Published in final edited form as:

Nutr Res. 2015 January ; 35(1): 7–13. doi:10.1016/j.nutres.2014.10.005.

Consumption of a high glycemic load but not a high glycemic index diet is marginally associated with oxidative stress in young women

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Abstract

Research studies have suggested that chronic consumption of high glycemic index foods may lead to chronically high oxidative stress. This is important because oxidative stress is suspected to be an early event in the etiology of many disease processes. We hypothesized that dietary glycemic index and glycemic load were positively associated with oxidative stress assessed by plasma F₂-isoprostanes in healthy, premenopausal women (BMI = 24.7 ± 4.8 kg/m² and age 25.3 ± 3.5 years, mean ± SD). We measured plasma F₂-isoprostanes in 306 healthy premenopausal women at the baseline visit for the Women In Steady Exercise Research (WISER) study, using gas chromatography-mass spectrometry (GC-MS). Dietary glycemic index and load were calculated from the National Cancer Institute Diet History Questionnaire, and participants were divided into quartiles of dietary glycemic index and of glycemic load. Plasma F₂-isoprostanes were compared across quartile groups of dietary glycemic index and glycemic load using linear regression models. Plasma F₂-isoprostanes (pg/mL) increased with quartile of glycemic load (test for linear trend, p

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= .033), and also increased with quartile of glycemic index in participants with BMI ≥ 25 ($p = .035$) but not in those with BMI < 25 ($p = .924$). After adjustment for BMI, alcohol consumption and total energy intake, both these positive trends remained marginally significant ($p = .123$ for quartiles of glycemic index and $p = .065$ for quartiles of glycemic load).

Keywords

glycemic index; young women; glycemic load; isoprostanes; overweight

1. Introduction

Carbohydrate quality has been suspected to play a key role in the etiology of a number of chronic diseases such as heart disease, diabetes, and cancer [1–3]. An important characteristic of carbohydrate-rich food is its glycemic index (GI), which is an indication of the glucose response after consumption [4]. However, glycemic index does not take into consideration the amount of carbohydrate present in foods, thus the concept of glycemic load (GL) was created [5]. GL represents both qualitative and quantitative measures of a food or diet and can be calculated by multiplying GI for a certain food by the gram amount of non-fiber carbohydrate in one serving of the food. In healthy young adults, GL has been found to be the best predictor of postprandial glycemia and insulinemia compared to GI and amount of carbohydrate alone [6].

Chronic consumption of high glycemic index foods is associated with a hyperglycemic state, which is thought to be associated with a number of diseases, including diabetes, coronary heart disease, and cancer [7–9]. A positive association between dietary glycemic index and load and the risk of type II diabetes and heart disease has been previously found [2, 3, 5, 10–16]. Additionally, cancers of the breast, prostate, colon and gallbladder have been shown to increase in the presence of high glycemic index diets [17–26]. Some studies have found stronger associations among overweight individuals, suggesting that body composition may enhance the association between high glycemic index diets and chronic disease risk [14, 19, 20, 22, 26].

Evidence suggests that oxidative stress is a major underlying pathogenic factor in the aging process and numerous chronic diseases associated with inflammation [27, 28]. Although several markers of lipid peroxidation are available, F_2 -isoprostanes are more commonly used as clinical markers of human diseases to reflect total body oxidative stress levels [29]. Isoprostanes are generated from the free radical attack on the polyunsaturated fatty acid, arachidonic acid. F_2 -isoprostanes circulate in the plasma and are excreted in urine. Quantification of these compounds in plasma and urine is representative of their endogenous production and a reflection of in vivo oxidative stress [30]. In addition, F_2 -isoprostanes are considered to be a long-term measurement of oxidative stress in healthy and diseased subjects because there is no significant daily variation [31].

