ORIGINAL ARTICLE

Elevated serum glycated albumin and glycated albumin : hemoglobin A$_{1c}$ ratio were associated with hippocampal atrophy in a general elderly population of Japanese: The Hisayama Study

Tomoyuki Ohara[1,2] iD, Yoshihiko Furuta[2,3], Naoki Hirabayashi[2,4], Jun Hata[2,3,5], Yoichiro Hirakawa[2,3], Takanori Honda[2] iD, Daigo Yoshida[2], Mao Shibata[2,4,5], Takanari Kitazono[3,5], Toshiharu Ninomiya[2,5,*] iD

[1]Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [3]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, and [5]Department of Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

ABSTRACT

Aims/Introduction: To investigate the association of alternative glycemic measures – namely, serum glycated albumin (GA), hemoglobin A$_{1c}$ (HbA$_{1c}$) and the GA : HbA$_{1c}$ ratio – with global brain and hippocampal atrophy in a general elderly Japanese population.

Materials and Methods: A total of 1,278 Japanese individuals aged ≥65 years in a community participated in brain magnetic resonance imaging scanning and screening examination of health status in 2012. We measured total brain volume (TBV), hippocampal volume (HV) and intracranial volume (ICV) using the data from the magnetic resonance imaging examination. The association of each glycemic measure with the ratios of TBV : ICV (an indicator of global brain atrophy) and HV : ICV (an indicator of hippocampal atrophy) was examined by analysis of covariance.

Results: The mean values of the TBV : ICV and HV : ICV ratios decreased significantly with elevating serum GA levels and GA : HbA$_{1c}$ ratio levels (all *P* for trend < 0.05), but not with higher HbA$_{1c}$ levels, after adjusting for age, sex, low education, systolic blood pressure, antihypertensive medication, diabetes mellitus, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits and regular exercise. These significant associations were still observed in the sensitivity analysis after excluding individuals with mild cognitive impairment and dementia. In addition, increased serum GA levels and the GA : HbA$_{1c}$ ratio levels, but not HbA$_{1c}$, were closely associated with lower mean values of the TBV : ICV and HV : ICV ratios, irrespective of the presence or absence of diabetes mellitus.

Conclusions: The present study suggests that higher serum GA and higher GA : HbA$_{1c}$ ratio are significantly associated with global brain and hippocampal atrophy.

INTRODUCTION

Brain atrophy, especially hippocampus atrophy, is one of the morphological features of the progression of Alzheimer's disease (AD)[1], and diabetes mellitus is known to be a risk factor for brain atrophy, cognitive decline and AD[2–4]. Several clinical studies using continuous blood glucose monitoring have reported significant associations between postprandial hyperglycemia or glycemic variability and cognitive impairment[5,6]. We previously reported that brain and hippocampal atrophy are prominent in patients with diabetes mellitus, especially those with an increased 2-h postload glucose level[3]. Although these findings raise the possibility that postprandial

hyperglycemia or glycemic variability might contribute to brain atrophy, increased postload glucose levels cannot be precisely extrapolated to postprandial hyperglycemia or glycemic variability[7]. Therefore, indicators for estimating glycemic variability in individuals with an ordinary lifestyle are necessary to elucidate this issue in a community-based epidemiological study.

There are several glycemic measures in clinical settings, and hemoglobin A_{1c} (HbA_{1c}) is a widely used marker of sustained hyperglycemia. Recently, glycated albumin (GA) has attracted clinical attention as an alternative glycemic measure of postprandial glucose fluctuations[8]. As the glycation speed of albumin is faster than that of hemoglobin[9], GA levels are reported to rise faster than HbA_{1c} levels in response to a rapid increase of plasma glucose levels[8,10]. In addition, the GA : HbA_{1c} ratio has been reported to be a suitable index for estimating a rapid increase in plasma glucose[11], and clinical studies have shown that the GA : HbA_{1c} ratio is closely associated with glycemic variability[12,13]. Our previous longitudinal study, which showed that elevated GA : HbA_{1c} ratio levels are significantly associated with an increased risk of developing AD[11], might support the notion that the alterations in glycemic levels precede brain atrophy. However, no epidemiological studies have assessed the association of alternative glycemic measures – namely, serum GA levels, HbA_{1c} and the GA : HbA_{1c} ratio – with the volumes of the global brain and hippocampus. The present study aimed to investigate the association between each glycemic measure and the brain and hippocampus volumes by using brain magnetic resonance imaging (MRI) in a general older population of Japanese adults.

