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May, 2008

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Applied nutritional investigation

Association between dietary glycemic index, glycemic load, and high-sensitivity C-reactive protein

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Manuscript received August 31, 2007; accepted December 27, 2007.

Abstract

Objective: This study examined the relation between quality of dietary carbohydrate intake, as measured by glycemic index (GI) and glycemic load (GL), and serum high-sensitivity C-reactive protein (hs-CRP) levels.

Methods: During a 1-y observational study, data were collected at baseline and at each quarter thereafter. GI and GL were calculated from multiple 24-h dietary recalls (24HRs), 3 randomly selected 24HRs at every quarter, with up to 15 24HRs per participant. The hs-CRP was measured in blood samples collected at baseline and each of the four quarterly measurement points. Multi-variable linear mixed models were used to examine the cross-sectional and longitudinal associations of GI, GL, and hs-CRP.

Results: Among 582 adult men and women with at least two measurements of diet and hs-CRP, average daily GI score (white bread = 100) was 85 and average GL was 198, and average hs-CRP was 1.84 mg/L. Overall, there was no association between GI or GL and hs-CRP. Subgroup analyses revealed an inverse association between GL and hs-CRP among obese individuals (body mass index ≥ 30 kg/m²).

Conclusion: Quality of dietary carbohydrates does not appear to be associated with serum hs-CRP levels. Among obese individuals, higher dietary GL appears to be related to lower hs-CRP levels. Due to the limited number of studies on this topic and their conflicting results, further investigation is warranted. © 2008 Elsevier Inc. All rights reserved.

Keywords:

Glycemic index; Glycemic load; High-sensitivity C-reactive protein; Diet; Carbohydrate; Cardiovascular diseases

Introduction

Cardiovascular disease and diabetes are two leading causes of morbidity and mortality in the United States and worldwide. According to the Centers of Disease Control and Prevention in 2005, it was estimated that 25.6 million non-

institutionalized Americans have some form of heart disease and more than 20 million have diabetes [1,2]. Among those with diabetes, 65% will die from heart disease or stroke [3].

High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, has been recognized as a risk factor for future cardiac events [4–12]. Although very high hs-CRP levels are likely the response to acute inflammation, slightly elevated levels are indicative of chronic inflammation present in such diseases as cardiovascular disease and diabetes. High-sensitivity CRP values are useful in determining disease progression or the effectiveness of treatments, and because many of these diseases are modifiable by lifestyle, tracking hs-CRP can be quite informative. It is im-

This work was supported by grants R01-HL52745 and 1 R21 HL074895-01 from the National Heart, Lung and Blood Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung and Blood Institute.

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portant to identify which lifestyle factors have the greatest impact because lifestyle factors may provide an important intervention opportunity to beneficially influence hs-CRP levels to reduce the risk of cardiovascular disease and diabetes.

Diet is one of the many modifiable risk factors for cardiovascular disease and diabetes. There is increasing evidence that quantity and quality of carbohydrate can modify disease risk [13,14]. One method to evaluate the quality of carbohydrate is the glycemic index (GI), a measurement of the blood glucose response to 50 g of carbohydrate from a particular food [15]. Glycemic load (GL) is the GI of a food multiplied by its carbohydrate content in grams (quality by quantity). The present study examined the relationship among GI, GL, and hs-CRP, a marker of inflammation, in a population of healthy adults.

Materials and methods

Data for this study was obtained from a 1-y prospective observational study designed to examine seasonal variations in blood lipid levels in a disease-free population in central Massachusetts [16]. The study began in 1996 with 641 eligible participants enrolled at baseline. Eligibility requirements included an age from 20 to 70 y, literacy in English, and not planning to leave the area within the next year [16]. Exclusion criteria included 1) using or planning to use lipid-lowering drugs, 2) following or planning to follow a weight control diet, 3) a history of cancer diagnosis (excluding non-melanoma) within the past 5 y, 4) a secondary cause of hyperlipidemia, or 5) a condition of psychiatric illness that would limit participation [16]. Data collection took place at baseline and quarterly (every 13 wk) thereafter for a total of five visits. Each visit included measurements of anthropometrics, blood, diet, physical activity, and psychosocial variables.

hs-CRP assessment

Participants were evaluated quarterly for a total of five visits over the 1-y follow-up. At each of their five clinic visits, participants provided blood samples. hs-CRP levels were measured at Children's Hospital in Boston at Dr. Nader Rifai's laboratory using latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Wilmington, DE, USA).

