Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 24, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.03.025

The Acute Effect of Various Glycemic Index Dietary Carbohydrates on Endothelial Function in Nondiabetic Overweight and Obese Subjects

Talya Lavi, RD,* Avraham Karasik, MD,*‡ Nira Koren-Morag, PHD,‡ Hannah Kanety, PHD,*‡ Micha S. Feinberg, MD,†‡ Michael Shechter, MD, MA†‡

Tel Hashomer and Tel Aviv, Israel

Objectives This study sought to explore the effect of glycemic-index dietary carbohydrates on endothelium-dependent flow-mediated dilation (FMD) in overweight and obese nondiabetic volunteers.

Background Post-prandial hyperglycemia has been recognized as a cardiovascular risk factor in both the diabetic and the general population. Endothelial dysfunction has been shown to occur in diabetic and hyperglycemic patients.

Methods We prospectively assessed brachial artery FMD in 56 healthy overweight and obese nondiabetic volunteers (38 [67.9%] men, mean age 48 ± 6 years) on 4 separate mornings, 1 to 2 weeks apart. After overnight fasting, the percent FMD (%FMD) improvement and endothelium-independent nitroglycerin-mediated dilation (%NTG) were assessed, after which subjects received 1 of 4 group meals at each visit (placebo [water] or a carbohydrate meal of glucose, cornflakes, or high-fiber cereal). Meals were distributed in a rotating randomized fashion, such that each subject received all 4 meals once throughout the study period.

Results Fasting and 2-h post-prandial serum glucose levels were similar in all 3 meals, whereas at 30 to 90 min, serum glucose levels were significantly higher after glucose and cornflakes (high glycemic) compared with fiber (low glycemic). Baseline %FMD, not significantly different in the 3 carbohydrate-based meals, was reduced 2 h post-prandially in all groups, showing statistical significance in only high-glycemic index meals: glucose (15 ± 9% vs. 10 ± 8%, $p < 0.01$), cornflakes (13 ± 7% vs. 9 ± 7%, $p < 0.01$). No correlation was observed between the %FMD reduction rate and glucose levels throughout the study period.

Conclusions High- compared with low-glycemic carbohydrate consumption significantly suppresses FMD in nondiabetic overweight and obese volunteers, suggesting a mechanism whereby high-glycemic meals may enhance cardiovascular risk. (J Am Coll Cardiol 2009;53:2283–7) © 2009 by the American College of Cardiology Foundation

Post-prandial hyperglycemia is recognized as a significant risk factor for cardiovascular disease (CVD) not only in diabetic patients, but also among the general population (1,2). Furthermore, high intake of rapidly digested carbohydrates increases this risk independent of conventional CVD risk factors (3–5).

Endothelial dysfunction is a systemic disorder and key variable in the pathogenesis of atherosclerosis and its complications, which reflects a vascular phenotype prone to atherogenesis, and may serve as a marker of inherent atherosclerotic risk (6).

Hyperglycemia, in response to oral glucose loading, rapidly suppresses endothelium-dependent flow-mediated dilation (FMD) in diabetic patients and healthy volunteers (7–9). However, because data relating the acute effect of various glycemic index dietary carbohydrates on FMD have not yet been explored, we aim to evaluate this effect on brachial artery FMD in healthy, nondiabetic, overweight and obese volunteers.

Methods

Study design and population. The study comprised 56 consecutive nondiabetic overweight and obese (mean body mass index [BMI] 32 ± 4 kg/m^2), predominantly male, nonsmoking, healthy volunteers (35 to 60 years of age), without prior hospitalizations for CVD, history of chest pain, or known chronic drug therapy. Of them, 63% had a family history of diabetes and/or CVD, and 17 (30%) had metabolic syndrome according to Adult Treatment Panel III

From the *Institute of Endocrinology and †Leviev Heart Center, Chaim Sheba Medical Center, Tel Hashomer, Israel; and the ‡Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. Part of this study was presented as an abstract at the XXVI Congress of the European Society of Cardiology, Stockholm, Sweden, August 30, 2005.

Manuscript received October 26, 2008; revised manuscript received February 18, 2009, accepted March 3, 2009.