METHODS

Study populations

The Hisayama Study is an ongoing population-based longitudinal study of cerebro-cardiovascular diseases that began in 1961 in the town of Hisayama, which is a suburban area adjacent to the city of Fukuoka in southern Japan[14]. We have also carried out comprehensive surveys of dementia every 6 or 7 years since 1985 (i.e., 1985, 1992, 1998, 2005 and 2012) in the elderly residents of this town[15]. In 2012, a total of 1,906 older residents aged ≥65 years (93.6% of the total population in this age group) participated in the screening examination for dementia, and 1,342 of them (70.4%) underwent brain MRI scanning[3]. After excluding one individuals who did not agree to participate in the study, 28 individuals with MRI imaging errors of any type, 26 individuals without available data of the screening examinations in 2012 and nine individuals without available measurement of HbA_{1c} and GA, the remaining 1,278 individuals (716 women and 562 men) were enrolled in the present study.

Ethical considerations

The institutional review board for Clinical Research of Kyushu University approved the present study. We obtained written informed consent from all participants.

MRI analysis

We analyzed turbo field echo T1-weighted three-dimensional images, conventional magnetic resonance angiograms, T2- and T1-weighted images, fluid-attenuated inversion recovery images, and T2*-weighted images of the brain obtained using a 1.5-T MRI scanner by Intera Pulsar, Philips Medical Systems (Best, the Netherlands) in the MRI examination. Details about the MRI examination and calculation of each brain volume have been published previously[3]. For determining brain and hippocampal atrophy, T1-weighted three-dimensional images were used. The Oxford Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Integrated Registration and Segmentation Tool implemented in the FSL software package, version 5.0.6 (Oxford University, Oxford, UK)[16] was used to measure the volume and segmentation of the hippocampus. We calculated hippocampal volume (HV) as the sum of the right and left hippocampal volumes, and visually checked all processed images for errors in segmentation. VBM8 Toolbox version 435 (University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm/) in SPM8 (Wellcome Department of Imaging Neuroscience, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) with the default settings running in MATLAB (MathWorks, Natick, MA, USA) was used to measure cerebrospinal fluid volume, white matter volume and gray matter volume of the brain. Total brain volume (TBV) was calculated by summing the white and gray matter volumes. We computed intracranial volume (ICV) as the sum of cerebrospinal fluid volume and TBV. In the present study, we evaluated two parameters – namely, the TBV : ICV ratio (%) and HV : ICV ratio (%), for their potential as indices of global brain atrophy and hippocampal atrophy, respectively.

Measurements of GA and HbA_{1c}

We collected serum specimens at the health examination in 2012, and serum GA levels were measured enzymatically by using an albumin assay reagent, ketoamine oxidase, and an albumin-specific proteinase (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan). We measured HbA_{1c} levels as a National Glycohemoglobin Standardization Program value by high-performance liquid chromatography (Arkray, Kyoto, Japan).

Measurements of other risk factors

Each participant answered a self-administered questionnaire that included medical treatment (antihypertensive and antidiabetic medications), medical history, physical activity, educational background, alcohol consumption and smoking habit. We defined low education as ≤9 years of formal education. An automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto, Japan) was used to measure blood pressure three times in the sitting position after rest for at least ≥5 min, and we used the mean of three measurements for the analysis. Hypertension was defined as current use of antihypertensive medication or blood pressure levels ≥140/90 mmHg. Diabetes mellitus was defined as follows: fasting glucose level

≥7.0 mmol/L, casual or 2-h postload glucose levels ≥11.1 mmol/L and/or antidiabetic medications. Serum total cholesterol levels were determined enzymatically. Body mass index was calculated with bodyweight and height, which were measured without shoes and with light clothing. Electrocardiogram abnormalities were defined by ST depression (Minnesota Code, 4-1, 2, 3), left ventricular hypertrophy (3-1) or atrial fibrillation (8-3). We classified smoking habits and alcohol drinking habits as being current habitual or not, and defined regular exercise as keeping to any forms of physical exercise three or more times a week during leisure time.