Dietary assessment

Trained registered dietitians assessed diet by telephone-based 24-h recalls (24HRs) using the Minnesota Nutrition Data System (NDS DOS, versions 2.6, 2.7, and 2.8) developed by the Nutrition Coordinating Center at the University of Minnesota. Three telephone interviews occurred at baseline and at four additional data collection periods, within a

window of 2 wk before 3 wk after the participants' quarterly clinic visits. Therefore, up to 15 d of dietary information was available per participant including weekdays and weekends, allowing for a comprehensive measurement of usual carbohydrate intake [17].

Methods of GI resolution

The quality of carbohydrate can be determined by the GI, which ranks foods according to their effect on blood glucose [15]. Although not all carbohydrate-containing foods have been tested for their GI, the GIs of more than 1500 foods has been determined and are available in the International Table of Glycemic Index and Glycemic Load Values, with additional foods continually added to an online database [15,18,19]. We assigned GI and GL values to foods reported on the 24HR using methods described previously [20]. Briefly, carbohydrate-containing foods derived from 24HRs were matched to the International Table of Glycemic Index and Glycemic Load Values. Mixed foods were disaggregated into individual ingredients. For specific foods not found in the table, we based estimates on similar foods according to physical and chemical factors that determine GI.

The GL was calculated to take into account the amount of carbohydrate that was consumed. GL equals the GI of a food times the amount of carbohydrate eaten divided by 100. For example, let us consider $\frac{1}{2}$ cup (37 g) of potatoes. The GI of potatoes is 102 (white bread as reference = 100). Using the formula, the GL for this portion is $102 \times 37\text{g} / 100 = 38$.

Covariate assessment

A number of factors have consistently been associated with hs-CRP [21,22]. We collected data on body mass index (BMI), smoking, infection status, physical activity, total energy, total cholesterol, age, and gender and included these variables in analyses.

Statistical analysis

Means and standard deviations were used to describe characteristics of participants and their hs-CRP, GI, and GL values. Scatterplot and smoothing curves (i.e., Loess curves) were used to explore graphically the relation of hs-CRP with GL and with GI.

To make use of the rich dataset we used a mixed model that examines the cross-sectional (between-subjects) association of CRP with GL and the longitudinal association (within-subject). We used all data in the analyses. The dependent variable for this analysis was CRP. The independent variable was GI or GL, with subject treated as a random effect. Specifically, the cross-sectional effects for a variable (GI or GL) were assessed by including a variable representing the subject mean; the longitudinal effects were assessed by including a variable representing the deviation

Table 1
Selected characteristics of the study population

Variable	
Age (y), mean $\pm$ SD	48 $\pm$ 12
Body mass index (kg/m ²), mean $\pm$ SD	27.4 $\pm$ 5.4
Race (%)	
White	86
Hispanic white	8.1
Asian	1.6
Black	2.7
Gender (%)	
Male	52
Female	48

from the subject mean from each quarter. Thus, the cross-sectional analysis examined the association between the average CRP and average GI or GL in subjects at each quarter. The longitudinal analysis compared individual changes in CRP and GI or GL between quarters. The cross-sectional and longitudinal effects were included in the same model. This method was used in our previous analyses of the association between dietary fiber and CRP [23]. If a covariate changed the exposure coefficient by $\geq 15\%$ and was statistically significant at $P = 0.15$, it was included in the final model. When calorie or fat intake was included in the model, it was not significant; the regression coefficient of hs-CRP with GI or GL was not changed, so neither calories nor fat intake was included in the final model. When we included season of year as a covariate, results were not changed, so it was not included in the final model. We assessed for effect modification by BMI category and gender.

