

Higher dementia incidence in older adults with type 2 diabetes and large reduction in HbA1c

Key words: glycemic changes; type 2 diabetes; dementia; older adults

Key points:

- A large drop in HbA1c might be an important factor in the development of dementia in older adults with type 2 diabetes.
- Optimizing or intensifying glycemic control in this population requires caution.
- Older adults with a significant decrease in HbA1c might warrant further clinical risk assessment for cognitive impairment.

Word count: 2,500

ABSTRACT

Background: Although type 2 diabetes increases risk of dementia by two fold, whether optimizing glycemic level in late life can reduce risk of dementia remains uncertain. We examined if achieving the glycemic goal recommended by the American Diabetes Association (ADA) within a year was associated with lower risk of dementia in 6 years.

Methods: In this population-based observational study, we examined 2,246 community-living dementia-free Chinese older adults with type 2 diabetes who attended the Elderly Health Centres in Hong Kong at baseline and followed their HbA1c level and cognitive status for 6 years. In line with the ADA recommendation, we defined the glycemic goal as HbA1c<7.5%. The study outcome was incident dementia in 6 years, diagnosed according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or Clinical Dementia Rating of 1-3.

Results: Those with HbA1c \geq 7.5% at baseline and HbA1c<7.5% in one year were associated with higher rather than lower incidence of dementia, independent of severe hypoglycemia, glycemic variability, and other health factors. Sensitivity analyses showed that a relative reduction of \geq 10%, but not 5-10%, in HbA1c within a year was associated with higher incidence of dementia in those with high (\geq 8%) and moderate (6.5-7.9%) HbA1c at baseline.

Conclusion:

A large reduction in HbA1c could be a potential predictor and possibly a risk factor for dementia in older adults with type 2 diabetes. Our findings suggest that optimizing or intensifying glycemic control in this population requires caution.

INTRODUCTION

Dementia is a global health problem. Dementia prevention is particularly important to people with type 2 diabetes because their number is growing [1], and they are twice as likely to develop dementia as those without [2]. One possible mechanism underlying higher dementia risk in diabetes is hyperglycemia [2-4]. While higher HbA1c is associated with higher dementia risk [5-8], it is unclear whether improving glycemic control could reduce the risk. With evidence suggesting that intensive glycemic lowering might paradoxically elevate risks of morbidities and mortality [9-11], studies that examine optimizing glycemic level and the associated risk of dementia are much needed.

In this study, we followed the glycemic level and cognitive status of community-living dementia-free older adults with type 2 diabetes, and examined the association of glycemic changes in one year with risk of dementia in 6 years. We hypothesized that maintaining HbA1c above the glycemic target recommended by the American Diabetes Association (ADA) was associated with higher dementia risk, whereas achieving the target within a year was associated with lower risk. Our findings might support and extend the previous literature that hyperglycemia is important to the development of dementia, and optimizing glycemic level, even in late life, can help prevent dementia.

METHODS

Study design, setting, and participants

This longitudinal observational study was based on all individuals aged 65 and older who completed baseline assessment at the Elderly Health Centres (EHCs) of the Department of Health of the Government of Hong Kong in the first 6 months of 2005 (N=18,298).

Inclusion criteria for this study were Chinese ethnicity, living in the community, and having known type 2 diabetes. Exclusion criteria were living in nursing homes; diagnosis of type 2 diabetes not confirmed by physicians; having stroke, Parkinson's disease, or clinical dementia; or scoring below the education-specific cutoff on the Cantonese version of the Mini-Mental State Examination (C-MMSE) at baseline [12]. Participants were followed up at the EHCs for 6 years to the outcome of incident dementia. Those who missed the follow-up assessments were traced and interviewed by geriatric psychiatrists at home, and the names of those not traceable were verified with the Deaths Registry.