Dementia and mild cognitive impairment (MCI) were ascertained using the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Revised Third Edition[17] and the clinical criteria defined by Petersen *et al.*[18] in 2001, respectively. In the screening survey, we used the Mini-Mental State Examination. For participants who were suspected of having MCI or dementia, secondary comprehensive investigations including the Wechsler Memory Scale of logical memory were carried out by trained psychiatrists, as described previously[15]. We defined MCI as either of: (i) objective cognitive impairment based on analysis of the neuropsychological data; or (ii) any cognitive complaint by a family member, the town's Health and Welfare Office members or local practitioners in individuals who showed no evidence of dementia. Expert psychiatrists and physicians of stroke in the study team adjudicated every case of MCI and dementia.

Statistical analysis

We carried out all of the statistical analyses by using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The values of GA, HbA$_{1c}$ and the GA : HbA$_{1c}$ ratio were divided into quartiles. Logistic or linear regression analysis were used to examine the differences in the age- and sex-adjusted frequencies or mean values of potential confounding factors between the highest and the lowest quartiles of each alternative glycemic measure, respectively. Analysis of covariance was used to estimate and compare the age- and sex-adjusted or multivariable-adjusted means and 95% confidence intervals of the TBV : ICV and HV : ICV ratios. We used a linear regression analysis to examine the linear trends in the TBV : ICV and HV : ICV ratios across each glycemic measure, where the values of each glycemic measure were assigned an ordinal number corresponding to its quartile (i.e., 1, 2, 3, 4). In all analyses, we defined a two-tailed *P*-value of < 0.05 as statistically significant.

RESULTS

The median values of GA, HbA$_{1c}$ and the GA : HbA$_{1c}$ ratio in this population were 15.6% (interquartile range 14.6–17.1%), 5.7% (interquartile range 5.5–6.1%) and 2.72 (interquartile range 2.55–2.93), respectively. Among the study population, 155 participants (12.1%) were diagnosed as having MCI, and 136 participants (10.7%) as having dementia. Table 1, Table S1 and Table S2 show the clinical characteristics of the study population

Table 1 | Age- and sex-adjusted baseline characteristics of the total study population and participants according to quartile of serum glycated albumin in 2012

Variables	Total population	Serum GA level (%)			
	(n = 1,278)	Q1 (<14.6) (n = 321)	Q2 (14.6–15.6) (n = 326)	Q3 (15.7–17.0) (n = 317)	Q4 (≥17.1) (n = 314)
Mean age, years (SD)	75 (7)	72 (5)	74 (6)**	75 (7)**	77 (7)**
Female (%)	56.0	58.6	60.4	57.0	47.8**
Education ≤9 years (%)	38.1	34.3	41.1	38.2	38.9
Hypertension (%)	70.3	66.0	64.7	70.7	80.3*
Mean systolic blood pressure, mmHg (SD)	134 (19)	135 (19)	132 (18)	133 (18)	138 (20)
Mean diastolic blood pressure, mmHg (SD)	76 (11)	78 (10)	76 (10)	75 (11)**	76 (11)
Antihypertensive medication (%)	55.4	47.7	50.9	56.2	67.2**
Diabetes mellitus (%)	23.2	6.9	11.3*	15.8**	59.6**
Mean HbA$_{1c}$, % (SD)	5.9 (0.7)	5.6 (0.3)	5.7 (0.3)**	5.7 (0.4)**	6.5 (1.0)**
Antidiabetic medication (%)	12.4	1.6	4.3*	6.6**	37.9**
Mean serum total cholesterol, mmol/L (SD)	5.1 (0.9)	5.3 (0.9)	5.2 (0.9)	5.1 (0.9)	5.0 (1.0)
Mean body mass index, kg/m^2 (SD)	23.1 (3.3)	23.8 (3.2)	23.2 (3.0)	22.4 (3.3)**	22.9 (3.6)*
Electrocardiogram abnormalities (%)	14.8	14.1	12.6	14.0	18.8
Smoking habits (%)	8.7	11.8	9.2	7.6	6.1
Alcohol drinking habits (%)	40.6	47.4	37.7	37.2	40.1
Regular exercise (%)	18.7	21.8	18.1	16.7	18.3
Mean MMSE (SD)	27 (4)	27 (3)	27 (3)	27 (3)	26 (6)

Age was sex-adjusted; female was age-adjusted. Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3 or 8-3. Regular exercise was defined as engaging in any forms of physical exercise at least three times per week during leisure time. HbA$_{1c}$, hemoglobin A$_{1c}$; MMSE, Mini-Mental State Examination; SD, standard deviation.
*P < 0.05
**P < 0.01 versus quartile 1 (Q1) for serum glycated albumin (GA).