Chronic consumption of high glycemic index foods has been shown to cause oxidative stress through formation of free radicals that are capable of damaging biological molecules and initiating abnormal cell growth through gene mutation [32–34]. Effects on oxidative stress

are thought to be a mechanism by which consumption of high glycemic index foods may increase risk of chronic inflammation [35, 36] and thus increase risk of diabetes [37] and cardiovascular disease [38]. However, few studies have examined the relationship between glycemic index and load and oxidative stress in humans. Our overall objective was to examine the relationship between oxidative stress and consumption of foods with high glycemic index and glycemic load. We hypothesized that dietary glycemic index and glycemic load would be positively associated with oxidative stress assessed by plasma F₂-isoprostanes. To test our hypothesis, we evaluated baseline measurements in 306 healthy, premenopausal women who participated in the Women in Steady Exercise Research (WISER) study [39].

2. Methods and materials

2.1. Study population

Baseline data collected from subjects enrolled in the Women In Steady Exercise Research (WISER) Study were used for the current analysis. The WISER study investigated the effects of exercise on breast cancer biomarkers in premenopausal women at the University of Minnesota, Twin Cities, between June 2006 and August 2009 [39]. The inclusion criteria were: generally healthy, defined as absence of any chronic disease, premenopausal, age 18–30 years, BMI between 18 and 40 kg/m², sedentary (less than 2 exercise sessions per week), not following any weight loss programs, non-smokers, eumenorrheic and no hormonal contraceptive use for 3 months prior to beginning the study. Total sample size for this analysis was 306 subjects. Written consent was obtained from all study subjects, and the protocol was approved by the University of Minnesota Institutional Review Board.

2.2. Dietary assessment

Dietary assessment for the preceding 12 months was performed using a food frequency questionnaire, the National Cancer Institute's Dietary History Questionnaire (DHQ). The DHQ calculates the mean glycemic load for an individual based on sex- and serving size-derived glycemic load values obtained from a compilation of glycemic index values (using glucose as the reference) published by Foster-Powell and colleagues [40]. This compilation was based on GI values published between 1981 and 2001 and included more than 750 individual food items. Subjects completed the assessment online within one week of the baseline blood draw for the biological analyses. Glycemic index was calculated using the following equation: Glycemic Index = Glycemic Load ÷ Non-Fiber Carbohydrate (grams) [41].

2.3. Laboratory methods

For each subject, a blood sample was collected after an overnight fast in the mid-follicular phase of the menstrual cycle (between menstrual cycle days 7–9) at the University of Minnesota General Clinical Research Center (GCRC). Blood samples were processed in a single flow manner within 2 hours of collection, and insulin and glucose were quantified at Fairview University Diagnostic Laboratories (Minneapolis, MN). Glucose was quantified using colorimetric reflectance spectrophotometry (Vitros Chemistry 5,1, Ortho-Clinical Diagnostics, Inc., Rochester, NY). The overall laboratory coefficient of variation for glucose

was 1.5%. Insulin levels were quantified by chemiluminescent immunoassay (Immulite 2000, Siemens Healthcare Diagnostics, Norwood, MA). The laboratory intra- and inter-batch coefficients of variation for insulin were 3.3% at 14.3 $\mu\text{U/mL}$ and 7.8% at 10.3 $\mu\text{U/mL}$, respectively.

Free F_2 -isoprostanes were measured in plasma by a gas chromatography-mass spectrometry (GC-MS)-based method described previously [42]. Briefly, the method utilized an internal standard, $[\text{H}_4]8\text{-iso-PGF}_{2\alpha}$ (>98% pure from Cayman Chemical), wherein the deuterium atoms were located at the non-exchangeable positions 3 and 4 of the molecule. The internal standard was added directly to the plasma samples before the initiation of analysis and therefore accounted for the recovery of F_2 -isoprostanes. Specificity of the assay for F_2 -isoprostanes has been demonstrated previously [43]. All batches of samples included three different control samples which had a range of concentrations. Overall analytical variation of the method was 10% for each of three control pools.