Assessment of glycemic control

At baseline and follow-up, HbA1c was measured in whole blood sample with the High Performance Liquid Chromatography at the Public Health Laboratory Centre of the Department of Health. All HbA1c measurements were in the Diabetes Control and Complications Trial (DCCT) units (%). Following the ADA recommendation, optimal glycemic control was defined as HbA1c<7.5% [13].

As glycemic variability is a potential risk factor for dementia independent of hyperglycemia [14], the intra-individual mean (HbA1c-MEAN), standard deviation (HbA1c-SD), and coefficient of variation (HbA1c-CV) of HbA1c were calculated for each participant. HbA1c-CV, defined as the ratio of HbA1c-SD to HbA1c-MEAN, serves as a better marker

for glycemic variability because it corrects for the larger SDs due to higher absolute values of HbA1c-MEAN [15].

With the possible link between severe hypoglycemia and dementia [16,17], we also reviewed the number of hospital admissions, including attendance to the emergency department, and duration of stay for each participant.

Identification of dementia cases

At baseline and follow-up, participants underwent comprehensive cognitive assessments by the EHC physicians, including a detailed history, the Abbreviated Mental Test, and the C-MMSE. Those interviewed by geriatric psychiatrists received the C-MMSE, clinical examination, and Clinical Dementia Rating (CDR). A clinical diagnosis of dementia was made according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or CDR of 1-3 [18].

Assessment of other variables

Demographics (age, sex, educational level, and socioeconomic status), physical and psychiatric comorbidities (hypertension, hypercholesterolemia, obesity, heart diseases, visual and hearing impairments, poor mobility, poor balance, and depression), physical health parameters (blood pressure, fasting total cholesterol level, and body mass index [BMI]), and lifestyle behaviors (physical and intellectual activities, and smoking) were examined during the assessment. All diseases were verified by physicians according to ICD-10. Obesity was defined as BMI ≥ 25 kg/m² according to the Asian references [19]. Visual and hearing impairments, poor mobility and balance, physical and intellectual activities, and smoking were defined as previously reported [20-22]. Low socioeconomic status was defined as receiving social security from the government.

Statistical analysis

Sample size estimation is available in Supplementary data, Appendix 1, in *Age and Ageing* online [23].

Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp). Continuous and categorical variables were compared between participants with and without incident dementia by the independent t-test and the Chi-squared (χ^2) test, respectively. The level of statistical significance was set at $P < 0.05$ (2-tailed). The proportion of participants with $\text{HbA1c} \geq 7.5\%$ over the first year was compared between those with and without incident dementia. Sensitivity analyses were performed to test if higher dementia incidence was observed in those with less stringent glycemic control ($\text{HbA1c} \geq 8.5\%$) and in those with larger glycemic variability over the first year. To test if optimizing glycemic level was associated with lower dementia incidence, the proportion of participants with $\text{HbA1c} \geq 7.5\%$ at baseline but $< 7.5\%$ by the end of Year 1 was compared between those with and without incident dementia. Multivariable logistic regression analysis was performed to test if the observed association remained robust after adjusting for glycemic variability, severe hypoglycemic episodes, cardiovascular risk factors, physical health parameters, physical impairments, depression, sociodemographic factors, and lifestyle behaviors. The ORs were computed to yield point estimates with 95% confidence intervals (95% CIs). To ascertain that the risk of incident dementia was associated with glycemic changes over the first year rather than changes in the following years, the analyses were repeated by additionally adjusting for the HbA1c-MEAN , HbA1c-SD , and HbA1c-CV from the first year to the year of assessment when the participant was found to have dementia, or to the year of last assessment if the participant remained free of dementia.

