Hemoglobin A_{1c} Variability Predicts Symptoms of Depression in Elderly Individuals With Type 2 Diabetes

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OBJECTIVE

This study aimed to analyze the relationship of variability in hemoglobin A_{1c} (HbA_{1c}) over years with subsequent depressive symptoms.

RESEARCH DESIGN AND METHODS

Subjects (*n* = 837) were participants of the Israel Diabetes and Cognitive Decline (IDCD) study, which aimed to examine the relationship of characteristics of long-term type 2 diabetes with cognitive decline. All pertain to a diabetes registry established in 1998, which contains an average of 18 HbA_{1c} measurements per subject. The results presented here are based on the IDCD baseline examination. Symptoms of depression were assessed using the 15-item version of the Geriatric Depression Scale (GDS). To quantify the association between variability in glycemic control (measured as the SD of HbA_{1c} measurements [HbA_{1c}-SD]) since 1998 with the number of depression symptoms at IDCD baseline, incidence rate ratios (IRRs) and corresponding 95% CIs were estimated via negative binomial regression modeling and used to account for the overdispersion in GDS scores.

RESULTS

Subjects' ages averaged 72.74 years (SD 4.63 years), and the mean number of years in the diabetes registry was 8.7 (SD 2.64 years). The mean GDS score was 2.16 (SD 2.26); 10% of subjects had a GDS score ≥6, the cutoff for clinically significant depression. Mean HbA_{1c} significantly correlated with HbA_{1c}-SD (r = 0.6625; P < 0.0001). The SD, but not the mean, of HbA_{1c} measurements was significantly associated with the number of subsequent depressive symptoms. For each additional 1% increase in HbA_{1c}-SD, the number of depressive symptoms increased by a factor of 1.31 (IRR = 1.31 [95% CI 1.03–1.67]; P = 0.03).

CONCLUSIONS

Variability in glycemic control is associated with more depressive symptoms.

Type 2 diabetes and depression both are highly prevalent among the elderly population and are associated with increased risk for morbidity and mortality. Major depression is a severely debilitating disease associated with significant burden and disability (1). Even subsyndromal depression, the most prevalent clinical presentation among the elderly (2), is associated with disability, functional limitations (3), and poorer psychiatric and functional longitudinal outcomes. The risk for depression is doubled in the presence of type 2 diabetes (4), which itself reaches a prevalence of 22–33% in those ≥65

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years old (5). In turn, in the presence of depression, individuals with type 2 diabetes adhere less to medical treatments, have worse glycemic control, and show increased risk for diabetes-related complications (4). Optimal interventions for reducing depression in type 2 diabetes could therefore not only ameliorate depression but also contribute to better results in other type 2 diabetes–related outcomes.

Degree of glycemic control has a central role in preventing some type 2 diabetes–related complications (6) and may therefore be relevant for preventing depression. Compared with younger subjects with type 2 diabetes, however, the elderly are at increased risk for hypoglycemia and other adverse effects of antidiabetes treatments (7,8). Therefore, despite the high susceptibility of older individuals to type 2 diabetes complications (e.g., myocardial infarction, visual impairment, and renal disease [7]) compared with all other age groups, guidelines generally agree that the potential benefits of achieving tight glycemic control in this population should be weighed against the risk of hypoglycemia (7,8) and that antidiabetes treatment should be personalized. Treatment guidelines for depression or its prevention are lacking in the context of diabetes in this older and growing segment of the population (8). Development of such guidelines may be hampered by the apparent inconsistencies regarding the association of glycemic control and risk for depression (9). These inconsistencies may partly be driven by the cross-sectional design applied in many studies, in which depression and hemoglobin A_{1c} (HbA_{1c}), the gold standard measurement of glycemic control, are assessed simultaneously, thereby preventing an understanding of the true nature of the relationship between these factors or its directionality. Compared with a single HbA_{1c} measurement or mean HbA_{1c}, long-term variability in glycemic control, expressed as the SD of all HbA_{1c} measurements (HbA_{1c}-SD), better reflects changes in glycemic control over time and, accordingly, has been shown to be associated with disease complications in type 1 diabetes (10) and in type 2 diabetes (11,12). However, scarce information describes the relationship of HbA_{1c} variability with depression.

