

GLYCOSYLATED HEMOGLOBIN LEVEL AND DEVELOPMENT OF MILD COGNITIVE IMPAIRMENT OR DEMENTIA IN OLDER WOMEN

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Abstract: Background: Biological mechanisms linking diabetes and cognition continue to grow, yet the association remains controversial in elders. Whether glycosylated hemoglobin (HbA_{1C}) level, a marker of glucose control, is predictive of the development of cognitive impairment or dementia is unknown. We determined the association between HbA_{1C} level and risk of developing cognitive impairment in older women, mostly without diabetes. Methods: We studied 1983 postmenopausal women (mean age, 67.2 years) with osteoporosis who had HbA_{1C} level measured at baseline. Development of mild cognitive impairment (MCI) or dementia over 4 years was determined as part of a dementia ancillary study. We analyzed risk of MCI or dementia for every 1% of HbA_{1C} as well as risk associated with HbA_{1C} ≥ 7%. Results: The mean level of HbA_{1C} was 5.8% (range 3.0% to 12.1%) and 86 (4.3%) women developed MCI or dementia. For every 1% increase in HbA_{1C}, women had a greater age-adjusted likelihood of developing MCI (OR= 1.50; 95% CI 1.14-1.97) and of developing MCI or dementia (OR=1.40; 95% CI 1.08 - 1.83). For those with HbA_{1C} level ≥ 7% (n=49), the age-adjusted risk for developing MCI was increased nearly 4-fold (OR= 3.70; 95% CI 1.51-9.09) and was increased nearly 3-fold for developing MCI or dementia (OR=2.86; 95% CI 1.17-6.98). When we excluded women with diagnosed diabetes (n=53), the association between HbA_{1C} and MCI lessened somewhat but remained elevated (unadjusted OR=1.59; 95% CI 1.01-2.50; age-adjusted OR=1.42; 95% CI 0.89-2.28). Multivariate analyses adjusted for age, education, race, depression, alcohol use and treatment with raloxifene yielded similar results. Interpretation: We found an association between HbA_{1C} level and risk of developing MCI or dementia in postmenopausal osteoporotic women primarily without diabetes. Our findings support the hypothesis that glucose dysregulation is a predictor for cognitive impairment.

Key words: Dementia, diabetes, mild cognitive impairment, glucose.

Introduction

Over 33% of women and 20% of men aged 65 and older will develop dementia during their lifetime, and many more will develop a milder form of cognitive impairment. (1) Several biological mechanisms support an association between impaired glucose regulation and dementia. (2) The recent finding that the insulin-degrading enzyme metabolizes β-amyloid in addition to insulin suggests that hypofunction of this enzyme could result in greater risk of Alzheimer's disease (AD) and cognitive impairment. (3) Several prospective studies have investigated the association between diabetes and change in cognition with the majority of studies supporting a negative association between diabetes and cognitive function. (4-6)

If diabetes is causally related to cognitive impairment, one also might expect to observe impaired cognitive performance in those elders with elevated glycosylated hemoglobin or hemoglobin A_{1C} (HbA_{1C}) level. However, few studies have investigated whether glucose dysregulation in elders with or without diabetes may also lead to cognitive dysfunction. No study to our knowledge has prospectively investigated the association between HbA_{1C} and risk of developing mild cognitive impairment (MCI) and dementia. In addition, there

has been no investigation between HbA_{1C} level and cognitive impairment in those without diabetes. We sought to determine the association between HbA_{1C} and risk of developing cognitive impairment in older women mostly without diabetes.

Methods

Study Subjects

Subjects were postmenopausal women with osteoporosis who had enrolled in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. 7705 postmenopausal women with osteoporosis at 180 sites in 25 countries were randomly assigned to receive raloxifene, 60 mg or 120 mg daily, or placebo for four years. Details of the study design and main results have been reported. (7) The human studies review board at each site approved the protocol; all women gave written informed consent. Our analytic cohort comprised the 1983 women who were randomly selected to have baseline HbA_{1C} level measured and who participated in the dementia ancillary study.

At study onset, we collected information on age, ethnicity, education, smoking, alcohol use, health conditions (based on self-report or medication use), prior postmenopausal estrogen

use, measured height and weight and calculated body mass index (BMI). Participants completed the 15-item Geriatric Depression Scale (GDS) with a score of ≥ 6 symptoms indicating depression as previously described. (8) At baseline, women were defined as having diabetes if they reported it as a pre-existing condition or were currently using a hypoglycemic medication. We also determined which women had a fasting blood glucose level ≥ 126 mg/dL (≥ 7.0 mmol/L) at baseline.