Given the possible U-shaped association between glycemic level and dementia risk [24], sensitivity analyses were conducted to examine the association of HbA1c changes with dementia incidence while considering the baseline HbA1c level. Stratification of HbA1c changes was based on 1) different tertiles of HbA1c level at baseline – HbA1c below the 25th percentile (<6.5%), between the 25th and 75th percentiles (6.5-7.9%), and above the 75th percentile (\geq 8.0%) were regarded as low, moderate, and high level; and 2) the relative changes of HbA1c levels from baseline to Year 1 – <-10%, -10% to +10%, and \geq +10% over the first year were regarded as a decreasing, stable, and increasing trend. The moderate-stable category served as reference for comparison with the others. To test if the association remained robust with milder HbA1c changes, the analyses were repeated with relatively smaller changes in HbA1c (5-10%) over the first year.

RESULTS

Incidence of dementia

A total of 2,246 were included into this study (Figure 1). They had a median follow-up period of 5.0 years. 297 (13.2%) participants were dead, and 242 (10.8%) had incident dementia in 6 years. Those who developed dementia were predominantly female and older, with lower educational attainment, more physical co-morbidities, and less healthy lifestyle practices (Table 1).

Glycemic control over the first year

The mean HbA1c at baseline was not significantly different between participants with and without incident dementia (Table 1). Neither those with $\text{HbA1c} \geq 7.5\%$ nor those with $\text{HbA1c} \geq 8.5\%$ at baseline (Table 1) or over the first year (see Supplementary Table 1 in *Age and Ageing* online) were significantly more prevalent in the incident dementia group. HbA1c variability over the first year was not significantly different between the two groups (see Supplementary Table 2).

Interestingly, the proportion of those with $\text{HbA1c} \geq 7.5\%$ at baseline but $< 7.5\%$ by Year 1 was higher in the incident dementia group than in the cognitively stable group (20 [8.3%] vs 117 [5.8%]; $P=0.14$). The OR for incident dementia was 1.92 (95% CI=1.05-3.52; $P=0.03$) after controlling for HbA1c-CV, severe hypoglycemic episodes, physical, psychosocial, and lifestyle factors. The association remained significant after additional adjustment for HbA1c-MEAN (OR=2.02; 95% CI=1.03-3.98; $P=0.04$), HbA1c-SD (OR=2.10; 95% CI=1.03-4.41; $P<0.05$), and HbA1c-CV (OR=2.10; 95% CI=1.00-4.39; $P<0.05$) over subsequent years.

Different categories of glycemic control

Sensitivity analyses showed that HbA1c changes were associated with dementia incidence after considering the baseline HbA1c level (Table 2). The high-increasing category was more prevalent in the incident dementia group (8 of 65 [12.3%] vs 41 of 535 [7.7%]; $P=0.20$), with an OR of 2.82 (95% CI=1.05-7.59; $P=0.04$).

Interestingly, the high-decreasing category was also more prevalent in the incident dementia group (18 of 75 [24.0%] vs 103 of 597 [17.3%]; $P=0.15$), with an OR of 2.76 (95% CI=1.39-5.47; $P=0.004$). Association with higher dementia incidence was not observed in participants with milder decrease in HbA1c over the first year (9 of 50 [18.0%] vs 53 of 366 [14.5%]; $P=0.51$).

The moderate-decreasing category was more prevalent in the incident dementia group (7 of 64 [10.9%] vs 27 of 521 [5.2%]; $P=0.06$), with an OR of 3.24 (95% CI=1.13-9.24; $P=0.03$). Those with milder decrease in HbA1c over the first year were more prevalent in the cognitively stable group, but the OR did not reach statistical significance (OR=0.33; 95% CI=0.39-2.70; $P=0.30$).

Although the OR for dementia was greater than 1 in the low-stable, moderate-increasing, and high-stable categories and less than 1 in the low-increasing category, none reached statistical significance (Table 2). The OR was not computed for the low-decreasing category due to limited number of participants.