2.4. Body composition

Total body fat was measured by dual energy x-ray absorptiometry (DEXA) in the total body scanning mode with a Lunar Prodigy DEXA apparatus (Lunar Radiation Corp., Madison, WI) at the GCRC. Intra-individual variability in body fat measured by DXA is $0.6 \pm 0.5\%$ according to Jensen and colleagues [44]. Correlations between 0.7 and 0.8 have been reported between body fat measurement by DXA compared with underwater weighing or total body potassium count [45]. Height and weight were measured at the GCRC using a digital scale and a scale mounted stadiometer (Scale-tronix 5005 stand-on digital scale, Scale-tronix, White Plains, NY), calibrated weekly. Body composition measurements were obtained during the luteal phase of the menstrual cycle, 7–9 days after subjects obtained a positive test on an ovulation predictor kit (Assure Ovulation Predictor, Conception Technologies, San Diego, CA).

2.5. Statistical methods

Insulin resistance was measured by the homeostatic model assessment (HOMA) index: $\text{HOMA} = [\text{Fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting glucose } (\text{mg/dL})] \div 405$. The HOMA index correlates well with insulin sensitivity as measured by the gold standard euglycemic clamp ($r = -0.83$) [46].

Alcohol consumption from the DHQ in grams per day was converted to drinks per day: consumption < 0.5 g/d = 0 drinks/day, 0.5 to 15 g/d = 1 drink/day, and consumption of 15 g/d or more = 2 drinks/day. Cut-off points were based on data from the Nurses' Health Study [47].

Table 1 reports means $\pm$ standard deviations, or percents. Participants were divided into quartiles by their dietary glycemic index, and independently by their glycemic load. In Table 2, means are reported for continuous demographic characteristics, which were compared by one-factor ANOVA with a linear-contrast test for linear trend across quartiles; the Cochran-Armitage trend test was used for linear trend with discrete characteristics, where percents are reported. F_2 -isoprostanes, insulin, and HOMA were log transformed for analysis because of marked skewness; we report geometric means and 95% confidence intervals, transformed

back to the original scale. In Table 3, F₂-isoprostanes were compared between quartiles with a linear-contrast test for linear trend using two linear regression models, the first without adjustment, and the second adjusting for BMI, alcohol consumption (drinks per day), and total energy intake. P-values less than .05 were taken as statistically significant, and $p < .10$ was taken as marginally significant. Analyses were performed in SAS (Version 9.3; SAS Institute, Cary, NC).

3. Results

There were 306 female participants in this analysis, mostly white, mean age 25.3 years and mean BMI 24.7 kg/m², ranging from 17.7 to 40.5 kg/m² (Table 1). Mean overall dietary glycemic index was 52.1 and mean dietary glycemic load was 104.8. Glycemic load was weakly correlated with glycemic index ($r=0.18$, $P=0.002$) but strongly correlated with carbohydrate intake ($r=0.99$, $P<0.0001$).

Participants were divided into quartiles of dietary glycemic index and of glycemic load; each quartile contained 76 or 77 participants. There were no differences between quartiles of glycemic index in age, BMI, body fat percent, glucose or HOMA (Table 2). There were positive associations with several dietary characteristics including total energy intake, fat, dairy, meat, and grain intake.

There were no differences between quartiles of glycemic load in age, glucose or HOMA (Table 2) but there were positive associations with BMI, body fat percent, and all dietary characteristics including total energy intake.

Plasma F₂-isoprostanes (pg/mL) increased with quartile of glycemic index in participants with BMI ≥ 25 ($p = .035$, data not shown) but not in those with BMI < 25 . Plasma F₂-isoprostanes increased with quartile of glycemic load ($p = .033$, Table 3), but there was no difference in the results for those with BMI < 25 or BMI ≥ 25 (data not shown). After adjustment for BMI, alcohol consumption and total energy intake, both positive trends remained marginally significant ($p = .123$ for quartiles of glycemic index and $p = .065$ for quartiles of glycemic load, Table 3). Table 3 also shows that total energy intake was positively associated with plasma F₂-isoprostanes ($p = .049$), but there was no association after adjusting for BMI and alcohol consumption ($p = .621$). In the adjusted comparisons, replacing BMI with percent body fat did not alter these conclusions.