Measurement of HbA_{1C} Level

At baseline, fasting whole blood was obtained on study participants. HbA_{1C} level was determined with ion-exchange high performance liquid chromatography (Bio-Rad DIAMAT, Covance Company, Atlanta, Georgia). The coefficient of variation 2.2% was with a sample mean of 5.3% and 1.6% with a sample mean of 10.4% and sensitivity of 3%. The standard cut-off for optimum glycemic control is an HbA_{1C} level $< 7\%$. (9)

Ascertainment of Cognitive Impairment and Dementia

The Short Blessed Test (10) was used as a screen for dementia and was administered at baseline and annually. Women with the worst 10% of Short Blessed scores at Year 3 in each country or with clinical symptoms of cognitive impairment were referred for a clinical dementia evaluation near the end of the study. This evaluation consisted of a standard clinical evaluation by a clinician expert in dementia and included interviews with the participant and caregiver, a physical and neurological examination and standard cognitive and functional scales. (11) Participants with evidence of dementia based on this evaluation were referred for a brain CT or MRI scan and dementia laboratory tests (fluorescent treponemal antibody, vitamin B12, serum folate, and thyroid-stimulating hormone). All brain scans were read by a neuroradiologist at the University of California, San Francisco.

The clinical dementia evaluation results were presented to a Dementia Adjudication Committee along with scores from all cognitive assessments (Short Blessed Test, Trails A and B, Word List Memory and Recall, Word Fluency). Two committee members independently judged cognitive status as cognitively normal, MCI, (12, 13) AD in accordance with National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, (14) vascular dementia, or other type of dementia. In our analysis we categorized outcomes as MCI and any clinically significant cognitive impairment including dementia or MCI. Mean length of follow-up in the trial was 3.96 ± 0.18 years.

Statistical Analyses

We determined baseline characteristics of the participants and determined whether these were associated with HbA_{1C} level by conducting linear regression analyses. We then examined the association between HbA_{1C} level (per 1%) and

development of MCI or any clinically significant cognitive impairment by using logistic models. We tested for the presence of a nonlinear (quadratic) effect of HbA_{1C} level on cognitive outcomes by adding a squared term to the models, but none were significant so the linear relationship was modeled. We also calculated the odds ratios and 95% CI for risk associated with HbA_{1C} level $\geq 7\%$. We then adjusted these models for age and additionally for education, race, depression, alcohol use and raloxifene treatment. Covariates were selected to be in the multivariate models if they were associated with both HbA_{1C} level and with cognitive impairment at the $p=0.05$ level. The analyses were repeated after excluding the 53 women with known or diagnosed diabetes.

Results

Of the 1983 women with measured HbA_{1C} at baseline and who participated in the dementia ancillary study, 97% were Caucasian. The mean age was $67.2 (\pm 6.5)$ years and the mean education was $11.7 (\pm 3.7)$ years (Table 1). At baseline, 53 (2.7%) women had known diabetes, 41 (2.1%) had a history of myocardial infarction, 7 (0.4%) had a history of stroke and 115 (5.8%) had elevated depression scores. The mean level of HbA_{1C} was 5.8% with range 3.0% to 12.1% and the levels were fairly normally distributed. HbA_{1C} level was positively associated with age, smoking, depression, and history of MI and negatively associated with being white and alcohol use ($p<0.05$ for all). As expected, it was also positively associated with characteristics linked to glucose control such as BMI, diagnosis of diabetes and fasting blood glucose level.

Table 1
 Baseline Characteristics of the 1983 Women with Hemoglobin A_{1C} Measurement.

