Published in final edited form as:

J Nutr Health Aging. 2009 February ; 13(2): 117–120.

Glycemic index and glycemic load are not associated with brain lesions in the elderly†

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Abstract

Objective—The goal of this study was to determine if brain lesion volume was correlated with dietary glycemic index and glycemic load in elderly individuals

Design and Setting—This cross-sectional study was performed at an academic medical center as part of a clinical study of late-life depression

Participants—Subjects (n=137) were age 60 or over, and were participating as non-depressed comparison subjects.

Measurements—Food intake was assessed using the Block 1998 food frequency questionnaire. Glycemic index and glycemic load measures were derived from reported food intake. Brain lesion volumes were calculated from magnetic resonance imaging (MRI).

Results—No significant associations were found between glycemic index or glycemic load, and brain lesion volume.

Conclusion—Dietary glycemic measures may be unrelated to brain lesions or may be related to brain lesions only in individuals with impaired glycemic control or other vascular risk factors. Further studies are needed to confirm this finding and to determine if glycemic control moderates this association.

Keywords

glycemic index; glycemic load; brain; aging; human

Introduction

Brain lesions commonly seen on magnetic resonance images of older adults represent damage to gray and white matter and have been shown to be deleterious by causing impaired cognition, gait, and balance (1,2). White matter lesions are associated with an increased risk of

†This work was presented at the American Association for Geriatric Psychiatry 2008 Annual Meeting, Orlando, FL

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cerebrovascular complications such as stroke (3). Brain lesions may be an indicator or contributor to late life depression as described by the vascular depression hypothesis (4,5).

Post mortem studies have found that large (non-punctate) brain lesions in both depressed and non-depressed adults are ischemic (6). One source of ischemic damage may be elevated glucose levels in the brain. The brain is the most metabolically active organ in the body and uses glucose, almost exclusively, as its energy source. This makes the regulation of glucose levels essential to brain function (7). It has been found that in rats there is no protective mechanism to limit the amount of glucose going into the brain, meaning that brain tissue may suffer the same damage as peripheral tissue when glucose levels are elevated (8). In addition to direct neuronal effects, elevated glucose may promote lesions via a vascular mechanism. Dietary glycemic measures have been associated with vascular risk (9) and it is well-established that vascular risk factors are related cross-sectionally and longitudinally to brain lesions (10–13).

Two ways of measuring average glucose levels from dietary intake are glycemic index (GI) and glycemic load (GL), which rank carbohydrates based upon their effects on serum glucose levels. GI reflects the rate and extent of the rise and fall of blood glucose after consumption. GL of a food takes into account the portion size as well as the glycemic index, accounting for both the quantity and quality of the carbohydrates consumed.

The objective of this cross-sectional analysis was to determine if the volume of brain lesions was correlated with dietary glycemic index and glycemic load in elderly individuals. We hypothesized a positive association between both glycemic index and glycemic load, and brain lesion volumes.

Materials and Methods

Study Design and Sample

This cross-sectional project was part of a longitudinal clinical study of depression in older adults, which began at Duke University Medical Center in 1994. This larger study contains two cohorts; patients diagnosed with major depression using DSM-IV criteria (14) for major depression, and a comparison cohort. The current analysis only includes subjects in the comparison group (no report of current or prior depression). Enrollment was restricted to those 60 years or older, and those who could speak and write English. Exclusion criteria included significant cognitive impairment, as indicated by their Mini-Mental State Examination (MMSE) (15) score of less than 26 (out of 30). Subjects were also excluded if they had metal in the body which was a contraindication for MRI. Subjects that met the eligibility criteria were interviewed about medical comorbidities and completed a Block Food Frequency Questionnaire annually. Subjects also received an MRI every two years.

Dietary Assessment

The nutrition protocol for this project has been described previously (16). In short, eligible patients were given a 1998 Block food frequency questionnaire (FFQ) to complete and return. This questionnaire estimates the person's dietary intake over the previous year. The 1998 Block FFQ has been validated and correlated with other nutritional assessment instruments and shows moderate correlation to them (17). The questionnaire asks the subject to estimate the frequency and typical serving size of listed food items. Glycemic index (GI) and glycemic load (GL) were calculated from the Block FFQ as described by Hu (18). GI values for FFQ food items were based upon data provided by the University of North Carolina Department of Nutrition to Block Dietary Data Systems and were derived in part from published data (19). The GI values utilized the glucose reference scale. GL was calculated by multiplying the GI of each food by its nonfiber carbohydrate content, reported frequency of consumption, and reported portion size,

and then the values for all foods were summed. Dietary GI was then calculated by dividing GL by the total amount of nonfiber carbohydrate consumed. As a result, GL represents both the quantity and the quality of carbohydrate intake, while GI represents the overall quality of carbohydrate in the diet.

