High-Viscosity Hydroxypropylmethylcellulose Blunts Postprandial Glucose and Insulin Responses

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OBJECTIVE — High-viscosity hydroxypropylmethylcellulose (HV-HPMC) is a modified cellulose fiber that produces a viscous gel in the gastrointestinal tract. Clinical trials demonstrate that consumption of HV-HPMC significantly lowers cholesterol, but limited information has been available on the influence of HV-HPMC on postprandial insulin and glucose responses. The objective of this investigation was to assess the influence of HV-HPMC on postprandial glucose and insulin responses in overweight and obese men and women.

RESEARCH DESIGN AND METHODS — Participants were 31 overweight or obese men and women without diabetes who underwent three breakfast meal tests in random order, separated by ≥72 h. Test meals containing 75 g carbohydrate plus 4 or 8 g HV-HPMC or control meals containing 8 g cellulose were delivered in a double-blind fashion.

RESULTS — Peak glucose was significantly lower ($P < 0.001$) after both HV-HPMC–containing meals (7.4 mmol/l [4 g] and 7.4 mmol/l [8 g]) compared with the control meal (8.6 mmol/l). Peak insulin concentrations and the incremental areas for glucose and insulin from 0 to 120 min were also significantly reduced after both HV-HPMC doses versus control (all $P < 0.01$).

CONCLUSIONS — These findings indicate that HV-HPMC consumption reduces postprandial glucose and insulin excursions, which may favorably alter risks for diabetes and cardiovascular disease.

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Insulin resistance and compensatory hyperinsulinemia are believed to play important pathophysiological roles in the development of a number of conditions, including diabetes, coronary heart disease, and hypertension (1,2). Insulin resistance is a state in which a given circulating concentration of insulin produces subnormal clearance of glucose from the blood (2).

In the presence of insulin resistance, the pancreas will increase insulin secretion to maintain normal glucose tolerance (2). However, the resulting excessive demand on the pancreatic β-cells may, over an extended period, lead to pancreatic exhaustion and the eventual development of glucose intolerance (1,2). Furthermore, insulin resistance may not be present to the same degree for all tissues and actions of insulin. Therefore, the hyperinsulinemia required to maintain normal glucose tolerance may produce undesirable physiological effects, including increased synthesis of VLDL, enhanced renal sodium reabsorption, and remodeling of vascular and cardiac tissues (1–3).

Slowing the absorption of digestible dietary carbohydrates shows promise as a way to reduce hyperinsulinemia and its unwanted consequences on pancreatic function and the development of hemodynamic disturbances (1,4–6). One class of medication, the α-glucosidase inhibitors, slows glucose absorption by reducing the rate of enzymatic digestion of starch, thereby delaying the release of glucose molecules for absorption. These agents reduce postprandial glucose and insulin levels (7). A Cochrane Review of five trials (2,360 participants) concluded that there is evidence that acarbose reduced the incidence of type 2 diabetes in subjects with impaired glucose tolerance (8). Relative risk reductions ranged from 22 to >50% over follow-up periods of 3–5 years. However, the authors also stated that, because of limitations in the available data, the review did not allow a determination of whether these results should be viewed as prevention, delay, or masking of diabetes. One of the studies reviewed, the Study to Prevent Non-insulin Dependent Diabetes (STOP-NIDDM) trial, also provided evidence for reductions versus placebo in cardiovascular events (9), new onset hypertension (9), and progression of carotid intima-media thickness (10), a marker for atherosclerotic disease progression. Thus, although the available outcomes trial data are limited at present, they suggest possible benefits associated with slowing carbohydrate absorption for individuals at high risk for the development of diabetes.

Dietary fibers that form viscous gels in the gastrointestinal tract also slow the absorption of glucose by creating a mechanical barrier through which glucose molecules must travel to reach the intestinal brush border (11). Incorporation of viscous fibers such as psyllium, guar gum, or β-glucan into a meal has been shown to reduce postprandial glucose and insulin responses in subjects with and without glucose intolerance (4,12–15). Because viscous fibers and α-glucosidase inhibitors affect postprandial glucose and insulin levels in a similar manner, it is reasonable to hypothesize that consuming such fibers might favorably influence risks for diabetes and cardiovascular disease.