Characteristic, mean (SD) or N (%)	All Participants (N=1983)
Age (years)	67.2 (6.5)
Education (years)	11.7 (3.7)
Current smoker, N (%)	324 (16.8)
Caucasian, N (%)	1932 (97.4)
History of myocardial infarction, N (%)	41 (2.1)
History of stroke, N (%)	7 (0.4)
Geriatric Depression score > 6	115 (5.8)
Short Blessed score	2.4 (2.8)
Past hormone replacement therapy, N (%)	468 (23.7)
Body mass index kg/m ²	25.1 (3.8)
Alcohol use > 3 drinks/week	360 (18.2)
Fasting blood glucose, mg/dL	95.4 (16.6)
Diabetes, N (%)	53 (2.7)
Hemoglobin HbA _{1C} , %	5.8 (0.6)

Over the four years of follow-up, 69 women were diagnosed with MCI and 17 were diagnosed with dementia of any etiology

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Table 2

The Likelihood of Developing Mild Cognitive Impairment (MCI) or Dementia Associated with Hemoglobin A_{1C} (HbA_{1C}) Level

HbA _{1C} at baseline, per 1% increase	Odds Ratio (95% confidence interval)		
	Unadjusted (N=1983)	Age-Adjusted (N=1983)	Multivariate Adjusted* (N=1966)
MCI (N=69)	1.56 (1.21 - 2.02)	1.50 (1.14 - 1.97)	1.37 (1.02 - 1.85)
MCI or dementia (N=86)	1.48 (1.16 - 1.90)	1.40 (1.08 - 1.83)	1.28 (0.96 - 1.71)

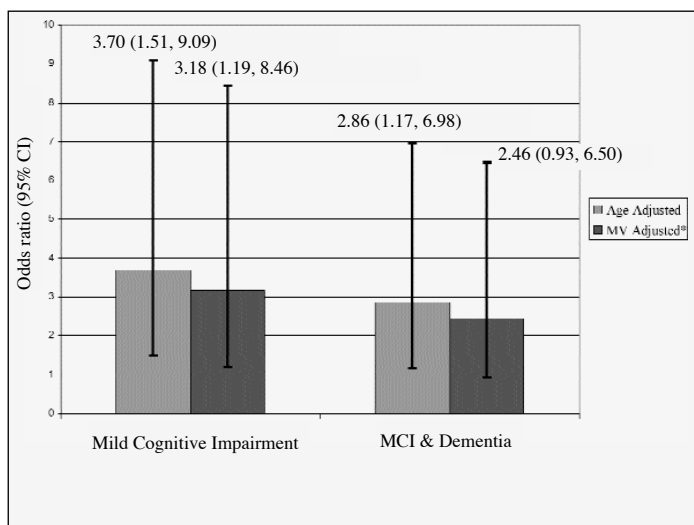
*Adjusted for age, education, race, depression, alcohol use, and raloxifene. 17 participants were missing one or more of the covariates.

(15 with AD). For every 1% increase in HbA_{1C}, women had a greater risk of developing MCI (unadjusted OR = 1.56; 95% CI 1.21-2.02 and age-adjusted OR=1.50; 95%CI 1.14-1.97) and a greater risk of developing MCI or dementia (unadjusted OR = 1.48; 95%CI 1.16-1.90 and age-adjusted OR= 1.40; 95% CI 1.08-1.83) (Table 2). Further adjustment for education, race, depression, alcohol use and raloxifene lessened the magnitude of the association slightly (Table 2). Of the 53 women with diabetes, 6 (11%) developed MCI and none developed dementia.

There were 49 (2.5%) women with baseline HbA_{1C} level ≥7 % and of these, 27 (55%) had known diabetes. Compared to those with HbA_{1C} level <7 %, women with level ≥ 7% had a 4-fold increase in developing MCI (unadjusted OR= 4.15; 95%CI 1.70-10.10 and age-adjusted OR= 3.70; 95% CI 1.51-9.09) and a greater than 3-fold increase in developing dementia or MCI (unadjusted OR= 3.23; 95%CI 1.34-7.82 and age-adjusted OR=2.86; 95% CI 1.17-6.98) (Figure). Further adjustment for age, education, race, depression, alcohol use and raloxifene led to similar results but the magnitude of the association was lessened slightly (OR= 3.17; 95%CI 1.19-8.44 for MCI and OR= 2.45; 95% CI 0.93-6.47 for MCI or dementia).

Figure

The association between Hemoglobin A_{1C} >7% and risk of developing mild cognitive impairment (MCI) or dementia over 4 years of follow-up



When we excluded the 53 women with diabetes, the mean level of HbA_{1C} was 5.7%, with range 3.0% to 8.7%, and the levels were normally distributed. The association between HbA_{1C} (per 1% increase) and MCI lessened somewhat but remained elevated (unadjusted OR=1.59; 95% CI 1.01-2.50 and age-adjusted OR=1.42; 95%CI 0.89-2.28). Similarly, the association between HbA_{1C} and odds of developing MCI or dementia was increased among women without diabetes (unadjusted OR=1.51; 95%CI 1.00-2.29 and age-adjusted OR = 1.33; 95%CI 0.87-2.05).