JACC Vol. 53, No. 24, 2009
June 16, 2009:2283–7

Abbreviations and Acronyms

BMI = body mass index
CVD = cardiovascular disease
FMD = flow-mediated dilation
hs-CRP = high-sensitivity C-reactive protein
NO = nitric oxide
NTG = nitroglycerin-mediated dilation

definition. All participants provided written informed consent, and the study was approved by the institutional review board. Baseline characteristics are shown in Table 1.

At each visit (on 4 separate mornings, 1 to 2 weeks apart) after an overnight fast of ≥12 h, %FMD and percent endothelium-independent nitroglycerin-mediated dilation (%NTG) were assessed noninvasively. After this, subjects received 1 of 4 group meals at each visit: placebo (water), or a carbohydrate meal of glucose, cornflakes, or high-fiber cereal. The 3 actual meals included 50 g each of carbohydrates and 200 μg of folic acid (Table 2). The order by which subjects received each of the 4 group meals was carried out in a rotating randomized fashion, such that each subject received all 4 meals once throughout the study period.

A repeat endothelial function test was performed 2 h post-prandially on all 4 randomly selected groups. Blood samples were taken for serum high-sensitivity C-reactive protein (hs-CRP) and lipoproteins at fasting (time 0), and after 120 min, and for glucose at fasting and at 30, 60, 90, and 120 min post-prandially. All subjects underwent resting electrocardiography and echocardiography for global, regional motion, and diastolic function assessment. Endothelial function in the form of endothelium-dependent brachial artery FMD was measured as previously described (10–12).

Table 1 Baseline Characteristics of Study Population (n = 56)

Variables	
Age (yrs)	47.9 ± 5.8
Body mass index (kg/m^2)	32.1 ± 4.3
Waist circumference, male (cm)	110 ± 11
Waist circumference, female (cm)	100 ± 12
Fasting blood glucose (mg/dl)	97 ± 3
Oral glucose tolerance test, glucose 120′ (mg/dl)	112 ± 37
Total cholesterol (mg/dl)	196 ± 28
Low-density lipoprotein cholesterol (mg/dl)	123 ± 26
High-density lipoprotein cholesterol (mg/dl)	43 ± 7
Triglycerides (mg/dl)	151 ± 80
Systolic blood pressure (mm Hg)	134 ± 13
Diastolic blood pressure (mm Hg)	82 ± 6
High-sensitivity C-reactive protein (mg/dl)	1.6 ± 1.8
Brachial artery diameter (mm)	6.05 ± 0.77
%FMD	13.5 ± 5.6
%NTG	15.5 ± 6.7

All data are expressed as mean ± SD.
%FMD = percent change from baseline in brachial artery diameter caused by flow-mediated dilation; %NTG = percent change from baseline in brachial artery diameter caused by nitroglycerin-induced dilation.

Table 2 Study Meal Composition

	Placebo	High-Fiber Cereals	Cornflakes	Glucose Solution
Amount containing 50 g carbohydrates	—	61 g	59 g	50 ml
Estimated glycemic index value	0	40	80	100
Folic acid content (μg)	0	200	100	0
Folic acid addition for equivalent content of folic acid of 200 μg (μg)	200	—	100	200

Statistical analysis. Baseline characteristics of the study population are expressed as mean ± SD. The distribution of the FMD parameter was tested by 1-sample Kolmogorov-Smirnov test and Q-Q plot graph. The FMD had normal distribution and was tested by parametric tests. Differences between clinical characteristics and brachial artery vasodilator responses were evaluated and analyzed by *t* tests. Comparison of biochemical measurements was performed using the unpaired *t* test and chi-square test. The differences between the FMD values before and after meals (Δ%FMD) were evaluated by repeated measures with analysis of variance and paired *t* test. Spearman correlation was used to test the linear relationship between ΔFMD and fasting glucose levels. A value of $p < 0.05$ was considered significant.

Results

Fasting serum glucose levels were similar in all 4 groups. However, at 30, 60, and 90 min, serum glucose levels were significantly higher in cornflakes and glucose groups compared with the placebo and high-fiber cereal groups, while remaining significantly higher at 120 min in the cornflakes group only (Fig. 1). The area under the curve, reflecting the glycemic index, was 100 for glucose, 77 for cornflakes, and 40 for high-fiber cereal, in accord with the literature (13).