Table 2 | Age- and sex-adjusted and multivariable-adjusted mean values of the total brain volume : intracranial volume ratios according to quartiles of each glycemic measure in 2012

	No. participants	Age- and sex-adjusted mean values (95% CI) of the TBV : ICV ratio (%)	*P*-value	Multivariable-adjusted mean values (95% CI) of the TBV : ICV ratio (%)[†]	*P*-value	Multivariable-adjusted mean values (95%CI) of the TBV : ICV ratio (%)[‡]	*P*-value
GA (%)							
Q1 (10.2–14.5)	321	78.2 (78.0–78.4)	(Reference)	78.2 (78.0–78.4)	(Reference)	78.1 (77.9–78.3)	(Reference)
Q2 (14.6–15.6)	326	78.1 (77.9–78.3)	0.88	78.1 (77.9–78.3)	0.90	78.0 (77.9–78.3)	0.96
Q3 (15.7–17.0)	317	78.2 (78.0–78.4)	0.99	78.2 (78.0–78.4)	0.99	78.2 (78.0–78.4)	0.96
Q4 (17.1–41.2)	314	77.4 (77.2–77.6)	<0.001	77.4 (77.2–77.6)	<0.001	77.5 (77.3–77.8)	0.001
		P for trend <0.001		*P* for trend <0.001		*P* for trend = 0.009	
HbA~1c~ (%)							
Q1 (4.4–5.4)	285	78.0 (77.8–78.2)	(Reference)	78.0 (77.8–78.2)	(Reference)	77.9 (77.7–78.1)	(Reference)
Q2 (5.5–5.7)	419	78.2 (78.0–78.0)	0.36	78.2 (78.0–78.4)	0.35	78.1 (77.9–78.3)	0.28
Q3 (5.8–6.0)	276	78.0 (77.8–78.2)	1.00	78.0 (77.7–78.2)	0.99	77.9 (77.7–78.2)	0.97
Q4 (6.1–13.6)	298	77.6 (77.4–77.8)	0.06	77.6 (77.4–77.8)	0.04	77.8 (77.6–78.1)	0.99
		P for trend = 0.005		*P* for trend = 0.04		*P* for trend = 0.69	
GA : HbA~1c~ ratio							
Q1 (1.89–2.55)	318	78.2 (78.0–78.4)	(Reference)	78.2 (78.0–78.4)	(Reference)	78.1 (77.9–78.3)	(Reference)
Q2 (2.55–2.72)	320	78.3 (78.1–78.5)	0.73	78.3 (78.1–78.5)	0.77	78.3 (78.1–78.5)	0.67
Q3 (2.72–2.93)	321	78.0 (77.8–78.2)	0.46	78.0 (77.8–78.2)	0.39	78.0 (77.8–78.2)	0.57
Q4 (2.93–4.45)	319	77.4 (77.2–77.6)	<0.001	77.4 (77.4–77.6)	<0.001	77.5 (77.3–77.7)	<0.001
		P for trend <0.001		*P* for trend <0.001		*P* for trend <0.001	

CI, confidence interval; GA, glycated albumin; GA : HbA~1c~ ratio, glycated albumin : hemoglobin A~1c~ ratio; HbA~1c~, hemoglobin A~1c~; ICV, intracranial volume; TBV, total brain volume.

[†]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits and regular exercise.

[‡]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits and regular exercise.

according to quartiles of each glycemic measure. For serum GA, compared with participants in the lowest quartile, frequencies of female, hypertension, antihypertensive medication, diabetes mellitus and antidiabetic medication, and mean values of age and body mass index were significantly higher in those in the highest quartile (Table 1). Similar findings were found in those in the highest quartile of HbA~1c~ levels, except for mean values of age and frequency of being female (Table S1). For the GA : HbA~1c~ ratio, participants in the highest quartile had significantly higher mean values of age, and frequencies of diabetes mellitus and antidiabetic medication than those in the lowest quartile, and higher levels of the GA : HbA~1c~ ratio were associated significantly with lower mean values of diastolic blood pressure and body mass index, and frequency of being female (Table S2).