In this report we analyze the relationship of long-term variability in HbA_{1c} with subsequent depressive symptoms in elderly subjects with type 2 diabetes participating in the Israel Diabetes and Cognitive Decline (IDCD) study.

RESEARCH DESIGN AND METHODS

The IDCD is a collaboration among the Icahn School of Medicine at Mount Sinai, NY, the Sheba Medical Center, Israel, and Maccabi Health Services (MHS), Israel. The study was approved by all three institutional review board committees.

Sample

This study consists of 1,288 elderly patients (≥65 years old) with type 2 diabetes who are engaged in the IDCD study, a longitudinal investigation assessing the relationship of long-term type 2 diabetes characteristics with cognitive decline and other outcomes of type 2 diabetes. The design and detailed methods have been published elsewhere (13). Briefly, subjects were randomly selected from the approximately 11,000 individuals with type 2 diabetes who are in the diabetes registry of MHS, the second largest health maintenance organization (HMO) in Israel. The MHS diabetes registry is an integral part of the MHS Electronic Patient Record system and was established in 1998 to facilitate disease management and to improve treatment. Criteria for addition to the registry are any of the following: *1*) HbA_{1c} >7.25%; *2*) glucose >200 mg/dL on two exams more than 3 months apart; *3*) purchase of antidiabetes medication twice within 3 months, supported by HbA_{1c} >6.5% or glucose >125 mg/dL within half a year; or 4) diagnosis of type 2 diabetes (ICD-9 code) by a general practitioner, internist, endocrinologist, ophthalmologist, or type 2 diabetes advisor, supported by HbA_{1c} >6.5% or glucose >125 mg/dL within half a year. These criteria have been validated by 20 physicians in MHS against their own practice records (14). In addition, age-specific prevalences were similar to those of a diabetes registry of another large HMO in Israel (14). The MHS diabetes registry collects detailed laboratory, medication, and medical diagnoses information of its subjects since 1998 or since the type 2 diabetes diagnosis (if after 1998) (14). Thus we have access to all data in the diabetes registry since 1998 (or since the type 2 diabetes diagnosis if after 1998) and until initiation of the IDCD study in 2009. This analysis presents relationships between historical data from the MHS and the baseline data of the IDCD. The longitudinal component of the IDCD is ongoing.

Eligibility Criteria for the IDCD Study

Subjects were eligible for the study if they were listed in the MHS diabetes registry; living in the central area of Israel; diagnosed with type 2 diabetes; aged ≥65 years; assessed as cognitively normal at baseline (based on a weekly multidisciplinary consensus conference); not suffering from major medical, psychiatric, or neurological conditions that affect cognitive performance; had three or more HbA_{1c} measurements in the diabetes registry; spoke Hebrew fluently; and had an informant for the study. The latter criterion was implemented to ensure data were obtained regarding the existence of functional impairments secondary to cognitive changes and of changes in behavior.

Subject Recruitment Process

The electronic records for patients in the MHS diabetes registry were thoroughly reviewed to identify potential subjects (Fig. 1). Patients with an ICD-9 code for dementia or its subtypes, those treated with prescribed cholinesterase inhibitors, and those with a major psychiatric or neurological condition (such as schizophrenia or Parkinson disease) that could affect cognitive performance were excluded. Potential subjects were randomly selected, contacted by mail and then by phone, and, after determining that they were fluent in Hebrew and had a family member or caregiver who was willing to be an informant for the study, asked whether they were willing to participate. Those who were willing to participate in the study were assessed in two phases. First they were visited by a study physician who obtained signed informed consent; performed medical, neurological, and geriatric assessments; and drew blood for inflammatory markers (interleukin-6, C-reactive protein), and haptoglobin and apolipoprotein E genotypes. In the second phase (optimally within 2 weeks from the physician's visit), the potential subjects were visited by a neuropsychologist who administered a comprehensive cognitive battery (described in detail elsewhere [15]) and administered questionnaires to the subject and informant to assess cognitive, mood, and functional impairment. All potential subjects' cognitive data were discussed by