4. Discussion

High glycemic index and load diets have been suggested to promote the initiation and progression of oxidative stress through the generation of reactive oxygen species produced in the mitochondria in response to glucose surges [33, 34, 48]. The purpose of this study was to assess the relationship between dietary glycemic index and glycemic load and oxidative stress assessed by plasma F₂-isoprostanes in young healthy women. F₂-isoprostanes are regarded as the gold standard for quantification of lipid peroxidation due to their stability and their presence in plasma of both healthy individuals and those with chronic diseases [49]. F₂-isoprostanes have been shown to be the only oxidative stress marker able to detect time and dose dependent effects of induced lipid peroxidation in liver of rodents [50].

Interestingly, the mean level of F₂-isoprostanes reported here (50 pg/mL) were slightly above the normal range of 5 to 40 pg/mL reported by Morrow and colleagues [51]. One possible explanation for higher levels of F₂-isoprostanes could be the changes in dietary patterns that occurred since 1990, which was the year the study by Morrow et al was published. Data from the Framingham Heart Study show an increase in the percentage of calories derived from total fat from 27.3 to 29.8% between 1991 and 2008 [52], probably due to an increase in consumption of omega-6 polyunsaturated fatty acids [53]. Given that F₂-isoprostanes are derived from the oxidation of arachidonic acid, for which omega-6 fatty acids are precursors, it would be reasonable to expect an increase in the levels of F₂-isoprostanes with increased intakes of omega-6 fatty acids. Furthermore, mean levels of plasma F₂-isoprostanes reported in a more recent study were also above the levels reported by Morrow et al, at around 45 pg/mL [54].

We found a positive association between increasing quartiles of dietary glycemic load and plasma F₂-isoprostanes and while this association was statistically significant using an unadjusted model, it was attenuated when adjusting for alcohol intake, BMI and total energy intake. Our study showed that approximately 98% of the variance in glycemic load was explained by carbohydrate, similar to a previous study [54]. Somewhat similar results were found for the association between glycemic index and F₂-isoprostanes, but only in participants who were overweight or obese. In these participants, the association between increasing quartiles of glycemic index and F₂-isoprostanes was significant before adjustment for BMI, alcohol intake, and total energy intake. However, adjustment for these variables led to a marginally significant association ($p = .087$).

Hu et al found a significant relationship between quartiles of glycemic index and oxidative stress, as reflected by both plasma malondialdehyde (MDA) and F₂-isoprostanes. Interestingly the relationship between MDA and quartiles of glycemic index was stronger in leaner participants ($BMI < 26.5 \text{ kg/m}^2$) than in overweight participants ($BMI \geq 26.5 \text{ kg/m}^2$) [54]. They proposed that within overweight individuals, MDA may already be elevated to a point where consumption of high glycemic index foods could have little further effect. In contrast, we did not find any associations between quartiles of glycemic index or glycemic load in subjects with BMI below 25 kg/m^2 . One possible explanation for the differing results is the difference in populations studied. The 292 subjects in the study of Hu et al were both male and female and had broader BMI and age ranges ($17.2\text{--}60.5 \text{ kg/m}^2$ and $18\text{--}75$ years). In addition, while Hu and colleagues reported average consumption of fruits and vegetables to be lower than 4 servings per day, the young women participating in our study reported higher intakes of fruits and vegetables (over 5 servings per day).

The relationship between dietary glycemic load and index and F₂-isoprostanes in renal patients undergoing hemodialysis was recently reported [55]. It was found that glycemic load was significantly associated with levels of F₂-isoprostanes even after adjustment for adipokines, BMI, waist to hip ratio and trunk fat, while glycemic index was not. It should be noted that the average BMI of the patients in this study was 27.9 kg/m^2 with an interquartile range between 24.7 and 34.2 kg/m^2 . Although we did not find a significant relationship between levels of F₂-isoprostanes and increasing quartiles of glycemic load in overweight participants, the difference in age and health status between participants in our study and in

the study by Limkunakul and colleagues may explain these results. It is also noted that the average glycemic index and glycemic load values in our population were lower than reported in the literature. Data from NHANES 2003–2006 [56] indicate that the average glycemic index and load for adult women are 55.5 and 116.4, respectively, compared to 52 and 105, respectively, reported in our study. Our findings are likely related to the high consumption of fruits and vegetables reported by study participants, which may lead to an increased intake of antioxidants with concomitant decrease in levels of oxidative stress.

