Long-term Glycemic Control and Dementia Risk in Type 1 Diabetes

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OBJECTIVE
Individuals with type 1 diabetes have experienced an increase in life expectancy; yet, it is unknown what level of glycemic control is ideal for maintaining late-life brain health. We investigated the association of long-term glycemic control with dementia in older individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS
We followed 3,433 members of a health care system with type 1 diabetes, ages ≥50 years, from 1996 to 2015. Repeated measurements of hemoglobin A1c (HbA1c), dementia diagnoses, and comorbidities were ascertained from health records. Cox proportional hazards models were fit to evaluate the association of time-varying glycemic exposure with dementia, with adjustment for age, sex, race/ethnicity, baseline health conditions, and frequency of HbA1c measurement.

RESULTS
Over a mean follow-up of 6.3 years, 155 individuals (4.5%) were diagnosed with dementia. Patients with ≥50% of HbA1c measurements at 8–8.9% (64–74 mmol/mol) and ≥9% (>75 mmol/mol) had 65% and 79% higher risk of dementia, respectively, compared with those with <50% of measurements exposed (HbA1c 8–8.9% adjusted hazard ratio [aHR] 1.65 [95% CI 1.06, 2.57] and HbA1c ≥9% aHR 1.79 [95% CI 1.11, 2.90]). By contrast, patients with ≥50% of HbA1c measurements at 6–6.9% (42–52 mmol/mol) and 7–7.9% (53–63 mmol/mol) had a 45% lower risk of dementia (HbA1c 6–6.9% aHR 0.55 [95% CI 0.34, 0.88] and HbA1c 7–7.9% aHR 0.55 [95% CI 0.37, 0.82]).

CONCLUSIONS
Among older patients with type 1 diabetes, those with majority exposure to HbA1c 8–8.9% and ≥9% had increased dementia risk, while those with majority exposure to HbA1c 6–6.9% and 7–7.9% had reduced risk. Currently recommended glycemic targets for older patients with type 1 diabetes are consistent with healthy brain aging.

Type 1 diabetes is associated with a number of micro- and macrovascular complications, among them retinopathy, neuropathy, nephropathy, stroke, and coronary artery disease (1,2). The Diabetes Control and Complications Trial (DCCT), a landmark clinical trial, demonstrated that intensive diabetes therapy, aimed at achieving glycemic control as close to the nondiabetes range as safely possible, decreases the risk for developing these complications (3–6). Studies have also found glycemic control to be an important predictor of cognition among people with type 1 and type 2 diabetes (7–11) and a predictor of dementia in individuals with type 2 diabetes as well as in people without diabetes (11–13). In recent decades, survival among individuals...
with type 1 diabetes has improved significantly (14). This increase in life expectancy is accompanied by an increased risk of developing aging-related diseases, such as dementia. Indeed, prior work has established type 1 diabetes as a risk factor for dementia (15). However, the relationship between glycemic control and subsequent risk of dementia in those with type 1 diabetes remains unclear.

Hemoglobin A$_{1c}$ (HbA$_{1c}$) is an established measure that integrates glucose control over the prior 2–3 months and is widely used to guide clinical management of type 1 diabetes (16,17). Cumulative glycemic exposure, as measured by multiple HbA$_{1c}$ measures over time, has previously been used to evaluate glycemic trajectories and their association with a number of diabetes complications (18,19). Electronic health records capture HbA$_{1c}$ values collected over time allowing for a more thorough long-term characterization of glycemic exposure than is reflected by a single HbA$_{1c}$ measure. In this study, we leverage data collected over a span of 19 years to examine the association of cumulative glycemic exposure, as measured by repeated HbA$_{1c}$ values, with incident dementia among older adults with type 1 diabetes. We also examine the potential for a threshold of glycemic exposure above or below which risk of dementia increases.