We estimated the association between mean values of the TBV : ICV ratio according to the quartiles of each glycemic measure (Table 2). The age- and sex-adjusted mean values of the TBV : ICV ratio decreased significantly with higher levels of serum GA, HbA~1c~ and the GA : HbA~1c~ ratio, respectively (serum GA: *P* for trend < 0.001; HbA~1c~: *P* for trend = 0.005; the GA : HbA~1c~ ratio: *P* for trend <0.001). Those significant trends were unchanged after adjustment for age, sex, low education, systolic blood pressure, antihypertensive medications, serum total cholesterol, electrocardiogram abnormalities, body mass index,

smoking habits, alcohol drinking habits and regular exercise (serum GA: *P* for trend <0.001; HbA~1c~: *P* for trend = 0.04; the GA/ HbA~1c~ ratio: *P* for trend <0.001). However, for HbA~1c,~ when adjusting for diabetes mellitus in addition to the above-mentioned factors, there was no significant association (*P* for trend = 0.69). In contrast, the multivariable-adjusted mean values of the TBV : ICV ratio decreased significantly with elevation of serum GA levels and the GA : HbA~1c~ ratio levels even after adjustment for diabetes mellitus (both *P* for trend <0.01). With regard to the volume of the hippocampus, both higher serum GA and higher the GA : HbA~1c~ ratio levels were associated significantly with lower mean values of the HV : ICV ratio in the multivariable adjustment including diabetes mellitus, whereas no significant association was observed between HbA~1c~ and the HV : ICV ratio (Table 3). In the sensitivity analysis after excluding 291 participants with MCI or dementia, there were significant associations of serum GA levels and the GA : HbA~1c~ ratio levels, but not HbA~1c,~ with the multivariable-adjusted mean values of the TBV : ICV ratio (Table 4). For the hippocampal volume, the mean values of the HV : ICV ratio decreased significantly with only a higher level of the GA : HbA~1c~ ratio.

We also carried out a subgroup analysis of the association of each glycemic measure with the TBV : ICV and HV : ICV ratios stratified by diabetes status (Table 5). Higher serum GA

Table 3 | Age- and sex-adjusted and multivariable-adjusted mean values of the hippocampal volume : intracranial volume ratios according to quartiles of each glycemic measure in 2012

	No. participants	Age- and sex-adjusted mean values (95% CI) of the HV : ICV ratio (%)	P-value	Multivariable-adjusted mean values (95% CI) of the HV : ICV ratio (%)[†]	P-value	Multivariable–adjusted mean values (95% CI) of the HV : ICV ratio (%)[‡]	P-value
GA (%)							
Q1 (10.2–14.5)	321	0.526 (0.519–0.533)	(Reference)	0.525 (0.519–0.533)	(Reference)	0.523 (0.517–0.532)	(Reference)
Q2 (14.6–15.6)	326	0.529 (0.522–0.535)	0.90	0.529 (0.522–0.536)	0.88	0.528 (0.520–0.534)	0.88
Q3 (15.7–17.0)	317	0.525 (0.518–0.532)	1.00	0.525 (0.518–0.532)	0.99	0.524 (0.517–0.531)	1.00
Q4 (17.1–41.2)	314	0.507 (0.500–0.514)	0.001	0.506 (0.499–0.514)	<0.001	0.511 (0.503–0.519)	0.05
		P for trend <0.001		P for trend <0.001		P for trend = 0.04	
HbA$_{1c}$ (%)							
Q1 (4.4–5.4)	285	0.523 (0.515–0.530)	(Reference)	0.524 (0.516–0.531)	(Reference)	0.520 (0.512–0.528)	(Reference)
Q2 (5.5–5.7)	419	0.525 (0.519–0.531)	0.91	0.526 (0.520–0.532)	0.95	0.522 (0.516–0.529)	0.89
Q3 (5.8–6.0)	276	0.522 (0.515–0.530)	1.00	0.522 (0.514–0.529)	0.96	0.521 (0.513–0.528)	0.99
Q4 (6.1–13.6)	298	0.515 (0.508–0.523)	0.38	0.514 (0.507–0.522)	0.20	0.522 (0.514–0.531)	0.96
		P for trend = 0.12		P for trend = 0.049		P for trend = 0.78	
GA : HbA$_{1c}$ ratio							
Q1 (1.89–2.55)	318	0.526 (0.518–0.533)	(Reference)	0.526 (0.519–0.533)	(Reference)	0.524 (0.517–0.532)	(Reference)
Q2 (2.55–2.72)	320	0.532 (0.525–0.539)	0.40	0.532 (0.525–0.539)	0.45	0.531 (0.524–0.539)	0.39
Q3 (2.72–2.93)	321	0.520 (0.513–0.527)	0.57	0.520 (0.513–0.527)	0.50	0.520 (0.513–0.527)	0.66
Q4 (2.93–4.45)	319	0.509 (0.502–0.516)	0.006	0.508 (0.501–0.516)	0.005	0.512 (0.503–0.518)	0.03
		P for trend <0.001		P for trend <0.001		P for trend = 0.003	