Results

A total of 641 participants with 2795 observations were available for analysis. Because our goal was to examine the longitudinal effect of dietary GI or GL on hs-CRP, participants with data available for fewer than two time points were excluded ($n = 49$ observations). An additional 617 observations were excluded because dietary measurements

Table 2
Mean, median, and range of average hs-CRP, average dietary glycemic index, and average dietary glycemic load (N = 582)

Characteristic	Mean	Median	Minimum	Maximum
hs-CRP (mg/L)	1.8	1.2	0.03	9.6
Log hs-CRP	0.06	0.08	3.73	2.27
Glycemic index	84.9	85.1	49.1	101.2
Glycemic load	198.0	184.5	45.4	488.2

hs-CRP, high-sensitivity C-reactive protein

Fig. 1. Scatterplot between average CRP and average GI. CRP, C-reactive protein; GI, glycemic index.

and hs-CRP were not available at the same quarter. We excluded 65 observations where hs-CRP was >10 mg/L because such elevated levels are likely to be caused by an acute infection or underlying medical problem not related to diet [24]. We also excluded one observation with an extreme outlier, GL = 1085. Therefore a total of 582 participants and 2063 observations remained for analysis. The hs-CRP values were highly skewed; therefore, the data were analyzed using log-transformed values for hs-CRP.

Table 1 presents participant characteristics. Participants were predominantly white (86%), with an average age of 48 y and approximately equal distributions of men and women. Average BMI was 27.4 kg/m², and 64% of participants were overweight or obese. Average and median hs-CRP values were 1.8 and 1.2 mg/L, respectively (Table 2). For this study GI is reported using white bread as the

Fig. 2. Scatterplot between average CRP and average GL. CRP, C-reactive protein; GL, glycemic load.

Table 3

Regression coefficients predicting log high-sensitivity C-reactive protein from linear mixed models

	Cross-sectional effect			Longitudinal effect		
	Regression coefficient	Standard error	P	Regression coefficient	Standard error	P
Glycemic index	0.008781	0.007439	0.2380	−0.00237	0.002743	0.3881
Glycemic load	−0.00194	0.000622	0.0019	−0.00005	0.000307	0.8689

reference, where white bread equals a GI score of 100. The average daily dietary GI score was 85, considered to be in the intermediate range for GI, with values ranging from 49 to 101 (Table 2). The average GL value was 198, considered to be in the high range for GL, with a minimum of 45 and a maximum value of 488 (Table 2). All-purpose flour, white sugar, white bread, white rice, and cola beverage were the top contributors to GL; these five foods alone accounted for a cumulative GL of 52. The graphs shown in Figures 1 and 2 suggest a slightly inverse relation between average GI or GL and hs-CRP levels.

We used a multivariable linear mixed model to examine the cross-sectional and longitudinal relations between log hs-CRP and GI or GL (Table 3). We found no association between GI and log hs-CRP in the cross-sectional analysis (regression coefficient [β] = 0.009, P = 0.24) or longitudinal analysis (β = −0.002, P = 0.39). However, we did observe the suggestion of an inverse association between GL and log hs-CRP in the cross-sectional analyses, but no association in the longitudinal analyses. Specifically, the coefficient for the cross-sectional effect of GL (β = −0.00194) was suggestive of an inverse relation with log hs-CRP (P = 0.002).

After statistically adjusting for BMI, smoking status, age, and infection status, the cross-sectional findings for GL and hs-CRP were attenuated and no longer statistically significant (P = 0.07). The longitudinal association was attenuated to −0.00012 (P = 0.72; Table 4). None of the variables produced notable changes in the strength or direction of the estimate.

We then stratified the analysis by BMI category and gender. Stratification by gender did not yield results of statistical significance (for cross-sectional results for GL: men β = −0.0055, P = 0.43, women β = −0.00141, P = 0.18). When stratified by BMI, we found that mean GL was a significant predictor of hs-CRP in the cross-sectional analysis only in obese individuals (β = −0.00185, P = 0.04; Table 5).

To further explore how BMI modified the relationship between dietary GL and hs-CRP, we fitted a linear model to clarify the interaction, without including any of the covariates. We then converted the results to the natural scale and plotted the predicted hs-CRP versus average GL (Fig. 3). An inverse relation was seen across all strata, with individuals in the highest BMI category having the greatest reduction of hs-CRP. However, as GL increased, there was no statistical difference between the slope for obese and the slope of the other BMI categories (P > 0.05).

Discussion

In this 1-y observational study, we did not observe a positive association among dietary GI, GL, and hs-CRP. Although the literature reporting the relationship between GI or GL and hs-CRP is limited, the results from this study are not in agreement with a previous study that reported a significant positive association between dietary GL and hs-CRP [25].