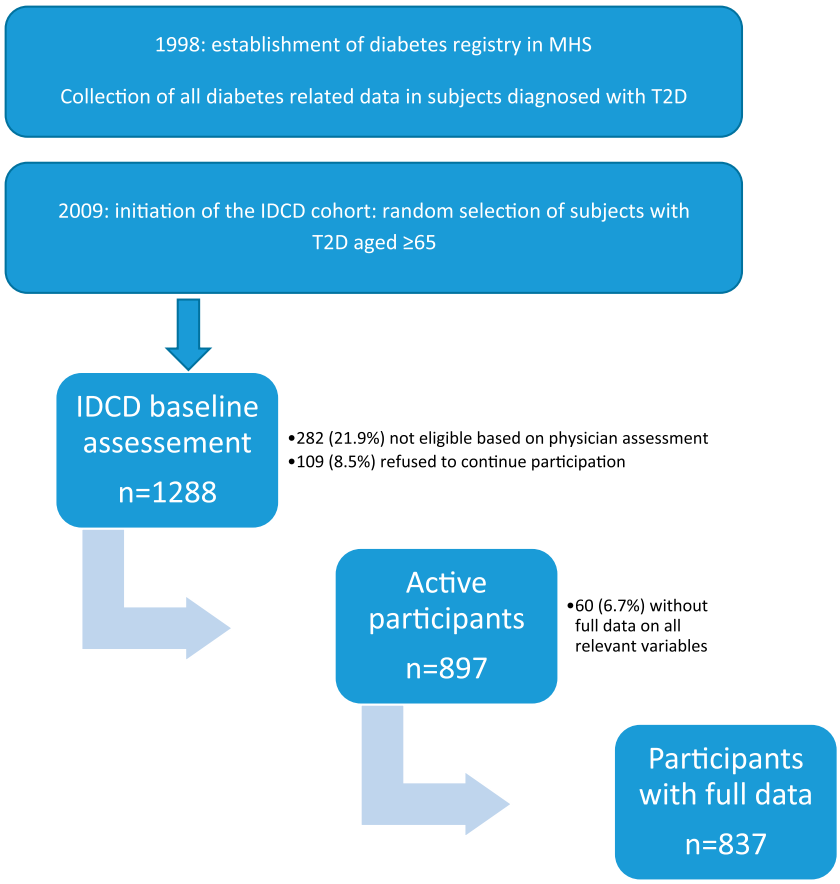

Figure 1—Study flowchart. T2D, type 2 diabetes.

a multidisciplinary team during consensus conferences in order to define the subjects' cognitive status (as cognitively normal, mild cognitive impairment, or dementia and their subtypes). To be eligible, subjects had to be cognitively normal at baseline.

HbA_{1c}

HbA_{1c} values were extracted from the diabetes registry. The data on HbA_{1c} are historical prospective data, that is, starting in 1998 or at the time of type 2 diabetes diagnosis (if after 1998) until the IDCD baseline assessment (2009). HbA_{1c} was measured with standard methods of high-performance liquid chromatography using an ion exchange column. Participants were assessed under fasting conditions approximately annually at the MHS (the mean and median of two assessments per year, with the 25th percentile of one and the 75th percentile of three yearly assessments). Variability of glycemic control is defined in this study as the HbA_{1c}-SD for each subject.

Symptoms of Depression

Symptoms of depression at entry into the IDCD study (2009) were assessed at the time of the cognitive assessment using the 15-item version of the Geriatric Depression Scale (GDS) (16), in which subjects answer a series of 15 questions regarding their recent mood. Higher scores represent more depressive symptoms.