CI, confidence interval; GA, glycated albumin; GA : HbA$_{1c}$ ratio, glycated albumin : hemoglobin A$_{1c}$ ratio; HbA$_{1c}$, hemoglobin A$_{1c}$; HV, hippocampal volume; ICV, intracranial volume.
[†]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits, and regular exercise.
[‡]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits, and regular exercise.

and the GA : HbA$_{1c}$ ratio levels, but not HbA$_{1c}$, were closely associated with lower mean values of the TBV : ICV and HV : ICV ratios, regardless of the presence or absence of diabetes mellitus. In addition, any heterogeneities in the association of each glycemic measure with the TBV : ICV and HV : ICV ratios among the subgroups were not observed (all of the P for heterogeneity >0.25).

DISCUSSION

The present cross-sectional study showed significant associations of higher serum GA and the GA : HbA$_{1c}$ ratio levels with lower global brain and hippocampus volumes in a general elderly population of Japanese. In particular, the multivariable-adjusted mean values of the TBV : ICV and HV : ICV ratios tended to decrease with higher serum GA levels and the GA : HbA$_{1c}$ ratio levels even in participants without MCI or dementia. Furthermore, subgroup analysis of the status of diabetes mellitus showed that those associations of the serum GA and the GA particular HbA$_{1c}$ ratio levels with the volumes of the global brain and hippocampus were observed in both participants with and without diabetes mellitus. These findings suggest that higher serum GA levels and the GA : HbA$_{1c}$ ratio levels are significantly associated with global brain and

hippocampal atrophy irrespective of the presence or absence of cognitive impairments or diabetes mellitus.

There have been no epidemiological studies examining the association of either serum GA levels or the GA : HbA$_{1c}$ ratio levels with global brain atrophy. Our previous longitudinal study showed that individuals with higher GA : HbA$_{1c}$ ratio levels were at significantly increased risk of the development of AD[11]. In the present study, the volumes of the total brain and hippocampus decreased significantly with higher GA : HbA$_{1c}$ ratio levels among participants without any cognitive impairment or dementia. This evidence suggests that individuals with higher GA : HbA$_{1c}$ ratio levels are likely to progress to brain and hippocampal atrophy before the onset of AD.

The hippocampus is reported to be more vulnerable to glycemic control and hypoxia than other brain regions[19,20]. In the present study, the hippocampal volume, as well as the total brain volume, decreased significantly with higher levels of GA, HbA$_{1c}$ and the GA : HbA$_{1c}$ ratio. However, the significant association of HbA$_{1c}$ levels, but not GA and the GA : HbA$_{1c}$ ratio, with brain and hippocampal atrophy disappeared after we adjusted for diabetes mellitus and other confounding factors. These findings were in line with our previous clinical findings that showed that higher GA : HbA$_{1c}$ ratio levels were

Table 4 | Multivariable-adjusted mean values of the total brain volume : intracranial volume ratios and hippocampal volume : intracranial volume ratios according to quartiles of each glycemic measure after excluding 291 individuals with mild cognitive impairment or dementia in 2012

	No. participants	Multivariable-adjusted mean values (95% CI) of the TBV : ICV ratio (%)[†] (an indicator of global brain atrophy)	Multivariable-adjusted mean values (95% CI) of the HV : ICV ratio (%)[†] (an indicator of hippocampal atrophy)
GA (%)			
Q1 (10.2–14.4)	250	78.5 (78.3–78.7)	0.536 (0.529–0.543)
Q2 (14.5–15.4)	236	78.5 (78.2–78.7)	0.542 (0.535–0.550)
Q3 (15.5–16.7)	250	78.6 (78.3–78.8)	0.533 (0.526–0.540)
Q4 (16.8–32.9)	251	78.0 (77.8–78.3)*	0.529 (0.521–0.537)
		P for trend = 0.03	*P* for trend = 0.14
HbA$_{1c}$ (%)			
Q1 (4.6–5.4)	206	78.2 (78.0–78.5)	0.534 (0.526–0.542)
Q2 (5.5–5.7)	337	78.5 (78.3–78.7)	0.535 (0.529–0.541)
Q3 (5.8–6.0)	216	78.3 (78.1–78.6)	0.531 (0.523–0.539)
Q4 (6.1–9.6)	228	78.3 (78.1–78.6)	0.540 (0.531–0.548)
		P for trend = 0.93	*P* for trend = 0.73
GA : HbA$_{1c}$ ratio			
Q1 (1.89–2.53)	246	78.5 (78.3–78.8)	0.539 (0.532–0.547)
Q2 (2.53–2.69)	247	78.7 (78.5–78.9)	0.542 (0.535–0.549)
Q3 (2.70–2.89)	248	78.3 (78.1–78.5)	0.533 (0.526–0.540)
Q4 (2.89–4.45)	246	78.0 (77.7–78.2)**	0.527 (0.519–0.534)
		P for trend < 0.001	*P* for trend = 0.008