RESEARCH DESIGN AND METHODS

Study Population

Kaiser Permanente Northern California (KPNC) is a large, integrated health care delivery system that provides comprehensive medical care to >4 million members representing ~30% of the surrounding geographic region. KPNC members are representative of the general population with respect to race/ethnicity and socioeconomic status except at the extreme tails of income distribution (20,21). KPNC maintains a Diabetes Registry that identifies all members with diabetes using a combination of pharmacy and laboratory information, hospitalization records, and outpatient diagnoses. Within the Diabetes Registry, we restricted the sample to individuals aged 50 years or older during the study period (1 January 1996 to 30 September 2015) and identified individuals with type 1 diabetes using the following three criteria, all of which had to be met: 1) at least two type 1 diabetes ICD-9 diagnoses without a type 2 diabetes code or $\geq$75% of the individual’s diabetes-related diagnostic codes indicating type 1 diabetes, 2) at least one insulin prescription indicative of type 1 diabetes filled during the study period, and 3) no filled prescriptions for any hypoglycemic agents other than insulin (22). We further excluded individuals with prevalent dementia at baseline ($n = 42$) and individuals with no HbA$_{1c}$ measurements during the study period ($n = 309$). Cohort entry was the first date between 1 January 1996 and 30 September 2015 that the patient was $\geq$50 years old and had type 1 diabetes based on the criteria described above. Once a person entered the cohort they were followed until one of the following occurred: diagnosis of dementia, KPNC membership lapse of $\geq$90 days, death, or the end of the study (30 September 2015).

Outcome

Dementia diagnoses were identified based on electronic medical records of inpatient and outpatient encounters from 1 January 1996 to 30 September 2015 based on the following ICD-9 codes: Alzheimer disease (331.0), non-specific dementia (290.0x, 290.1x, 290.2x, 290.3x, 294.1x, 294.2x, and 294.8), and vascular dementia (290.4x). A similar algorithm for the diagnosis of dementia has been used in previous studies on this population (23,24).

Exposure

Clinical measurements of HbA$_{1c}$ measurements were obtained from the KPNC laboratory database from the time of cohort entry to the end of follow-up. For each patient, we extracted every HbA$_{1c}$ laboratory value that was measured during the time the patient was in follow-up. Beginning with their first available HbA$_{1c}$ measure, each patient was categorized based on the percent of their HbA$_{1c}$ measurements that fell into the following categories: HbA$_{1c}$ $<6$% (42–52 mmol/mol), 6–6.9% (53–63 mmol/mol), 7–7.9% (64–74 mmol/mol), and $\geq$8% (75 mmol/mol). Each time a new value was captured, we recalculated their cumulative glycemic exposure. We operationalized the exposure two ways: 1) percent of HbA$_{1c}$ measurements (<10% [referent group], 10 to $<25$, 25 to $<75$, or $\geq75$) that fell within the above-mentioned HbA$_{1c}$ categories and 2) as a binary indicator of whether $\geq$50% of an individual’s HbA$_{1c}$ measures fell within the aforementioned HbA$_{1c}$ categories.

Covariates

Demographic characteristics such as age, sex, race, and ethnicity were obtained through KPNC membership databases and were recorded at cohort entry. We collected diagnoses of the following health conditions at baseline: peripheral artery disease, nephropathy, retinopathy, neuropathy, stroke, myocardial infarction, and severe hypoglycemic and hyperglycemic events resulting in emergency room visit or hospitalization (ICD-9 codes used to define these covariates are available in Supplementary Table 1). We also calculated the frequency of HbA$_{1c}$ measurement for each patient; this was operationalized as a time-varying covariate that was updated each time a new HbA$_{1c}$ measurement was captured for a given individual to reflect the total number of HbA$_{1c}$ measurements collected for that individual divided by their total follow-up time.

Statistical Analysis

We examined the distribution of patient demographics and comorbidities at baseline in the overall sample and by dementia status using $\chi^2$ and t tests. We specified Cox proportional hazards models to estimate the association between categories of cumulative exposure to HbA$_{1c}$ and risk of dementia. Because dementia risk is highly correlated with aging, age was used as the time scale (as opposed to time in the study) beginning with age at cohort entry up to age at the end of follow-up.