DISCUSSION

While high and increasing HbA1c was associated with higher dementia incidence, we found that achieving the glycemic goal within a year was associated with higher rather than lower dementia incidence, independent of severe hypoglycemia, glycemic variability, and other physical, psychosocial, and lifestyle factors. This association was observed in both high ($\geq 8\%$) and moderate HbA1c (6.5-7.9%) at baseline followed by a large drop (a relative reduction of $\geq 10\%$), but not milder decrease (a relative reduction of 5-10%), within a year. Our findings suggest that the rate of decline in glycemic level might be an important factor in the development of dementia in older adults with diabetes, and from a clinical perspective, healthcare professionals need to be mindful of older adults who experience a sudden large drop in HbA1c, be cautious in optimizing glycemic level in those with hyperglycemia, and be aware of the possible elevated risk of dementia in intensifying glycemic control in those not having high HbA1c.

Comparison with other studies

Although previous literature suggests that hyperglycemia is associated with different pathologies of dementia, including altered amyloid metabolism, microvascular changes, insulin dysregulation and changes in insulin and insulin-like growth factor-1 (IGF-1) signaling, overproduction of reactive oxygen species, and increased pro-inflammatory cytokines [2-4], we did not find an association between hyperglycemia alone and higher dementia incidence. As the pathologies often take many years, if not decades, to develop, a longer duration of hyperglycemia might be required before dementia risk increases [25]. Alternatively, higher glycemic levels might be needed for dementia to develop [5-8]. Although we did not find such association with $\text{HbA1c} \geq 8.5\%$, we found that worsening of hyperglycemia was associated with higher dementia incidence. This might be explained by an

accelerated accumulation of dementia pathologies in the brain, thus advancing the clinical manifestation of dementia.

We did not find lowering glycemic level to the recommended target within a year associating with risk reduction. This is not fully explained by severe hypoglycemia, glycemic variability, or subsequent glycemic changes. It might be that once developed, the dementia pathologies are irreversible, even with improved glycemic control in late life. More importantly, we found that a significant drop in HbA1c was associated with higher dementia risk. While the precise mechanisms remain to be elucidated, we speculate that older adults with hyperglycemia but not yet having dementia may be at the stage when compensatory mechanisms are still functioning, so the detrimental effect of dementia pathologies is moderated, and their cognition maintains relatively unimpaired. However, once the blood glucose level falls too quickly and stays much lower than previously, the abrupt change in glycemic level may predispose the older adults to metabolic dysfunction and abnormal glucose and energy homeostasis in the brain, triggering oxidative stress and inflammation and thereby leading to decompensation and onset of dementia symptoms.

In line with the ADVANCE and ACCORD studies, which did not find intensive glycemic control preventing cognitive decline [9-11], our findings highlight the concern of intensifying glucose lowering in older adults whose HbA1c levels are not particularly high. Indeed, low HbA1c is associated with increased frailty and mortality [26-29]. Differences in other outcomes between the ADVANCE and ACCORD studies, possibly explained by variations in how intensive glycemic control was attained, also highlight the potential importance of the rate of drop in HbA1c as suggested by our findings. It would be important to further examine what the optimal glycemic target for older adults should be, and how it should be achieved, so that the risk of diabetic complications can be minimized without adversely affecting cognition.

Limitations and strengths

Given the nature of our study design, care should be taken when making an inference about a causal relationship between glycemic changes and dementia risk. The possibility of reverse causation could not be completely excluded because the baseline cognitive capacity and the onset, duration, and treatment of diabetes were not assessed [25]. Although our participants were screened negative for significant cognitive impairment at baseline, the potential confounding problems of people having poorer treatment compliance and suboptimal glycemic control owing to subtle cognitive impairment might still be present. For logistic reasons, examination of other diabetes-related complications, mild or asymptomatic hypoglycemic episodes, and daily glycemic variability, detailed neuropsychological assessments, genotyping, and brain imaging were not conducted. Given the studies showing that significant hypoglycemia is associated with the development of dementia [16,17] and the problem that hypoglycemia is often asymptomatic in the elderly, asymptomatic or mildly symptomatic hypoglycemia might contribute to the link found between the rapid decline in HbA1c and development of dementia. Moreover, categorizing baseline HbA1c levels and subsequent changes into different groups might introduce the problems of multiple comparisons and loss of power, though with a *P*-value of 0.004 in the high-decreasing category type I error is unlikely. Furthermore, direct application of our findings to older populations with more severe diabetes, from later generations, and of other ethnicities requires caution, as our cohort was relatively healthy, had lower educational attainment, and were ethnic Chinese, who in general have lower prevalence of Apolipoprotein E4, higher prevalence of hypertension, lower BMI cutoff for obesity, and higher susceptibility to developing diabetes at lower BMI [30].