CI, confidence interval; GA, glycated albumin; GA : HbA$_{1c}$ ratio, glycated albumin : hemoglobin A$_{1c}$ ratio; HbA$_{1c}$, hemoglobin A$_{1c}$; HV, hippocampal volume; TBV, total brain volume.
*$P < 0.05$
**$P < 0.01$ versus quartile 1 (Q1) of each glycemic measure.
[†]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits and regular exercise.

significantly associated with developing dementia, especially AD[11]. Clinical studies have shown that the GA : HbA$_{1c}$ ratio is more closely associated with glycemic variability than either GA or HbA$_{1c}$ alone[13], suggesting that brain atrophy might be preceded by not only chronic hyperglycemia, such as that in diabetes mellitus, but also glycemic variability. Acute hyperglycemia or postprandial hyperglycemia are reported to increase the production of oxidative stress more than chronic hyperglycemia[21,22]. Therefore, a possible mechanism of the association between higher serum GA levels and the GA : HbA$_{1c}$ ratio levels and global brain and hippocampus atrophy might involve an increase in oxidative stress, which is known to cause both neurodegeneration and vascular damage[23]. This possible mechanism that oxidative stress underlies the association with global brain and hippocampus atrophy also supports our previous clinical findings that higher GA : HbA$_{1c}$ ratio levels were associated significantly with developing dementia[11]. Another possible mechanism is microvascular ischemic damage in the brain caused by glucose variablity[24]. Chronic brain hypoxia causes microglia activation, phosphorylation of tau and cell death, any one of which could lead to atrophy of the brain, including the hippocampus[25].

Intriguingly, the present study found that the volumes of the total brain and hippocampus tended to decrease with higher serum GA levels and the GA : HbA$_{1c}$ ratio levels in both participants with and without diabetes mellitus, without any heterogeneities in the association between the subgroups of diabetes status, suggesting that the present findings might not simply reflect the association of the severity of diabetic states with brain atrophy. As acute hyperglycemia and glycemic variability are reported to cause an increment of oxidative stress even in non-diabetic individuals[22,26], acute hyperglycemia and glycemic variability might progress to brain atrophy irrespective of diabetes status. These associations should be further investigated in large-scale studies to clarify the underlying mechanisms.

Several limitations of the present study should be addressed. First, as the present findings were derived from cross-sectional data, estimation of a causal association between each glycemic measure and brain atrophy was difficult. Second, there was a possibility of a selection bias caused by the exclusion of individuals from the present study ($n = 628$). Individuals who were excluded from the present study were more likely to be female and older, and had a greater prevalence of dementia than those included. This might result in an underestimation of the present findings. Third, the generalizability of the present findings to other ethnicities, especially to Western populations, might be limited due to the quite different lifestyles and genetic backgrounds.

Table 5 | Multivariable-adjusted mean values of the brain volume : intracranial volume ratios and hippocampal volume : intracranial volume ratios according to quartiles of each glycemic measure in the subgroups of diabetes status