Statistical Analyses

Sample characteristics are summarized as the mean (SD) and median (range) for continuous variables and number (percentage) for categorical variables. To quantify the association between the SD of HbA_{1c} measures taken while in the IDCD registry (starting in 1998 or later, at the time of type 2 diabetes diagnosis, until IDCD baseline in 2009) and GDS scores at time of entry into the IDCD study (2009), incidence rate ratios (IRRs) and corresponding 95% CIs were estimated via negative binomial regression modeling. Negative binomial regression was used to account for the overdispersion of GDS scores. These models were adjusted for sociodemographic, cardiovascular, and diabetes-related covariates (described below). Examination of the relationship of HbA_{1c} variability with depression is new, so to enable comparison with analyses of other cohorts, we applied six distinct models controlling for covariates similar to those used in previous studies that addressed the relationship of HbA_{1c} variability with other diabetes-related complications (10,11). Model A was unadjusted; model B adjusted for age; model C also adjusted for number of years in the registry (17), years of education, and sex; model D additionally adjusted for HDL, LDL, and total cholesterol, systolic and diastolic blood pressures, glomerular filtration rate, and diabetes medication group; and model E also adjusted for mean HbA_{1c}. Finally, in model F, the Mini-Mental State Examination (MMSE) total score was added to the model. Our primary model was model C (adjusting for age, number of years in the registry, years of education, and sex). However, because of the novelty of the associations of HbA_{1c} variability with depression, we believe that including all models will deepen our understanding regarding the association between HbA_{1c} variability and depression and the factors contributing to this relationship, thus stimulating a larger number of comparable replication studies.

All hypotheses testing was two-sided and conducted at the 5% level of significance. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Description of the Sample

A total of 1,288 subjects completed the preliminary screening, expressed interest in participating, were approached by a study physician, and signed informed consent. Of them, 282 (21.1%) were excluded from the study because of incompatibility with eligibility criteria (primarily clinical impairment) and 109 (8.5%) refused to continue their participation in the study, so 897 subjects remained active participants. The analyses include the 837 subjects who had complete data on sociodemographic, cardiovascular, and diabetes-related covariates.

Table 1 describes the sample characteristics of the final 837 subjects included in the analysis. The mean age of the patients in the sample was 72.74 years (SD 4.63 years), and the mean number of years in the diabetes registry was 8.7 (SD 2.64 years). Mean number of HbA_{1c}

measurements per subject was 17.83 (SD 9.56). Mean MMSE score was 28.02 (SD 1.79), consistent with normal cognitive status, and mean GDS score was 2.16 (SD 2.26); 10% of subjects had a GDS score ≥6, the cutoff for clinically significant depression. Most subjects (87%) were treated with antidiabetes medications: oral medications alone, insulin alone, or a combination of both. Other demographic and health-related characteristics are presented in Table 1.

Relationship of Mean HbA_{1c} and HbA_{1c}-SD Since 1998 (or Since Time of Entry into the Diabetes Registry) and Number of Depressive Symptoms at IDCD Baseline (2009)

Mean HbA_{1c} was significantly correlated with HbA_{1c}-SD (r = 0.6625; $P < 0.0001$). Mean HbA_{1c} was not associated with the number of depressive symptoms in any of the statistical models (IRR 0.93 [95% CI 0.81–1.06]; P = 0.26, for the fully adjusted model F). By contrast, greater HbA_{1c}-SD was significantly associated with a larger number of depressive symptoms in all statistical models, such that for each additional 1% increase in HbA_{1c}-SD, the number of depressive symptoms increased by a factor of 1.29, representing a 29% increase (IRR 1.29 [95% CI 1.03–1.55]; P = 0.0078) in the basic model adjusting for age, number of years in the diabetes registry, years of education, and sex (model C; Table 2). In the fully adjusted model (model F), for each additional 1% increase in HbA_{1c}-SD, the number of depressive symptoms increased by a factor of 1.31, representing a 31% increase (IRR 1.31 [95% CI 1.03–1.67]; P = 0.03). Table 2 presents IRRs for the unadjusted and partially adjusted statistical models.