Limitations of this study include its cross-sectional nature, the risk of under- and over-reporting with any self-reported dietary intake analysis, and the lack of published data on glycemic index values for foods, which may lead to inaccurate values in the DHQ. Nonetheless, it should be noted that dietary intakes of total energy, macronutrients, and servings per food group in this study were representative of USDA recommendations, and biological measures were within normal, healthy limits.

Our data partially support our hypothesis that dietary glycemic index and glycemic load are positively associated with oxidative stress assessed by plasma F₂-isoprostanes in healthy, premenopausal women. We only found a marginally significant association between levels of F₂-isoprostanes and increasing quartiles of glycemic load adjusted for BMI, alcohol intake and total energy intake. However, since the dietary intake of our population seemed to be healthier than that of the US population with respect to fruit and vegetable consumption (data from NHANES indicated that only 3.5% of women 19 years and above met the recommendations for fruit and vegetable intake [57]), further investigation of the relationship between glycemic index and load and oxidative stress in the context of a healthy diet is warranted.

Acknowledgment

The authors thank the study subjects, nursing staff at the University of Minnesota GCRC, and Robert J. Hecker at the University of Minnesota, Molecular Epidemiology and Biomarker Research Laboratory, for assisting with the analytical laboratory work. This work was supported by grant 1U54CA116849-010003 from the National Institutes of Health/National Cancer Institute and grant M01-RR00400 from the National Institutes of Health/National Center for Research Resources. The opinions or assertions contained herein are the private ones of the authors and are not considered as official or reflecting the National Institutes of Health. The study ID NCT00393172 is registered at www.clinicaltrials.gov.

ABBREVIATIONS

BMI	body mass index
WISER	women in steady exercise research
DHQ	diet history questionnaire
GCRC	general clinical research center
DEXA	dual x-ray absorptiometry
HOMA	homeostasis model assessment

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Table 1Characteristics of study participants^{a,b}.

Age (y)	25.3 ± 3.5
BMI (kg/m ²)	24.7 ± 4.8
Body fat (%)	36.2 ± 8.5
Plasma glucose (mg/dL)	80.6 ± 7.7
Plasma insulin ^c (μU/mL)	6.1 (5.7 – 6.5)
HOMA ^c	1.2 (1.1 – 1.3)
Plasma F ₂ -isoprostanes ^c (pg/mL)	50 (48 – 52)
Glycemic load	105 ± 55.4
Glycemic index	52 ± 3.2
Energy intake (kcal/d)	1660 ± 800
Fat intake (g/d)	61 ± 34
Carbohydrate intake (g/d)	217 ± 110
Protein intake (g/d)	62.4 ± 31.6
Dietary fiber intake (g/d)	17.0 ± 9.4
Folate intake (μg/d)	352 ± 181
Cholesterol intake (mg/d)	173 ± 107
Fruit intake (cups/d)	2.5 ± 3.0
Vegetable intake (cups/d)	3.2 ± 2.2
Dairy intake (cups/d)	1.6 ± 1.2
Grain intake (oz/d)	5.0 ± 2.7
Meat intake (oz/d)	2.4 ± 2.0
Alcohol intake ^d	
0 drinks/day	24%
1 drink/day	71%
2 drinks/day	5%

^aData are mean ± standard deviation^bn=306^cGeometric mean (95% confidence interval)^dPercent of sample

TABLE 2

Participants' characteristics by quartile (Q) of dietary glycemic index and glycemic load^{a,b}.