	No. participants	Multivariable-adjusted mean values (95% CI) of the TBV : ICV ratio (%)[†] (an indicator of global brain atrophy)	P for heterogeneity	Multivariable-adjusted mean values (95% CI) of the HV : ICV ratio (%)[†] (an indicator of hippocampal atrophy)	P for heterogeneity
GA (%)					
Diabetes mellitus (−)					
Q1 (10.2–14.3)	299	78.2 (78.0–78.5)		0.529 (0.521–0.536)	
Q2 (14.4–15.6)	289	78.1 (77.9–78.3)		0.530 (0.523–0.538)	
Q3 (15.7–17.1)	267	78.3 (78.0–78.5)		0.527 (0.519–0.535)	
Q4 (17.2–40.6)	127	77.7 (77.3–78.0)*		0.510 (0.499–0.522)*	
		P for trend = 0.07	0.25	P for trend = 0.042	0.69
Diabetes mellitus (+)					
Q1 (10.2–14.3)	22	77.3 (76.5–78.1)		0.491 (0.465–0.518)	
Q2 (14.4–15.6)	37	78.1 (77.5–78.8)		0.522 (0.502–0.543)	
Q3 (15.7–17.1)	50	77.9 (77.3–78.4)		0.516 (0.499–0.533)	
Q4 (17.2–40.6)	187	77.2 (76.9–77.4)		0.502 (0.493–0.511)	
		P for trend = 0.02		P for trend = 0.50	
HbA1c (%)					
Diabetes mellitus (−)					
Q1 (4.4–5.3)	277	78.0 (77.8–78.2)		0.524 (0.517–0.532)	
Q2 (5.4–5.7)	393	78.3 (78.1–78.5)		0.528 (0.522–0.534)	
Q3 (5.8–6.1)	223	78.1 (77.9–78.3)		0.525 (0.517–0.534)	
Q4 (6.2–13.4)	89	77.8 (77.4–78.2)		0.527 (0.513–0.540)	
		P for trend = 0.62	0.73	P for trend = 0.83	0.92
Diabetes mellitus (+)					
Q1 (4.4–5.3)	8	78.1 (76.8–79.5)		0.517 (0.473–0.560)	
Q2 (5.4–5.7)	26	77.2 (76.4–77.9)		0.500 (0.476–0.524)	
Q3 (5.8–6.1)	53	77.3 (76.8–77.9)		0.505 (0.488–0.522)	
Q4 (6.2–13.4)	209	77.4 (77.2–77.7)		0.507 (0.485–0.515)	
		P for trend = 0.89		P for trend = 0.84	
GA : HbA1c ratio					
Diabetes mellitus (−)					
Q1 (1.89–2.55)	255	78.3 (78.1–78.5)		0.529 (0.521–0.537)	
Q2 (2.55–2.72)	260	78.3 (78.1–78.5)		0.537 (0.529–0.545)	
Q3 (2.72–2.93)	252	78.2 (77.9–78.4)		0.523 (0.515–0.531)	
Q4 (2.93–4.44)	215	77.7 (77.4–77.9)**		0.514 (0.505–0.522)	
		P for trend 0.001	0.29	P for trend = 0.004	0.61
Diabetes mellitus (+)					
Q1 (1.89–2.55)	63	77.5 (77.0–78.0)		0.511 (0.494–0.527)	
Q2 (2.55–2.72)	60	78.3 (77.8–78.8)		0.512 (0.497–0.529)	
Q3 (2.72–2.93)	69	77.2 (76.8–77.7)		0.509 (0.493–0.523)	
Q4 (2.93–4.44)	104	76.9 (76.6–77.3)		0.498 (0.486–0.511)	
		P for trend 0.001		P for trend = 0.039	

CI, confidence interval; GA, glycated albumin; GA : HbA1c ratio, glycated albumin : hemoglobin A1c ratio; HbA1c, hemoglobin A1c; HV, hippocampal volume; TBV, total brain volume.
*$P < 0.05$
**$P < 0.01$ vs quartile 1 of each glycemic measure.
[†]The values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive medication, serum total cholesterol, electrocardiogram abnormalities, body mass index, smoking habits, alcohol drinking habits and regular exercise.

In conclusion, the present data showed that increased serum GA levels and the GA : HbA1c ratio levels are significantly associated with atrophy of the global brain and hippocampus in a general elderly population, irrespective of the presence or absence of diabetes mellitus. Our findings suggest that postprandial hyperglycemia or glycemic variability might be closely associated with the risk of hippocampus atrophy. Further clinical and basic research is required to verify the findings from the present study.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Age- and sex-adjusted baseline characteristics of the total study population and participants according to quartile of hemoglobin A_{1c} in 2012.

Table S2 | Age- and sex-adjusted baseline clinical characteristics of the total study population and participants according to quartile of the glycated albumin : hemoglobin A_{1c} ratio levels in 2012.