Clinical trials have demonstrated that HbA_{1c} ≤7% is associated with reduced risk for development and progression of type 2 diabetes–related microvascular complications compared with HbA_{1c} >7%, and thus is considered a reasonable treatment goal (18). To facilitate translation of the current results to the clinical setting, we repeated the analyses, stratifying the sample by HbA_{1c} above and below 7%, the HbA_{1c} target for most patients with type 2 diabetes (19). The relationship of HbA_{1c}-SD with depressive symptoms had the same direction in both groups (i.e., higher variability was associated with more depression symptoms) but was stronger in the group with HbA_{1c} >7% in all statistical models (Table 2).

During the first year after type 2 diabetes diagnosis, high variability in HbA_{1c} may reflect treatment initiation and decreased glucose levels in the blood thereafter; therefore, we repeated the analysis excluding HbA_{1c} values from the first year after entry into the diabetes registry. The results remained essentially unchanged in that higher HbA_{1c}-SD was significantly associated with a larger number of depressive symptoms in statistical models 1–4 (Table 3).

The primary goal of the study was to examine whether HbA_{1c} variability predicts depressive symptoms. To rule out the possibility of reverse causality, that is, that depression predicts HbA_{1c} variability (20), we examined the relationship of depression at entry into the diabetes registry with variability in HbA_{1c} thereafter. The GDS, the primary depression questionnaire used by the IDCD study, is not used by MHS. Thus we exploited from the diabetes registry data related to depression within ≤1 year of entry into the diabetes registry (1998 or the time of type 2 diabetes diagnosis if after 1998) to predict variability in HbA_{1c}. We operationalized depression diagnosis based on ICD-9 codes for depression or treatment with antidepressants within ≤1 year of entry into the diabetes registry (data relating to HbA_{1c} values from the first year after entry into the diabetes registry were not included in the analysis). In all models adjusting for demographic, health-related, and cognitive factors, the association between depression at entry into the diabetes registry and subsequent HbA_{1c}-SD was not significant (Table 4).

Table 1—Characteristics of the sample (n = 837) at IDCD baseline

	Mean (SD) or n (%)	Median (min–max)
HbA_{1c}-SD (%)	0.52 (0.38)	0.40 (0.04–3.32)
Mean HbA_{1c} (%)	6.82 (0.77)	6.70 (4.88–10.14)
HbA_{1c} measures (n)	17.83 (9.56)	16 (2–60)
Years in the diabetes registry	8.7 (2.64)	9.89 (0.99–15.07)
Age (years)	72.74 (4.63)	72 (66–88)
Years of education	13.17 (3.45)	12 (0–26)
Mean HDL (mg/dL)	47.82 (10.93)	45.89 (25.04–104.6)
Mean LDL (mg/dL)	101.43 (19.88)	101.02 (24.7–169.41)
Mean cholesterol (mg/dL)	180.57 (25.18)	179.06 (93.93–264.97)
Systolic BP (mmHg)	134.74 (9.38)	134.20 (103.09–170.25)
Diastolic BP (mmHg)	77 (4.85)	77.21 (56.06–96.19)
GFR (mL/min/1.73 m^2)	81 (26.26)	78.54 (13.51–185.11)
GDS	2.16 (2.26)	1 (0–14)
MMSE total score	28.02 (1.79)	28 (13–30)
Female sex	501 (60%)	
Diabetes medications		
Hypoglycemic only	652 (78%)	
Insulin only	8 (1%)	
Insulin + hypoglycemic	71 (8%)	
None	106 (13%)	
GDS score		
0	219 (26%)	
1	200 (24%)	
2	145 (17%)	
3	82 (10%)	
4	72 (8%)	
5	42 (5%)	
6	31 (4%)	
7	15 (2%)	
8	14 (2%)	
≥9	17 (2%)	

BP, blood pressure; GFR, glomerular filtration rate.