Treatment effect on endothelial function. Baseline %FMD, similar in all 4 groups ($p = 0.549$) (Table 1), decreased 2 h post-prandially, but was statistically significant in the glucose and cornflakes groups only (Fig. 2). Pre- and post-prandial baseline brachial artery diameters were similar in all subjects. Therefore, the brachial artery diameter achieved after blood pressure cuff release (reactive hyperemia) followed the same direction as %FMD in all study participants. Differences between Δ%FMD values (baseline and post-prandial %FMD) were significant in the glucose and high-fiber cereal groups only ($p = 0.024$) (Fig. 3). No correlation was observed between Δ%FMD and age, BMI, and lipoproteins at fasting and 2 h after meals, hs-CRP, and baseline %FMD. Furthermore, no correlation was observed between Δ%FMD and serum glucose levels at all time points.

The %FMD by sex, age, family history of CVD and/or diabetes, and BMI pre- and post-prandially is shown in Table 3. No significant differences were observed between

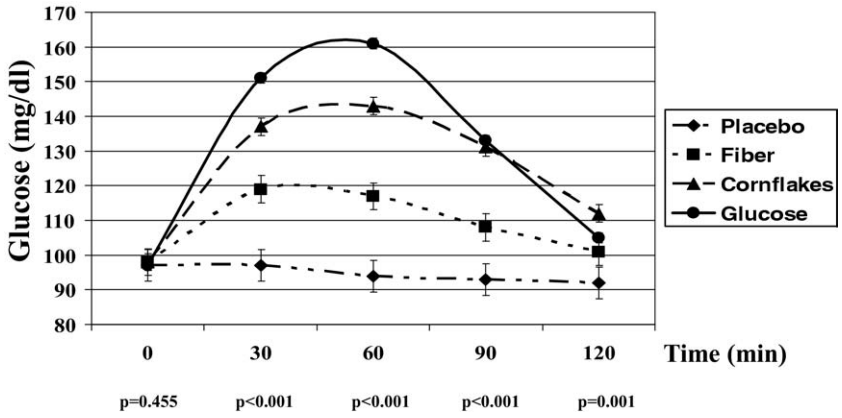

Figure 1 Post-Prandial Serum Glucose Levels

Post-prandial serum glucose levels of 3 different carbohydrate-based meals and placebo in 56 healthy subjects. Data are expressed as mean ± SE.

subjects with and without metabolic syndrome in the %FMD response to meals. Reduction in %FMD was significant in the glucose group in both male and female subjects of all ages, for those with and without a family history of CVD and/or diabetes, and for those with a BMI of ≥30 or <30 kg/m^2 (Table 3).

Discussion

This study shows for the first time that high-glycemic-index carbohydrate meals significantly suppress brachial artery FMD in nondiabetic, overweight and obese, healthy volunteers whose mean baseline %FMD was normal.

As in our study, Reed et al. (14) found no correlation between Δ%FMD and serum glucose levels at all time points, suggesting that an additional mechanism is responsible for variations in endothelial function suppression. Acute, moderate hyperglycemia, performed by glucose infusion, did not cause short-term impairment of endothelial function in a healthy human forearm brachial artery (15); however, the studies examined intravenous glucose infusion-induced hyperglycemia, which may have different metabolic manifestations compared with post-prandial hyperglycemia as in our study.

Exogenous physiological hyperglycemia raises the possible role of metabolic and hormone (e.g., insulin, adiponectin, and ghrelin) changes mediating and leading to endothelial dysfunction, thereby showing that glucose itself may not be the main mediator of endothelial dysfunction. It is known that the secretion of insulin, a vasoactive hormone mediated by nitric oxide (NO) (16), correlates with glycemic response and binds to its receptor on the endothelial cell stimulating a signal path, which in turn leads to endothelial NO synthase stimulation and NO production in the endo-

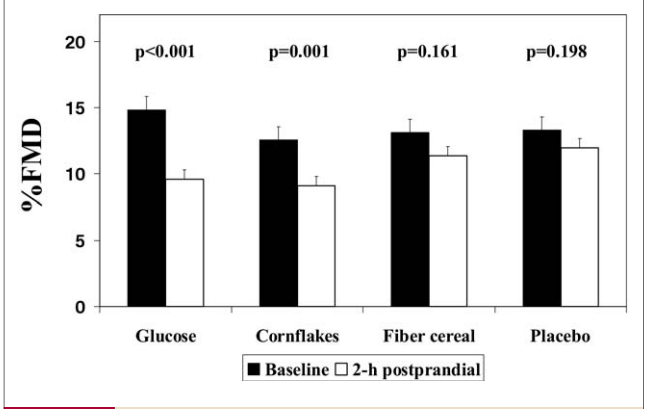

Figure 2 Acute Effect of Various Glycemic Index Carbohydrates on FMD

Bar graph showing the percent change in endothelium-dependent brachial artery flow-mediated dilation (%FMD) from baseline in 56 healthy subjects who received 3 different carbohydrate-based meals and placebo at baseline **(solid bars)** and 2 h post-prandially **(open bars)**. Data are expressed as mean ± SE.