We used a multistep approach to examine robustness of findings to model specification. Four models were examined: 1) an unadjusted model using dementia as the outcome, HbA$_{1c}$ thresholds as the exposure, and age as the time scale; 2) a model adjusted for sex and race/ethnicity; 3) a model additionally adjusted for baseline health conditions, including peripheral artery disease, nephropathy, neuropathy, stroke, myocardial infarction, and prior severe hypo- and hyperglycemic hospitalization events; and 4) a model additionally adjusted for frequency of HbA$_{1c}$ measurement. Sensitivity analyses were
conducted among the subset of patients who were ≥65 years of age at baseline. We used SAS, version 9.3, for all analyses.

RESULTS

The final analytic cohort consisted of 3,433 individuals (mean age at cohort entry = 56.1 years old; 47.1% female) (Table 1). On average, individuals who developed dementia during follow-up were older at cohort entry (64.4 vs. 55.7 years) and were more likely to have a history of stroke (7.7% compared with 3.5%) at baseline. The mean follow-up time was 6.3 years (median 4.8 years [interquartile range (IQR) 1.7, 9.9]), and the mean number of HbA1c measurements was 13.5 (median 9.0 [IQR 3.0, 20.00]). By the end of follow-up on 30 September 2015, 155 members (4.5%) were diagnosed with dementia, 860 (25.1%) had a lapse of at least 90 days in membership coverage, 519 (15.1%) died without a dementia diagnosis, and 1,899 (55.3%) were still alive without dementia diagnosis. Among the 155 members who developed dementia over follow-up, the mean age at dementia diagnosis was 64.6 years (median 63.6 years [IQR 56.1, 72.3]).

In Cox proportional hazards models, dementia risk was higher in those with increased exposure to HbA1c 8–8.9% (64–74 mmol/mol) and ≥9% (∼75 mmol/mol) and lower in those with HbA1c 6–6.9% (42–52 mmol/mol) and 7–7.9% (53–63 mmol/mol). In fully adjusted models, compared with those with minimal exposure (≤10% of HbA1c measurements) to HbA1c 8–8.9% and ≥9%, those with prolonged exposure (≥75% of measurements) were 2.51 and 2.13 times more likely to develop dementia, respectively (HbA1c 8–8.9% fully adjusted hazard ratio [aHR] 2.51 [95% CI 1.23, 5.11] and HbA1c ≥9% aHR 2.13 [95% CI 1.13, 4.01]) (Table 2). In contrast, prolonged exposure to HbA1c 6–6.9 and 7–7.9% was associated with a 58% lower and 61% lower risk of dementia, respectively (HbA1c 6–6.9% aHR 0.42 [95% CI 0.21, 0.83] and HbA1c 7–7.9% aHR 0.39 [95% CI 0.18, 0.83]).

Results were similar in Cox models examining cumulative glycemic exposure based on whether a majority (>50%) of an individual’s available HbA1c measurements fell into the following categories of HbA1c: ≤6, 6–6.9, 7–7.9, 8–8.9, and ≥9% (Table 3). Majority exposure to HbA1c...
8–8.9 and ≥9% was associated with an increased risk of dementia (HbA1c 8–8.9% aHR 1.65 [95% CI 1.06, 2.57] and HbA1c ≥9% aHR 1.79 [95% CI 1.11, 2.75]), while majority exposure to HbA1c 6–6.9 and 7–7.9% was associated with a reduced risk of dementia (HbA1c 6–6.9% aHR 0.55 [95% CI 0.34, 0.88] and HbA1c 7–7.9% aHR 0.55 [95% CI 0.37, 0.82]). Majority exposure to HbA1c <6% (<42 mmol/mol) was associated with increased dementia risk in age-adjusted models (HR 2.06 [95% CI 1.11, 3.82]), though findings did not remain significant in fully adjusted models (aHR 1.45 [95% CI 0.71, 2.92]). Findings were similar in sensitivity analyses among the subset of members who were ≥65 years of age at baseline (n = 1,082 [32% of the sample]), though the increased risk associated with majority time at HbA1c ≥9% was no longer statistically significant (Supplementary Table 2).