CONCLUSIONS

The results of this study demonstrate that variability in HbA_{1c} over time (mean 8.7 years) is associated with the subsequent number of depressive symptoms in elderly subjects with type 2 diabetes. This

Table 2—Association between variability in HbA_{1c} and GDS

HbA_{1c}-SD	IRR (95% CI)	*P* value
Overall (*n* = 837)		
Model A	1.20 (1.001–1.44)	0.0485*
Model B	1.22 (1.02–1.47)	0.0285*
Model C	1.29 (1.07–1.55)	0.0078*
Model D	1.24 (1.02–1.51)	0.0318*
Model E	1.33 (1.04–1.70)	0.0230*
Model F	1.31 (1.03–1.67)	0.0273*
Sample stratified by mean $HbA_{1c} \leq 7$ (*n* = 555)		
Model A	1.17 (0.82–1.67)	0.3939
Model B	1.18 (0.82–1.68)	0.3728
Model C	1.31 (0.90–1.89)	0.1550
Model D	1.26 (0.86–1.83)	0.2341
Model E	1.30 (0.87–1.93)	0.1979
Model F	1.30 (0.88–1.92)	0.1943
Sample stratified by mean $HbA_{1c} > 7$ (*n* = 282)		
Model A	1.22 (0.93–1.61)	0.1516
Model B	1.30 (0.98–1.71)	0.0650
Model C	1.41 (1.07–1.86)	0.0139*
Model D	1.40 (1.06–1.86)	0.0185*
Model E	1.41 (1.02–1.94)	0.0351*
Model F	1.41 (1.03–1.93)	0.0331*

IRR (95% CI) data were estimated using a negative binomial regression modeling score for the entire sample (*n* = 837) and stratified by mean HbA_{1c}. Model A was unadjusted; model B was adjusted for age; model C was adjusted for age, years in the registry, years of education, and sex; model D was adjusted for age, years in the registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, glomerular filtration rate (GFR), HDL, LDL, and diabetes medication group; model E was adjusted for age, years in the registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, GFR, diabetes medication group, HDL, LDL, and mean HbA_{1c}; and model F was adjusted for age, years in the registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, GFR, diabetes medication group, mean HbA_{1c}, HDL, LDL, and MMSE total score. *Indicates statistical significance.

relationship is particularly relevant for subjects with poor glycemic control (mean $HbA_{1c} > 7\%$). We cannot rule out that the opportunity for detecting significance in this group was greater, because higher mean levels were associated with greater SD and the group with mean $HbA_{1c} > 7\%$ was substantially larger. Results were not affected by adjustment for sociodemographic, type 2 diabetes, and health-related characteristics that may be associated with depression, nor by adjustment for a global cognitive score. Larger variability in HbA_{1c} was associated with higher mean HbA_{1c}; nevertheless, we found no correlation between mean HbA_{1c} and the number of depression symptoms. To exclude the potential contribution of variability in HbA_{1c} close to type 2 diabetes diagnosis—when adequate glycemic control is being instantiated—to the overall HbA_{1c} variability over years, we repeated the analyses, excluding HbA_{1c} measurements from the first year after the type 2 diabetes diagnosis. Results remained mostly unchanged. Though long-term effects of initially uncontrolled diabetes on brain biology and mood cannot be ruled out, our results suggest that long-term variability in glycemic control, rather than initial variability after type 2 diabetes diagnosis, is associated with symptoms of depression. These results stress the potential value of HbA_{1c} variability, which may better reflect the course of type 2diabetes over time, in predicting depression.

Table 3—Association of variability in HbA_{1c} and GDS score, excluding HbA_{1c} values from the first year after entry into the diabetes registry

	Mean HbA_{1c}-SD			
Model	1	2	IRR (95% CI)	*P* value
0	2.29	2.61	1.14 (0.96–1.35)	0.1293
1	2.15	2.61	1.21 (1.02–1.45)	0.0321
2	2.09	2.48	1.18 (0.99–1.42)	0.0633
3	3.26	3.91	1.20 (1.01–1.43)	0.0422
4	3.26	3.89	1.19 (0.98–1.45)	0.0811

Model 0 was unadjusted; model 1 was adjusted for age, years in registry, years of education, and sex; model 2 was adjusted for age, years in registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, and MMSE score; model 3 was adjusted for age, years in registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, MMSE score, and depression status at baseline; and model 4 was adjusted for age, years in registry, years of education, sex, total cholesterol, systolic blood pressure, diastolic blood pressure, MMSE score, depression status at baseline, and mean HbA_{1c}.