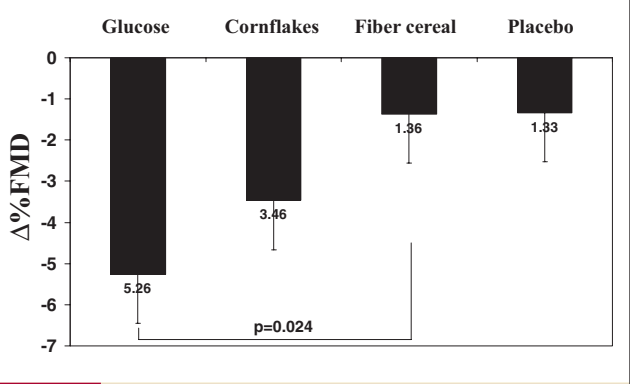

Figure 3 Pre- and Post-Prandial FMD

Differences between endothelium-dependent brachial artery flow-mediated dilation (%FMD) values pre- and post-prandially (Δ%FMD) in 56 healthy subjects who received 3 different carbohydrate-based meals and placebo. Data are expressed as mean ± SE.

Table 3 %FMD Before and After Meals by Sex, Age, Family History of Cardiovascular Disease and/or Diabetes, and BMI

	Placebo (n = 56)			Fiber Cereal (n = 56)			Cornflakes (n = 56)			Glucose (n = 56)		
	Before	After	p Value	Before	After	p Value	Before	After	p Value	Before	After	p Value
Sex												
Male	11.0 ± 4.4	9.2 ± 6.6	0.14	11.2 ± 5.2	8.8 ± 5.6	0.03	11.2 ± 6.6	7.2 ± 4.6	0.01	12.4 ± 7.8	7.7 ± 5.8	0.01
Female	17.8 ± 8.5	17.3 ± 4.4	0.82	16.6 ± 4.2	18.2 ± 5.6	0.36	15.5 ± 6.9	13.0 ± 7.5	0.23	20.4 ± 7.5	13.8 ± 6.5	0.02
Age, yrs												
<48	14.7 ± 5.7	12.0 ± 6.9	0.09	12.7 ± 5.8	11.5 ± 6.4	0.44	13.3 ± 7.7	9.3 ± 6.6	0.02	14.5 ± 8.5	10.5 ± 6.9	0.04
≥48	12.0 ± 7.5	11.8 ± 7.4	0.88	12.7 ± 5.3	11.2 ± 7.5	0.24	11.9 ± 6.4	8.9 ± 6.1	0.02	15.0 ± 8.6	8.9 ± 6.4	0.01
Family history*												
No	14.0 ± 5.6	11.3 ± 7.8	0.08	13.5 ± 6.3	12.2 ± 7.3	0.33	12.3 ± 7.3	9.3 ± 5.9	0.06	17.4 ± 10.4	10.2 ± 7.5	0.01
Yes	12.7 ± 7.5	12.3 ± 6.7	0.75	12.2 ± 4.9	10.8 ± 6.8	0.30	12.6 ± 6.9	8.9 ± 6.5	0.01	13.2 ± 6.7	9.2 ± 6.1	0.01
BMI, kg/m^2												
<30	11.2 ± 6.3	11.2 ± 5.1	0.98	11.8 ± 5.5	10.1 ± 6.2	0.17	13.3 ± 7.1	9.3 ± 7.9	0.02	15.9 ± 9.0	8.5 ± 7.0	0.01
≥30	13.9 ± 6.9	12.2 ± 7.6	0.12	13.3 ± 5.4	12.1 ± 7.4	0.41	12.0 ± 6.9	8.9 ± 4.8	0.02	13.9 ± 8.1	10.4 ± 6.3	0.04