Regarding the strengths of this study, we followed this community cohort for a long time, with measures taken to minimize attrition rate. Dementia was identified from cognitive assessments rather than solely from hospital records. Various health problems and behaviors and diabetes-specific factors, including severe hypoglycemia and glycemic variability, were controlled in the analyses.

Conclusion

With a large decrease in glycemic level being a potential predictor and possibly a risk factor for dementia in older adults with diabetes, our findings suggest the need for being attentive to both increasing and decreasing HbA1c levels, with an emphasis on not only achieving a particular glycemic target but also promoting moderation of glycemic level.

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Conflict of interest:

None.

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Ethical approval:

This study was approved by both the Ethics Committee of the Department of Health of the Government of Hong Kong and the Ethics Committee of the University.

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FIGURE

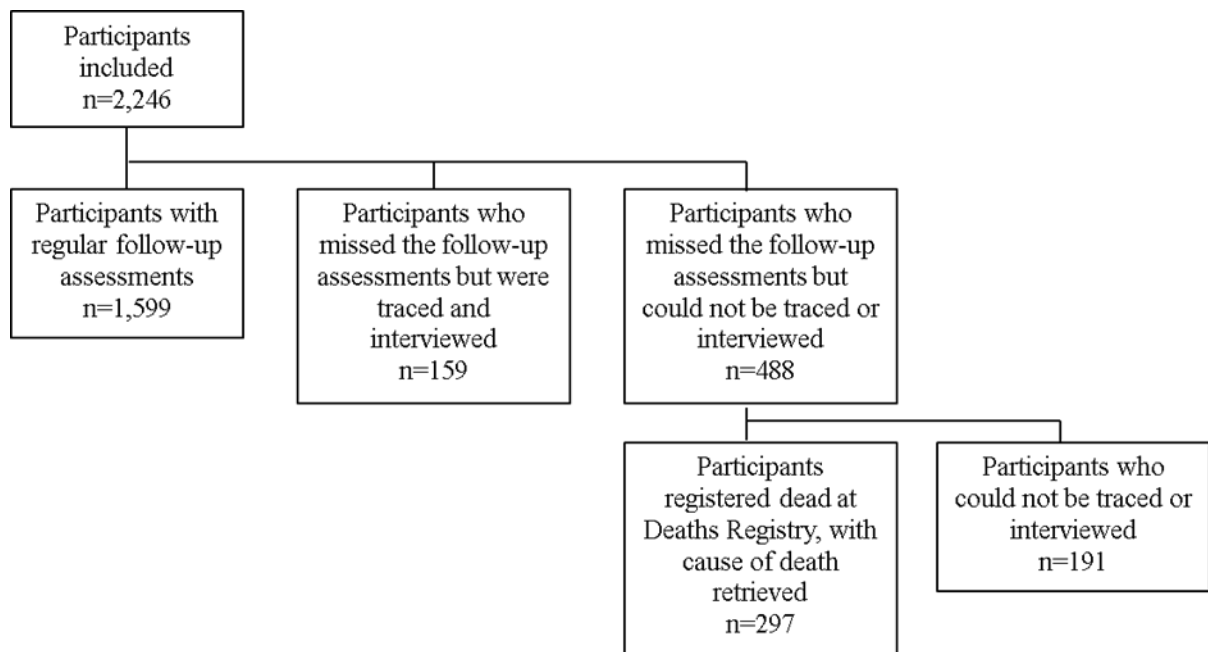


Figure 1. Flowchart of the participants in the study.