The directionality of the association of type 2 diabetes with depression is not clear, and some view it as bidirectional (21); most studies suggest that prediabetes states and HbA_{1c} predict depression at follow-up, including in subjects who were not depressed at baseline (22). However, in subjects already suffering from type 2 diabetes, lack of positive affect has also been associated with future higher levels of HbA_{1c} (23). Within type 2 diabetes, the relationship of glycemic control (a core contributor to other type 2 diabetes–related complications [6]) with depression, and the directionality of this relationship, remains to be elucidated. In this study we considered reverse causality, that is, that depression at the time of entry into the diabetes registry (1998 or at time of type 2 diabetes diagnosis if later than 1998) may be associated with subsequent variability in HbA_{1c} thereafter, but such a relationship was not detected. Although, in the context of an HMO, defining depression based on an ICD-9 code or on prescription of antidepressant medications may underestimate its true prevalence, our results provide evidence for a possible causal path from poor glycemic control to a higher risk for depression, rather than the opposite.

Previous studies have shown that poor glycemic control at baseline was associated with increased risk for the presence (9,24) and persistence of depressive symptoms (25) at follow-up in old community-dwelling subjects. One cross-sectional study demonstrated a positive association between poor glycemic control and anxiety, but not depression scores, in a sample including both patients with type 1 and patients with type 2 diabetes, with a wide age range (20–75

Table 4—Association of depression* at entry into the diabetes registry with variability in HbA_{1c} thereafter**

Model†	No baseline depression	Baseline depression	Ratio of geometric means (95% CI)	*P* value
0	0.41	0.28	1.50 (1.28–1.76)	<0.0001
1	0.40	0.35	1.14 (0.98–1.32)	0.0947
2	0.40	0.35	1.13 (0.97–1.31)	0.1038
3	0.39	0.38	1.05 (0.91–1.20)	0.5111

*Defined as a depression diagnosis or antidepressant medication prescription within 1 year of entry into the diabetes registry. **HbA_{1c}-SD measurements following 1 year of entry to registry until IDCD baseline assessment (2009). †Model 0 was unadjusted; model 1 was adjusted for age, years in the diabetes registry, years of education, and sex; model 2 was adjusted for age, years in the diabetes registry, years of education, sex, cholesterol, systolic blood pressure, diastolic blood pressure, and MMSE score; and model 3 was adjusted for age, years in the diabetes registry, years of education, sex, cholesterol, systolic blood pressure, diastolic blood pressure, MMSE score, and mean HbA_{1c}.

years) (26). In summary, previous studies generally demonstrated that worse glycemic control is associated with a higher risk for incident depression; however, there is still no consensus regarding the nature of the emotional outcome and the characteristics of the population at risk. Differences in methodologies used to measure glycemic control and depression, as well as differences in study design (cross-sectional vs. longitudinal), may explain, at least partially, the inconsistent findings regarding the relationship of glycemic control with depression.

Mean HbA_{1c} is recognized as a predictor of some diabetes-related complications (11); however, HbA_{1c} variability, independent of mean HbA_{1c} levels, has been shown to be positively associated with micro- and macrovascular complications and mortality in diabetes (27), and to outweigh the predictive value of the mean for cardiovascular disease (11,28,29) and retinopathy (11,12,30). The relationship of HbA_{1c} variability and brain-related outcomes has been demonstrated in elderly patients with type 2 diabetes, in whom higher HbA_{1c} variability was significantly associated with poorer cognitive function, even after adjusting for mean HbA_{1c} values (31).