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Abbreviations: HV-HPMC, high-viscosity hydroxypropylmethylcellulose; IAUC, incremental area under the curve.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

High-viscosity hydroxypropylmethylcellulose (HV-HPMC) is a modified cellulose fiber that produces a viscous gel in the gastrointestinal tract (16). Previous trials demonstrated that consumption of 5.0–30.0 g/day HV-HPMC significantly lowers total and LDL cholesterol concentrations (17,18). Studies in animals have shown that HV-HPMC delays glucose absorption and that the extent of this effect is related to the viscosity of the solution administered (16,19).

The influence of HV-HPMC on postprandial glucose responses in humans was investigated in only one previous trial. Reppas et al. (20) showed that the peak blood glucose concentration after a standard meal was reduced by 24% in subjects with type 2 diabetes when 10 g HV-HPMC was consumed in a meal, compared with a cellulose control. The area under the plasma glucose curve from 0 to 6 h was also reduced by 15% (20). However, no significant effects of HV-HPMC were observed on the peak glucose value or the area under the curve in 10 healthy volunteers. Thus, additional research is required to further evaluate the postprandial effects of HV-HPMC in subjects without diabetes. The present trial was designed to assess the influence of consuming two doses of HV-HPMC on postprandial glucose and insulin excursions in overweight and obese men and women without diabetes.

RESEARCH DESIGN AND METHODS

— This was a randomized, double-blind, controlled, crossover clinical trial conducted at a single clinical research center. An institutional review board (Schulman Associates Institutional Review Board, Inc., Cincinnati, OH) approved the protocol before the initiation of the study.

To participate, subjects aged 18–64 years were required to have a waist circumference ≥102 cm (men) or ≥88 cm (women) and had to be in apparent good health, as indicated by medical history and routine laboratory tests. Subjects were excluded if they had BMI ≥40.0 kg/m^2, diagnosed diabetes, fasting glucose ≥7.0 mmol/l, or fasting triglycerides ≥5.7 mmol/l. Use of medications known to influence carbohydrate metabolism, including, but not limited to, cyclic hormone products, adrenergic blockers, diuretics, thiazolidinediones, metformin, or systemic corticosteroids, was an exclusion factor as was uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg on two consecutive visits).

Qualified subjects were randomly assigned to a treatment sequence, and study products were packaged in coded, single-serving containers so that neither the staff nor the subject was aware of which treatment was being received on a given day. Subjects ingested one of the three double-blind treatments at each test visit, in random order.

Clinic visits

Subjects had a screening visit and three subsequent test visits (each visit separated by ≥72 h). Informed consent and medical history were obtained at screening as well as samples for serum chemistry, hematology, urinalysis, and a fasting lipid profile. Weight and vital signs were measured at all clinic visits, and a 48-h diet recall and a meal tolerance test were completed at each testing visit. A venous catheter was inserted for collection of samples for measurement of plasma glucose and serum insulin concentrations before the meal and at t = 15, 30, 45, 60, 90, 120, 150, and 180 min, where t = 0 was the start of test meal consumption.

Test meals

Each test meal consisted of a bagel, butter, 23 g of anhydrous glucose, and a powdered beverage mix (sugar-free Crystal Light lemonade) into which the HV-HPMC or control (cellulose) had been incorporated. The nutrient totals for the test meals were as follows: 421 kcal, 75.1 g carbohydrate, 9.7 g protein, and 9.1 g fat. HV-HPMC was Fortefiber (Dow Chemical, Midland, MI), with nominal viscosity of 100,000 cP, measured in a 2% aqueous solution. For the control test, subjects received 8 g cellulose (Avicel; FMC BioPolymer, Philadelphia, PA). For the 4-g HV-HPMC test, subjects received 4 g HV-HPMC plus 4 g cellulose; subjects received 8 g HV-HPMC with no cellulose during the 8-g HV-HPMC test.