TABLES

Table 1. Comparison of baseline characteristics between older adults with type 2 diabetes with and without incident dementia in 6 years.

Characteristic	Incident Dementia		<i>P</i> value
	No (n=2004)	Yes (n=242)	
HbA1c, %	7.3 ± 1.3	7.4 ± 1.3	0.50*
HbA1c ≥ 7.5%, n (%)	772 (38.5)	92 (38.0)	0.88 [†]
HbA1c ≥ 8.5%, n (%)	277 (13.8)	41 (16.9)	0.19 [†]
Hospital admissions, episodes	0.2 ± 0.5	0.2 ± 0.4	0.42*
Age, years	74.4 ± 4.6	77.0 ± 4.9	<0.001*
Female, n (%)	1218 (60.8)	182 (75.2)	<0.001 [†]
No schooling received, n (%)	529 (26.4)	99 (40.9)	<0.001 [†]
Low socioeconomic class, n (%)	258 (12.9)	39 (16.1)	0.16 [†]
Hypertension, n (%)	1535 (76.6)	199 (82.2)	<0.05 [†]
Systolic blood pressure, mmHg	144 ± 21	143 ± 19	0.66*
Diastolic blood pressure, mmHg	71 ± 10	70 ± 11	0.05*
Hypercholesterolemia, n (%)	805 (40.2)	87 (36.0)	0.21 [†]
Fasting total cholesterol, mmol/L	5.2 ± 1.0	5.3 ± 1.0	0.75*
Obesity, n (%)	877 (43.8)	114 (47.1)	0.32 [†]
Body mass index, kg/m ²	24.8 ± 3.3	25.0 ± 3.7	0.36*
Heart diseases, n (%)	273 (13.6)	39 (16.1)	0.29 [†]
Visual impairment, n (%)	198 (9.9)	37 (15.3)	0.009 [†]
Hearing impairment, n (%)	478 (23.9)	57 (23.6)	0.92 [†]
Poor mobility, n (%)	181 (9.0)	35 (14.5)	0.007 [†]
Poor balance, n (%)	499 (24.9)	86 (35.5)	<0.001 [†]
Depression, n (%)	85 (4.2)	14 (5.8)	0.27 [†]
Physical exercise, n (%)	592 (29.5)	54 (22.3)	0.02 [†]
Intellectual activities, n (%)	1322 (66.0)	120 (49.6)	<0.001 [†]
Smoking, n (%)	102 (5.1)	8 (3.3)	0.22 [†]

Values are mean ± standard deviation for continuous variables as determined by the independent t-test*, and n (%) for categorical variables as determined by the χ^2 test[†]

Table 2. Estimated odds ratios (ORs) and 95% confidence intervals (95% CI) for incident dementia among older adults who had type 2 diabetes and were free of dementia.

HbA1c trajectory*	Model 1		Model 2†	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Low and stable	1.39 (0.77-2.50)	0.28	1.20 (0.63-2.29)	0.58
Low and increasing	0.86 (0.35-2.13)	0.75	0.76 (0.27-2.13)	0.61
Moderate and decreasing	3.50 (1.41-8.70)	0.007	3.24 (1.13-9.24)	0.03
Moderate and increasing	1.51 (0.83-2.76)	0.43	1.35 (0.69-2.64)	0.37
High and decreasing	2.36 (1.27-4.40)	0.007	2.76 (1.39-5.47)	0.004
High and stable	1.52 (0.84-2.76)	0.17	1.46 (0.77-2.75)	0.25
High and increasing	2.63 (1.13-6.12)	0.02	2.82 (1.05-7.59)	0.04

*Comparison was made with the moderate and stable HbA1c trajectory.

†Adjusted for severe hypoglycemic episodes, sociodemographic factors, cardiovascular risk factors, physical health parameters, physical impairments, depression, and lifestyle behaviors.