Magnetic Resonance Imaging (MRI)

The imaging procedures used were developed by the Neuropsychiatric Imaging Research Laboratory (NIRL) as a semi-automated method to quantify gray and white matter lesions and have been described previously (20). Subjects were imaged with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head radiofrequency coil.

Quantitative measurements were made using a dual-echo fast spin echo acquisition. The images were acquired in two separate acquisitions with a 3 mm gap so that the resulting data consisted of contiguous sections. The images were then transferred to the NIRL for processing. The NIRL processing method is a supervised, semi-automated method that uses multiple MR contrasts to identify different tissue classifications; such as gray matter, white matter, cerebrospinal fluid, lesions, and background. Gray and white matter lesion areas were selected based upon a set of rules that allow trained analysts to select lesion regions reliably. Total lesion volumes were comprised of both gray matter lesions and white matter lesions. Inter-rater reliability for the two raters demonstrated intraclass correlation coefficients of 0.99 for both white and gray matter lesions.

Analyses

All statistical analyses were done using JMP software (Cary, NC). Statistical analyses used lesion volumes from the MRI closest to the time of the nutrition assessment. This meant that for most subjects the MRI and nutrition assessments were separated by less than one year. In order to minimize the time interval either assessment could precede the other. The closest annual comorbidity assessment was used. Bivariate comparisons were made between individuals with acceptable FFQs (responders) and those who did not return or returned an unacceptable questionnaire (nonresponders) to assess the potential for responder bias. Variables used included age, sex, heart trouble (y/n), hypertension (y/n), diabetes (y/n), and lesion volume.

Simple regression models were used to examine lesion volume by glycemic index and glycemic load. A backwards stepwise regression with a probability threshold of 0.20 was used to determine covariates for the multiple regression models. Covariates examined this way included age, sex, heart trouble, hypertension, diabetes, BMI, alcohol intake, and total kilocalories. The models were constructed with the natural log of lesion volume as the dependent variable because this variable tends to be more normally distributed than unadjusted lesion volume. In separate models, GI and GL were entered as independent variables along with the covariates selected through the stepwise regression.

Results

A total of 150 subjects were given a nutrition assessment; 137 successfully completed and returned one. There were no significant differences between responders and nonresponders in terms of age, sex, hypertension, heart trouble or lesion volume, but there was a trend for diabetes ($p=0.056$) to be more common among nonresponders.

Table 1 presents sample characteristics. Bivariate analysis of lesion volume by glycemic index and glycemic load were not significant ($p=0.65$ and $p=0.13$, respectively). A backwards

stepwise regression identified age, hypertension, diabetes, and body mass index (BMI) as covariates to include in the multivariable models (at $p < 0.2$). Two separate regression models (glycemic index and glycemic load) were constructed with these covariates. As shown in Table 2, neither glycemic index nor glycemic load were significant predictors of lesion volume in multivariable models. In both models, age and hypertension were positively associated with lesion volume.

Discussion

This preliminary investigation found no significant associations between dietary glycemic index or dietary glycemic load and the volume of brain lesions in elderly subjects, even after controlling for potential confounders. Our findings may indicate that dietary glycemic index and load are unrelated to brain lesions in the absence of poor glycemic control or diabetes. Previous research has shown that diabetes is associated with increases in lesion volume in a study sample that overlaps with this study's group (21), indicating that glycemic control or vascular risk may be important factors in the etiology of lesions. Poor glycemic control has also been shown to be associated with cognitive impairment in diabetic individuals (22). Since there were no measures of glycemic control available (such as HbA_{1C}), an analysis of this factor was not possible. Of note, there was a trend for diabetic subjects to be less likely to complete the nutrition assessment.

