight diabetic control, it is unlikely that a randomized trial of the effect of tight control on second complications would be acceptable on ethical grounds. Third, mean HbA1c may be an imprecise representation of overall glycemic control in those subjects for whom there were few measurements during the study period. While using first HbA1c as the predictor variable allows more uniform comparison across different...
subjects, it does not take into account the range of data available about glycemic control. Further, we could not measure the effect of other potentially important confounders such as smoking status because these data were not reliably available in patient charts. Lastly, this was a study of older type 2 diabetes patients, and our results may not be generalizable to younger patients.

Conclusions

In sum, treating diabetic patients is a delicate balancing act, particularly in patients with end-organ diabetic complications and when diabetes may be only one of several chronic diseases. This study was an attempt to provide evidence on which to base clinical decisions by addressing the question of whether a policy of tight glycemic control should still be advocated in patients who already have a significant diabetes complication. While our analysis indicates that tight control still matters in this population, further studies with longer follow-up are needed to confirm this result, to account for other potential confounders, and to consider the balance between the benefits of fewer complications and the risks associated with tight control.

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[References]