One explanation for the difference in findings may be due to differences in the study populations. Among 244 middle-aged female participants in the Women's Health Study, Liu et al. reported that dietary GL was positively associated with hs-CRP [25]. In that study, the average GI and GL values were 75 and 166, respectively, considered to be low GI and intermediate GL values compared with an intermediate GI of 85 and a high GL of 197 found in this study in men and women. This suggests that, as a whole, the dietary carbohydrate quality of participants in the present study was poorer and may have limited our ability to detect an association between GI or GL and hs-CRP. In addition, average hs-CRP values were considerably lower in the present study than in the study by Liu et al. [25]. Differences in age, BMI, and smoking status may contribute to the differences observed between the two studies. However, the two studies

Table 4

Regression coefficients predicting log high-sensitivity C-reactive protein from multivariable linear mixed models

	Cross-sectional effect			Longitudinal effect		
	Regression coefficient	SE	P	Regression coefficient	SE	P
Glycemic index*	0.002671	0.006269	0.6702	−0.00396	0.002832	0.1627
Glycemic load†	−0.00096	0.000528	0.0683	−0.00012	0.000331	0.7197

* Multivariate model includes body mass index, smoking status, and age.

† Multivariate model includes body mass index, smoking status, age, and infection status.

Table 5

Regression coefficients predicting log high-sensitivity C-reactive protein from multivariable linear mixed models for glycemic load stratified by BMI categories*

BMI category(kg/m ²)	Cross-sectional within participant			Longitudinal between participants		
	Regression coefficient	SE	P	Regression coefficient	SE	P
Normal (18.5–24.9)	−0.00100	0.000888	0.2595	−0.00070	0.000658	0.2907
Overweight (25.0–29.9)	−0.00063	0.000929	0.4966	−0.00022	0.000472	0.6449
Obese (≥30)	−0.00185	0.000915	0.0440	0.000710	0.000484	0.1433

BMI, body mass index

* Multivariate model includes BMI, smoking status, age, and infection status.

controlled for age, BMI, and smoking in the analysis, although residual confounding by these factors is still possible.

In a recent publication examining the association of GI, GL, and cereal fiber intake with risk of type 2 diabetes in a cohort of United States black women, risk of diabetes was not statistically significantly associated with GL [26]. The investigators explained that it can be difficult to study GL because of its high correlation with total carbohydrate intake, because cereal fiber intake increased with quintiles of GL, whereas whole grains (a major source of cereal fiber) contributed to GL. Previously, dietary fiber has been associated with lower CRP in this population [23].

There are a few limitations and strengths to this study. First, the cross-sectional study design does not allow for assessment of a temporal relation because carbohydrate quality and hs-CRP were measured at the same time points. However, by using multiple prospective measurements in the longitudinal analysis, we were able to determine how hs-CRP changes as GI or GL changes, which provides a better understanding of the relation between dietary carbohydrate quality and hs-CRP.

Second, there may be potential confounders for which we were unable to control. It is possible that there are other unknown factors that influence hs-CRP and may be associ-

ated with GI and GL. The direction of the association would be unknown so the bias could be an over- or underestimation of the true.

A strength of this study is the detailed dietary assessment. We used a comprehensive dietary assessment, collecting dietary information from up to 15 24HRs. The recalls allowed us to collect detailed information on each food consumed. The GI of individual foods is very specific and can vary within food types, e.g., between types of breads having whole grain characteristics, differences in fiber, or with added influencing GI factors such as butter. Having such detailed information allowed for a more accurate calculation of GI. However, this study relied on published GI values and estimates derived from the 24HRs and, like all studies of GI, a methodology to estimate the GI of untested foods.

Conclusion

In this prospective observational study, we found no association between dietary GI or GL and hs-CRP. This is a surprising finding, given a previous study's positive findings and the observation by our group that fiber, in agreement with other studies, was inversely associated with hs-CRP in our study population [23]. This is interesting because fiber is a very strong factor in the determination of GI, and one would expect that GI would also be associated. Due to the limited number of studies on this topic and the conflicting results, further investigation is warranted.