Values are expressed as mean ± SD. *Family history of cardiovascular disease and/or diabetes.
BMI = body mass index; other abbreviations as in Table 1.

thelial cell. At the same time, insulin can stimulate endothelin-1 synthesis, a central vasoconstrictor, through the mitogen-activated protein kinase pathway (16). Because disturbance in the PI3-k pathway stimulation is common in the presence of insulin resistance, the dominant path will be dispensed on Ras/mitogen-activated protein kinase, which then leads to an increased release of endothelin-1 and reduced NO production (17). It is therefore logical to assume that most of our overweight, otherwise healthy subjects were insulin resistant. Although higher levels of blood insulin after a high-glycemic-index meal could improve endothelial function, insulin resistance caused by overweight in our study subjects could lead to a dysfunctional endothelial response.

Study limitations. A major limitation of the current study is that it does not provide insight into the potential mechanisms linking hyperglycemia to endothelial dysfunction. Other potential causes for enhanced endothelial function, such as changes in free fatty acids and inflammatory cytokines, insulin, adiponectin, and ghrelin, as well as other parameters of endothelial function, such as NO, endothelial NO synthase expression, intracellular adhesion molecules, or endothelin, were not measured. Finally, because of the relatively small sample size of our study, order effects and analysis of contrast could not be evaluated.

Conclusions

Our study shows that high-glycemic-index carbohydrate meals significantly suppress brachial artery FMD in nondiabetic, healthy, overweight and obese volunteers, an effect not necessarily caused by post-prandial blood glucose levels alone. Furthermore, the link between high-glycemic-index foods and endothelial dysfunction could play a major role in the association between high-glycemic-index foods intake and CVD risk. Further research examining hormonal and cytokine signals resulting from high-glycemic-index meals and their influence on endothelial function is warranted.

Reprint requests and correspondence: Dr. Michael Shechter, Leviev Heart Center, Chaim Sheba Medical Center, 52621 Tel Hashomer, Israel. E-mail: shechtes@netvision.net.il.

REFERENCES

1. Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998;21:360–7.
2. Meigs JB, Nathan DM, D'Agostino RB Sr., Wilson PW. Framingham Offspring Study. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002;25:1845–50.
3. Hu FB, Willett WC. Diet and coronary heart disease: findings from the Nurses' Health Study and Health Professionals' Follow-up Study. J Nutr Health Aging 2001;5:132–8.
4. McMillan-Price J, Petocz P, Atkinson F, et al. Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. Arch Intern Med 2006;166:1466–75.
5. Ludwig DS. Clinical update: the low-glycaemic-index diet. Lancet 2007;369:890–2.
6. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653–8.
7. Kawano H, Motoyama T, Hirashima O, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. J Am Coll Cardiol 1999;34:146–54.
8. Title LM, Cummings PM, Giddens K, Nassar BA. Oral glucose loading acutely attenuates endothelium-dependent vasodilation in healthy adults without diabetes: an effect prevented by vitamins C and E. J Am Coll Cardiol 2000;36:2185–91.
9. Williams SB, Goldfine AB, Timimi FK, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. Circulation 1998;97:1695–701.
10. Corretti MC, Anderson TJ, Benjamin EJ, et al., for the International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.
11. Shechter M, Sharir M, Labrador MJ, Forrester J, Silver B, Bairey Merz CN. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation 2000;102:2353–8.

12. Shechter M, Matetzky S, Feinberg MS, Chouraqui P, Rotstein Z, Hod H. External counterpulsation therapy improves endothelial function in patients with refractory angina pectoris. J Am Coll Cardiol 2003;42:2090–5.
13. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5–56.
14. Reed AS, Charkoudian N, Vella, Shah P, Rizza RA, Joyner MJ. Forearm vascular control during acute hyperglycemia in healthy humans. Am J Physiol Endocrinol Metab 2004;286:E472–80.
15. Houben AJHM, Schaper NC, DeHaan CHA, et al. Local 24-h hyperglycemia does not affect endothelium-dependent or -independent vasoreactivity in humans. Am J Physiol Heart Circ Physiol 1996;270: H2014–20.
16. Vincent MA, Montagnani M, Quon MJ. Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium. Curr Diab Rep 2003;3:279–88.
17. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113:1888–904.

Key Words: endothelium ■ glucose ■ nitric oxide ■ nutrition ■ vasodilation.