Discussion

In this prospective study of elderly women, we found that higher HbA_{1C} level is associated with increased risk of developing cognitive impairment. For every increase in 1% unit of HbA_{1C}, there was a 40% increase in risk of developing MCI or dementia. Women with HbA_{1C} level over 7% were at even higher risk for developing cognitive impairment. This finding supports the hypothesis that abnormal glycemic control is linked to an increased risk of developing cognitive impairment and dementia in elderly women.

Our results are in support of those from several cross-sectional studies that have reported an inverse association between diabetes and cognitive performance in older adults (15-17) and from several prospective studies that have reported an association between diabetes and worse cognitive function longitudinally. (5, 6, 18) As part of the Rancho Bernardo Study, we found that older women with diabetes had a more rapid 4-year decline in verbal fluency compared to women with normal glucose tolerance. Glycemic control may partially mediate this association as adjustment for HbA_{1C} level attenuated the magnitude of the effect. (4) Other prospective studies have failed to find an association between diabetes and change in cognitive performance. (19, 20) However, these studies may have been limited by the small sample size of diabetic subjects, loss to follow-up, and insensitive cognitive measures. None of these studies investigated the association of glucose dysregulation with cognitive impairment among non-diabetics.

There are several mechanisms whereby glucose dysregulation may cause cognitive impairment. (2) One mechanism is the development of diabetic complications such as renal disease, stroke, hypertension, hyperlipidemia and

ischemic heart disease that may lead to impaired cognitive performance. In addition, there are several possible mechanisms related to elevated glucose per se that may be related to impaired cognitive function. Chronic hyperglycemia could cause cognitive impairment either by direct neuronal damage, possibly by advanced glycosylated endproducts (AGEs), or by indirect neuronal damage from cerebral microvascular and macrovascular atherosclerotic disease. Patients with AD have higher brain concentrations of AGEs, such as pyraline and pentosidine, compared to normal controls and AGEs may be involved in the neurotoxic pathway of β -amyloid in the pathogenesis of AD. (21) In addition, both small and large cerebral vessel atherosclerosis have been associated with cognitive impairment and increased risk of dementia, including vascular dementia and AD. (22, 23) Finally, hyperinsulinemia and insulin resistance may be independently associated with cognitive impairment. (24, 25) Recently, the insulin-degrading enzyme has been found to catabolyze β -amyloid in addition to insulin. This suggests that hypofunction of this enzyme could be linked to the development of AD directly. (3) Compared to normal controls, patients with AD have reduced levels of hippocampal insulin-degrading enzyme, especially in those with the Apolipoprotein E e4 allele. (26) Thus, insulin level in the central nervous system or insulin-degrading enzyme activity may underlie both risk of developing AD and diabetes.

Our study has many strengths including the large sample size and inclusion of relatively high-functioning community-dwelling women who agreed to participate in the trial. To our knowledge, this is the first study to prospectively examine the association between HbA_{1C} level and risk of cognitive impairment not just among elders with diabetes. We performed an extensive clinical evaluation for cognitive impairment. Finally, we were able to adjust for possible confounders such as age, education, depression, and race.

There are several limitations in our study that may limit the interpretation of the results. The rate of dementia occurrence in our study was not sufficient to allow us to analyze the effect of HbA_{1C} level on risk of specific types of dementia. Therefore, we are unable to quantify the effect of HbA_{1C} on vascular mediated versus AD mediated cognitive impairment. Similarly, the rate of diabetes and other chronic health conditions was lower than expected most likely due to willingness to participate and the selection into a 4-year randomized controlled trial. As our study was composed of mostly white women with osteoporosis, we do not know if our findings apply to men or to women of other ethnic groups. While we were able to statistically adjust for several possible confounders, there were some variables on which we had limited information such as physical activity and thus, we may have had some residual confounding.

This study demonstrates that women with higher levels of HbA_{1C} have greater risk of developing cognitive impairment

and dementia. Our results support the growing link between abnormal glucose regulation and neurodegenerative diseases of aging. Future research should determine whether more aggressive control of glucose dysregulation in elders might lessen the risk of developing cognitive impairment.

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