Acknowledgments

The authors thank Laura Robidoux and Priscilla Cirillo for their assistance with study recruitment and data collection; Kelly Scribner for coordination of the 24HRs; and dietitians who conducted the 24HRs: Susan Nelson, Christine Singelton, Pat Jeans, Karen Lafayette, Deborah Lamb, Stephanie Olson, and Eileen Capstraw; Dr. Nader Rifai for his assistance with hs-CRP measurements; and Dr. Eric Rawson for his contribution in the development of the hs-CRP project. They also thank Drs. Charles Matthews and

Fig. 3. Predicted high-sensitivity CRP versus average glycemic load by body mass indexes <25 kg/m² (diamonds), 25–30 kg/m² (squares), and ≥30 kg/m² (triangles). CRP, C-reactive protein.

Patty Freedson for their contribution on physical activity measurements.

References

- [1] National Center for Health Statistics, Fast Stats. Heart Disease. www.cdc.gov/nchs/faststats/heart.htm. Accessed April 15, 2007.
- [2] National Estimates on Diabetes, CDC National Center for Chronic Disease Prevention and Health Promotion, Diabetes Public Health Resource. www.cdc.gov/diabetes/pubs/estimates05.htm. Accessed April 15, 2007.
- [3] American Diabetes Association, Diabetes: Heart Disease and Stroke. www.diabetes.org/diabetes-heart-disease-stroke.jsp. Accessed April 15, 2007.
- [4] Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:731–3.
- [5] Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. *Circulation* 1999;99:237–42.
- [6] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–43.
- [7] Rutter MK, Meigs JBL, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004;110:380–5.
- [8] Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West Scotland Coronary Prevention Study. *Circulation* 2003;108:414–9.
- [9] Laaksonen DE, Niskanen L, Nyyssonen K, Punnonen K, Tuomainen TP, Valkonen VP, et al. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia* 2004;47:1403–10.
- [10] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and the risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327–34.
- [11] Shuhei N, Kiminori Y, Nozomu K, Masamichi O, Nobuoki K. Elevated C-reactive protein is a risk factor for development of type 2 diabetes in Japanese Americans. *Diabetes Care* 2003;26:2745–57.
- [12] Hu F, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of type 2 diabetes in women. *Diabetes* 2004;53:693–700.
- [13] Liu S, Willett W, Stampfer M, Hu F, Franz M, Sampson L, Hennekens CH. A prospective study of dietary glycemic load, carbohydrate intake and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000;71:1455–61.
- [14] Schulze MB, Liu S, Rimm E, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr* 2004;80:348–56.
- [15] Brand-Miller J, Wolever TMS, Foster-Powell KF, Colagiuri S. The new glucose revolution. New York: Marlowe & Company; 2003.
- [16] Merriam PA, Ockene IS, Hebert JR, Rosal MC, Matthews CE. Seasonal variation of blood cholesterol levels: study methodology. *J Biol Rhythms* 1999;14:330–9.
- [17] Willett W. Nutritional epidemiology. New York: Oxford University Press; 1998.
- [18] Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values. *Am J Clin Nutr* 2002;76:5–56.
- [19] The Official Website of the Glycemic Index and GI Database. <http://www.glycemicindex.com>. Accessed April 15, 2007.
- [20] Olendzki BC, Ma Y, Culver AL, Ockene IS, Griffith JA, Hafner AR, Hebert JR. Methodology for adding glycemic index and glycemic load values to 24-hour dietary recall database. *Nutrition* 2006;22:1087–95.
- [21] Aronson D, Bartha P, Zinder O, Kerner A, Shitman E, Markiewicz W, Brook GJ. Association between fasting glucose and C-reactive protein in middle-aged subjects. *Diabet Med* 2003;21:39–44.
- [22] Miller M, Zhan M, Havas S. High attributable risk of elevated C-reactive protein levels to conventional coronary heart disease risk factors. *Arch Intern Med* 2005;165:2063–8.
- [23] Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ III, et al. Association between dietary fiber and serum C-reactive protein. *Am J Clin Nutr* 2006;83:760–6.
- [24] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease applications to clinical and public health practice. A statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511.
- [25] Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high dietary glycemic load and plasma concentrations of high sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr* 2002;75:492–8.
- [26] Krishnan S, Rosenberg L, Singer M, Hu FB, Djousse L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med* 2007;167:2304–9.