	Glycemic Index					Glycemic Load					P for trend
	Q1 (39.1–52.2)	Q2 (52.2–54.2)	Q3 (54.2–59.8)	Q4 (59.8–64.3)	P for trend	Q1 (16.9–7.3)	Q2 (7.5–97.8)	Q3 (97.9–123.8)	Q4 (124.3–431.7)		
Sample n	76	77	77	76		76	77	77	76		
Glycemic Load	88.0	101.8	113.3	116.2		-	-	-	-		
Glycemic Index	-	-	-	-		51.3	52.1	52.4	52.7		
<hr/>											
Age (y)	25.0	25.7	24.9	25.5	.58	25.1	25.7	25.4	25.1	.91	
BMI (kg/m ²)	25.1	24.6	24.4	24.8	.62	24.4	23.9	24.3	26.4	.009	
Body fat (%)	36.7	36.3	35.9	36.1	.66	35.6	35.1	35.4	38.9	.02	
Glucose (mg/dL)	81.2	8.6	79.8	8.9	.66	8.2	8.9	8.3	81.0	.65	
Insulin ^c (μU/mL)	6.5	5.7	6.4	5.8	.48	5.6	6.2	5.7	6.7	.67	
HOMA ^c	1.3	1.1	1.2	1.2	.48	1.1	1.2	1.1	1.3	.17	
Energy intake (kcal/d)	1520	1654	1728	1749	.06	923	1361	1795	2575	<.0001	
Fat intake (g/d)	54.2	6.0	62.6	67.2	.02	35.7	51.5	66.6	9.2	<.0001	
Carbohydrate intake (g/d)	201	217	231	223	.15	115	171	231	354	<.0001	
Protein intake (g/d)	6.9	62.5	63.6	62.7	.70	34.4	53.3	68.9	93.2	<.0001	
Dietary fiber intake (g/d)	17.1	18.0	17.4	15.5	.28	9.8	13.9	19.1	25.2	<.0001	
Folate intake (μg/d)	322	362	358	364	.19	200	276	395	537	<.0001	
Cholesterol intake (mg/d)	158	167	167	191	.05	108	146	190	249	<.0001	
Fruit intake (cups/d)	2.7	2.8	2.4	1.9	.06	1.4	1.8	2.4	4.3	<.0001	
Vegetable intake (cups/d)	3.1	3.5	3.2	3.0	.57	2	2.5	3.7	4.6	<.0001	
Dairy intake (cups/d)	2.1	1.6	1.5	1.2	<.0001	.9	1.4	1.9	2.4	<.0001	
Grain intake (oz/d)	3.6	4.5	5.7	6.0	<.0001	2.5	4.1	5.3	8.0	<.0001	
Meat intake (oz/d)	2	2.4	2.5	2.8	.02	1.3	2.1	2.6	3.6	<.0001	
Percent consuming at least 1 drink/day	76%	75%	71%	64%	.09	63%	73%	77%	75%	.09	

^a Values are means or percents. P-values are for test of linear trend within each set of quartiles, with no adjustment (one-factor ANOVA)

^b n=306

^c Geometric means

TABLE 3

Plasma F₂-isoprostanes (pg/mL) by quartiles (Q) of dietary glycemic index and glycemic load and energy intake^{a,b}.

	Unadjusted F ₂ -isoprostanes	Adjusted F ₂ -isoprostanes ^c
Glycemic Index		
Q1 (<i>low</i>)	48 (44 – 51)	47 (44 – 51)
Q2	51 (47 – 55)	51 (47 – 54)
Q3	48 (45 – 52)	49 (45 – 52)
Q4 (<i>high</i>)	52 (49 – 56)	52 (48 – 56)
<i>P</i> for trend	.271	.123
Glycemic Load		
Q1 (<i>low</i>)	47 (43 – 50)	46 (42 – 50)
Q2	49 (45 – 53)	49 (46 – 53)
Q3	50 (47 – 54)	51 (47 – 55)
Q4 (<i>high</i>)	52 (48 – 57)	53 (48 – 58)
<i>P</i> for trend	.033	.065
Energy Intake		
Q1 (<i>low</i>)	46 (43 – 50)	48 (45 – 52)
Q2	50 (47 – 54)	50 (47 – 54)
Q3	50 (45 – 53)	50 (46 – 54)
Q4 (<i>high</i>)	53 (49 – 57)	50 (46 – 54)
<i>P</i> for trend	.049	.621

^aValues are geometric means (pg/mL) and 95% confidence intervals. P-values are from linear trend tests across quartiles

^b
n=306

^cAdjusted for BMI, alcohol intake (drinks per day), and total energy intake; comparison of quartiles of energy intake is adjusted for BMI and alcohol intake