**CONCLUSIONS**

In this large sample of older adults with type 1 diabetes, we found that cumulative exposure to higher levels of HbA1c (8–8.9 and ≥9%) was associated with an increased risk of dementia, while
cumulative exposure to well-controlled HbA1c (6–6.9 and 7–7.9%) was associated with a decreased risk of dementia. In fully adjusted models, compared with those with minimal exposure to HbA1c, 8–8.9% and HbA1c ≥9%, those with prolonged exposure were more than twice as likely to develop dementia over the course of follow-up (Table 2). By contrast, dementia risk was ~60% lower among those with prolonged exposure to well-controlled HbA1c (6–6.9 and 7–7.9%) compared with those with minimal time at well-controlled levels of HbA1c.

To our knowledge, this is the first study to investigate the association between long-term glycemic control and the risk of dementia in older individuals with type 1 diabetes. Our results complement and extend previous studies that have reported an association between chronic hyperglycemia and decreased cognitive function in children and adolescents with type 1 diabetes (25,26), as well as studies reporting an association between poor glycemic control and decreased cognitive functioning in middle-aged adults with type 1 diabetes and older adults with type 2 diabetes (7–11). Our findings are also consistent with previous studies that found an increased dementia risk associated with poorer glycemic control among adults with type 2 diabetes and adults without diabetes (11–13). Whether these findings applied to dementia risk among older adults with type 1 diabetes was previously unknown.

Another interesting finding from our study was the suggestion that cumulative exposure to HbA1c <6% was associated with a nonsignificant increased risk of dementia. However, the number of individuals with majority exposure to HbA1c <6% was very small, and, as such, we are underpowered to further investigate this association in the current study. Therefore, this should be treated as a preliminary and hypothesis-generating finding that should be examined in greater detail in future studies with larger sample sizes and the appropriate power to explore these potential associations.

In our study of 3,433 older adults with type 1 diabetes, 155 (4.5%) individuals developed dementia over an average of 6.3 years of follow-up. Among those who developed dementia, the average age at dementia diagnosis was 64.6 years. A large-scale study using administrative health data from 1998 to 2011 in England reported a similar incidence of dementia among a subset of adults aged ≥50 years with type 1 diabetes (3.99% developed dementia), though the average length of follow-up was not reported for this specific age-group (15). Prior studies have also found type 1 diabetes to be a risk factor for dementia (15) and have reported the average age at onset of dementia to be 2–5 years earlier in those with diabetes compared with those without diabetes (27,28). Taken together, these results provide further evidence that older adults with type 1 diabetes are at increased risk of developing dementia and may have increased risk at younger ages than the general population. Our results, however, suggest that effective glycemic control could be an important tool for reducing risk of dementia among older adults with type 1 diabetes.

Accumulating evidence suggests an increasing trend in the incidence of type 1 diabetes (29–31). Additionally, as a result of treatment advances in recent decades, individuals with type 1 diabetes are living longer, resulting in an increased proportion of the population with type 1 diabetes living into old age (32–34). While extensive research has been done to determine appropriate glycemic targets for vascular complications in type 1 diabetes (3–6), little is known about the role of glycemic control on dementia. Given the aging population of individuals with type 1 diabetes and the importance of cognitive function in type 1 diabetes self-care, understanding the role of glycemic control on dementia risk is of great importance.