Another possible explanation for our findings is that the subjects in our study had diets which tended to exhibit low or moderate glycemic measures, and may have been too healthy to demonstrate the effects that were hypothesized. Our sample mean values for GI and GL (53.1 and 105.4, respectively) are similar but slightly lower than those found in a study which utilized identical methodology for calculating GI and GL (54.5 and 113.0)(18). Prior studies which have reported substantially higher mean values, such as (9), generally used white bread as the reference scale and included fiber in their carbohydrate calculations. GI values from the white bread scale are 1.4 times higher than those from glucose scale (23). In addition to methodological differences, the age of our sample may have led to lower GI and GL values.

A third possibility to explain our negative findings relates to the use of cross-sectional data. Brain lesions develop over many years and, most likely, decades. A cross-sectional analysis may not identify dietary factors which are important to etiology given such a long-term process, particularly if subjects' diets have not been stable. Given that diet-associated conditions, including hypertension and diabetes, are related longitudinally to brain lesions (13,21), it is reasonable to suspect that dietary glycemic measures may be as well. Longitudinal studies are needed to examine the relationship of glycemic index and glycemic load to the development of brain lesions.

There are several limitations to this study, including the modest sample size. The nutrition assessment used may not have adequately detected differences in dietary glycemic measures across subjects. In addition, a food frequency questionnaire does not provide the meal context of food intake which is important in determining the glycemic response. This study did not include any medical measurements to confirm self report of comorbid conditions. Standard lab tests, including those to measure serum glucose control, were not performed. Finally, we acknowledge that a cross-sectional analysis cannot detect or refute a causal association between dietary factors and brain lesions.

In conclusion, this study found no associations between dietary glycemic index or glycemic load, and brain lesions in the elderly. These findings may indicate that dietary glycemic measures are unrelated to brain lesions, or are related to brain lesions only in individuals who have impaired glycemic control or other vascular risk factors. Further studies are needed to

confirm these findings. A longitudinal study is needed to evaluate the possible causal association of glycemic index and glycemic load with brain lesions, particularly in individuals with impaired glycemic control.

Acknowledgments

The authors wish to thank the participants of this research project for their dedication to furthering knowledge of aging. The authors also acknowledge the following individuals from Duke University Medical Center for their assistance with subject recruitment and assessment: Ms. Denise F. Messer, Ms. Cortnee W. Pierce, and Ms. Carrie B. Dombeck. The authors also thank Ms. Messer for the lesion volume measurements. Finally, the authors acknowledge the following individuals from Campbell University for their guidance on research and statistical methodology: Dr. Brenda D. Jamerson and Mr. Robert J. Schmid.

This project was funded by the following National Institute of Mental Health grants: MH40159, MH54846, MH60451, and MH70027.

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Table 1Sample characteristics¹

Characteristic	Mean (+/- SD)
Age (years)	71.39 (+/- 5.76)
Sex (% Female)	70.8 % (n=97)
Heart Disease (% yes)	12.4% (n=17)
Hypertension (% yes)	26.28% (n=36)
Diabetes (% yes)	5.84% (n=8)
BMI (kg/m ²) ²	25.39 (+/- 4.43)
Lesion Volume (mL) ³	5.47 (+/- 7.43)
Log Lesion Volume ^{3,4}	1.32 (+/- 0.77)
Glycemic index	53.10 (+/- 3.72)
Glycemic load	105.42 (+/- 38.71)
Total energy (kcal/day)	1670.11(+/- 647.81)
Alcohol (g/day)	9.22 (+/- 11.85)

¹ n=137 except where noted² n = 135³ n = 136⁴ natural log transformation of lesion volume

Table 2Glycemic models for brain lesion volume¹

	Glycemic Index			Glycemic Load		
	Estimate (SE)	t ratio	p value	Estimate (SE)	t ratio	p value
Glycemic measure	-0.016827 (0.01555)	-1.08	0.2812	0.0014231 (0.001489)	0.96	0.3410
Age	0.0545216 (0.010036)	5.43	<0.0001	0.0535132 (0.010116)	5.29	<0.0001
Hypertension	0.203429 (0.067521)	3.01	0.0031	0.193839 (0.067179)	2.89	0.0046
Diabetes	0.219348 (0.133975)	1.64	0.1040	0.218983 (0.134136)	1.63	0.1050
Body Mass Index	-0.025475 (0.013573)	-1.88	0.0628	-0.025322 (0.013596)	-1.86	0.0648

¹Two separate multivariable linear regression models for lesion volume