Late-life depression is strongly associated with cognitive status and may result from common underlying mechanisms (32). Nevertheless, in this study, the relationship of HbA_{1c} variability with depression was unaltered after adjusting for cognitive performance, reflecting the robustness of the relationship.

Several mechanisms may explain the relationship of glycemic control with depression. Periods of sustained hyperglycemia have detrimental long-term effects and therefore, even if HbA_{1c} levels are lower thereafter (a process that would affect HbA_{1c} variability), episodes of uncontrolled type 2 diabetes, expressed as increased variability in HbA_{1c}, carry a high risk for long-term complications (33). The risk for microvascular complications of type 2 diabetes increases exponentially rather than linearly with increasing HbA_{1c} (34,35). Vascular pathology, in turn, has been proposed as an underlying mechanism for vascular depression, which is highly prevalent in late-life diabetes (36). In addition, high glucose levels, which require more aggressive treatment regimens, specifically insulin injections, may also be more strongly associated with adverse psychological states and with increased type 2 diabetes disease burden and distress (37). In this study, however, adjustment for type of antidiabetes treatment did not affect the results. The population participating in our study comprised elderly subjects. Older brains, specifically areas involved in depression, may be most vulnerable to the effects of worse glycemic control, as demonstrated in a study examining the association of fasting serum glucose with cerebral glucose metabolism, a measure of neural circuity (assessed with fluorodeoxyglucose positron emission tomography), whereby increasing fasting plasma glucose levels were associated with lower cerebral glucose metabolism in frontal and parietal association cortices in normal elderly and even more so in elderly subjects with late-life depression, but not in young controls (38).

The elderly are also at higher risk for the detrimental effects of hypoglycemic episodes on the brain, as demonstrated by the increased risk for cognitive decline and dementia in the elderly with type 2 diabetes who experience episodes of severe hypoglycemia (39). The mechanism underlying this relationship is unclear; some reports suggest neuronal death and changes in brain structure (40). Such effects could also lead to depression. In this regard, in contrast to mean HbA_{1c}, variability of glycemic control better reflects the presence of larger HbA_{1c} fluctuations over time from hyper- and hypoglycemia.

Strengths of this study include the large sample; validated type 2 diabetes diagnoses for each subject; an average of 18 HbA_{1c} measurements; strong validity for risk factor levels and medical diagnosis; and a thorough cognitive evaluation, permitting the verification of intact cognition at the time of GDS assessment and examining overall cognition as a potential confounder.

This study is observational, and at this point only cross-sectional cognitive data are available, preventing conclusions regarding the causality and directionality of the association between variability in glycemic control and symptoms of depression. Depression diagnosis at entry into the diabetes registry was not associated with subsequent variability in HbA_{1c}. However, we cannot rule out the possibility that subsyndromal symptoms of depression that were not captured by ICD-9 codes for depression or by the use of antidepressant treatments lead to more erratic self-management of type 2 diabetes via poor lifestyle characteristics and worse adherence to medications, factors that we could not control for in this study. Brain imaging was not available, thus limiting our ability to evaluate the contribution of brain volume and vasculature to the association of variability in HbA_{1c} with depression score. We used time since entry into the diabetes registry, rather than time of type 2 diabetes diagnosis, as a measure of diabetes duration. For those who entered the diabetes registry at the time of its establishment, in 1998, we have no access to data regarding duration of diabetes prior to 1998. In addition, the definition of depression outcome in the study is based on the GDS score rather than clinical diagnosis. A relatively small number of subjects were treated with insulin (9%), possibly limiting our ability to examine the role of this treatment in the relationship of HbA_{1c} variability and symptoms of depression. Finally, we do not have information on episodes of severe hypoglycemia, which may substantially contribute to variability in HbA_{1c} and may be associated with depression (41), thereby potentially affecting the relationship found in this study.

In conclusion, these results indicate that higher variability in glycemic control is associated with more depressive symptoms, suggesting that long-term stability of glycemic control may help prevent depressive symptoms in elderly individuals with type 2 diabetes.

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