Pathophysiological mechanisms by which glycemic control may affect dementia risk are still poorly understood but are hypothesized to result from structural brain abnormalities stemming from chronic exposure to hyperglycemia and/or recurrent severe hypoglycemia. Studies in adults and youth with type 1 diabetes have reported an association between chronic hyperglycemia (defined using lifetime HbA1c history and using retinopathy as an indicator of chronic exposure) and gray matter density loss (35–37). Studies examining the association between severe hypoglycemic events and changes in brain structure have been less consistent, with some reporting increased gray matter density loss and a higher prevalence of cortical atrophy in those with a history of frequent exposure to severe hypoglycemia (36,38), while another study reported no association (37). In the ACCORD MIND (Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes) trial, compared with standard glycemic control, intensive glycemic control was associated with greater total brain volume, suggesting that intensive glycemic control may reduce brain atrophy related to diabetes (39). The goal of this study was to determine whether an association exists between patterns of HbA1c control and risk of dementia in this population of adults with type 1 diabetes; this was previously unknown. Understanding why glycemic patterns are associated with dementia is a much-needed area for future study, particularly with regard to the potential role of intercurrent micro- and macrovascular complications.

The current study has several strengths. To our knowledge, it is the first study to investigate the association between long-term glycemic control and dementia in a large population of older adults with type 1 diabetes. The availability of multiple longitudinal HbA1c measurements (mean 13.5 [SD 12.6]) allows for a more accurate characterization of long-term glycemic control, and the longitudinal design allows for observation of incident dementia. Finally, KPNC maintains high-quality electronic health record data with a low turnover rate and uniform access to quality medical care allowing for inclusion of a range of diabetes-specific comorbidities and observation of incident dementia.

There were several limitations to our study as well. One of the biggest limitations was the reliance on clinical data for our analyses. Because clinical data are collected for reasons other than research, our data may be subject to hidden confounding and bias; for this reason, we suggest that our findings be interpreted as hypothesis generating as opposed to conclusive evidence. Another limitation was the lack of information regarding age of diabetes onset. Age of onset may significantly affect glycemic control in later life as well as risk of dementia. Additionally, we did not have data on cognitive performance measures. As such, in this study, we were unable to assess the association between long-term glycemic control and changes in cognition. We were also unable to investigate the possible reverse effects
of cognitive decline on glycemic control. A clinical diagnosis of dementia is likely preceded by a period of cognitive decline during which one’s ability to properly manage glycemia may be impacted; this is an especially important limitation in this population of older adults with type 1 diabetes where self-care plays such an important role in disease management. The use of medical diagnoses rather than routine cognitive testing to assess dementia status is another possible limitation in this study that may have resulted in underascertainment of the true number of incident cases. Additionally, based on the available data, we were unable to distinguish between different types of dementia as we did not have brain imaging, and we were not able to examine the potential mediating role of vascular and renal complications on the association between dementia and glycemic patterns. This study was performed in a unique cohort of individuals with type 1 diabetes who have survived to older ages, which may induce selective survivorship bias, a bias in which the study population is comprised of healthy survivors who outlived their peers; if present, this bias would likely underestimate the true association of long-term glycemic control on dementia risk. Another important limitation was the sourcing of our cohort from a single large health care system in northern California, which may limit generalizability of our findings. Finally, HbA1c is an integrated measure of glucose levels over time. While HbA1c is the best assessment available to evaluate long-term glycemic trajectories, it does not reflect day-to-day glycemic variability or glycemic excursions.

In conclusion, among older patients with type 1 diabetes, increased exposure to HbA1c ≥ 8–8.9% (64–74 mmol/mol) and ≥9% (>75 mmol/mol) was associated with an increased risk of dementia, while maintaining HbA1c <6–6.9% (42–52 mmol/mol) and 7–7.9% (53–63 mmol/mol) was associated with a significant reduction in dementia risk. Our study complements previous literature by extending the association between HbA1c and dementia to a previously unstudied population in an older cohort with type 1 diabetes. We are also able to suggest HbA1c thresholds and the risk associated with percentage of time spent beyond these thresholds. It is gratifying to see that the current recommendations for glycemic control in older adults with diabetes are largely consistent with the levels needed to protect the brain (40,41). The increasing incidence of type 1 diabetes coupled with advances in treatment of type 1 diabetes has resulted in an unprecedented number of older adults living with and managing type 1 diabetes. Our findings suggest glycemic control as an important and potentially modifiable factor that can be targeted to reduce dementia risk among older adults with type 1 diabetes.

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