Gastrointestinal tolerance

Subjects were contacted ~24 h after the start of each test meal to record intensity and frequency of gastrointestinal symptoms. These were measured on a 5-point scale, where 0 = absent, 1 = much less than usual, 2 = somewhat less than usual, 3 = usual, 4 = somewhat more than usual, and 5 = more than usual.

Laboratory measurements

Elmhurst Memorial Hospital (Elmhurst, IL) conducted all laboratory analyses using instruments from Beckman (Fullerton, CA) except as otherwise noted: LX20 for serum chemistry analysis, 750 for hematology testing (performed on EDTA whole blood), and IRIS/200 (IRIS International, Chatsworth, CA) for urinalysis. Plasma glucose was measured via the glucose oxidase method. Insulin was determined from serum samples via chemiluminescent immunoassay.

Sample size

An evaluable sample of 28 subjects was expected to provide 80% power (two-sided adjusted $\alpha = 0.05$ after correction for two comparisons versus control) to detect a difference in response of 12.0% in the incremental area under the glucose concentration curve across conditions, assuming a pooled SD of 20%.

Statistical analyses

Statistical analyses were generated using SAS (version 9.1; SAS Institute, Cary, NC). Data are presented for an efficacy evaluable population, which includes all subjects who consumed the study product at all three test visits and had at least 120 min of valid postprandial glucose and insulin values on each test day. The incremental areas under the curves (IAUCs) for glucose and insulin from 0 to 120 and 180 min were calculated using the trapezoidal rule, with postprandial concentrations that were below the 0-min value counted as the time 0 value, as described by Wolever et al. (21).

IAUCs and peak values for glucose and insulin were compared between treatment conditions by repeated-measures ANOVA. No evidence was present for material sequence or period effects. Therefore, data for the two treatment sequences were pooled. Comparisons between each active condition versus placebo were completed for peak and IAUC values using Dunnett's test for multiple comparisons. Additional exploratory analyses were also completed for the insulin and glucose values at each time point. Responses to the gastrointestinal tolerability questionnaire items were assessed by Cochran's Q test using the frequencies of responses ≥4 ("somewhat more than usual" and "more than usual") as the dependent variables.

All tests of significance, unless otherwise stated, were performed at $\alpha = 0.05$, two-sided. Assumptions of normality of

Table 1—*Demographic and baseline characteristics of subjects*

Characteristic	Value
Sex	
Male	6 (19.4)
Female	25 (80.6)
Race/ethnicity	
Non-Hispanic white	28 (90.3)
Other	3 (9.6)
Age (years)	48.8 ± 2.2
BMI (kg/m^2)	33.5 ± 0.7
Systolic blood pressure (mmHg)	130.4 ± 3.1
Diastolic blood pressure (mmHg)	78.0 ± 2.1

Data are *n* (%) or means ± SEM.

residuals and homogeneity of variance were investigated for each response measurement. If it was determined that the distribution could not be approximated by a normal curve, an analysis using ranks was performed.

RESULTS — Recruitment occurred during March and April 2006, and the last subject exited on 29 April 2006. Fifty-four subjects were screened, 34 of whom were randomly assigned. None of the randomly assigned subjects dropped out of the trial. However, data from three subjects were not included in the efficacy evaluable population, two because of illness at the time of at least one test and one because of difficulty with obtaining blood samples during a test. Of the subjects, ~81% (25 of 31) were women, and 90% (28 of 31) of the subjects were of non-Hispanic white ethnicity. Subjects had a mean age of 48.8 years and a mean BMI of 33.5 kg/m^2 (Table 1).

Glucose and insulin responses

Table 2 and Fig. 1*A* and *B* show glucose and insulin responses by test condition. Peak glucose was significantly ($P < 0.001$) lower after both HV-HPMC–containing meals (7.4 mmol/l [4 g] and 7.4 mmol/l [8 g]) compared with the control meal (8.6 mmol/l). Peak insulin concentrations and the incremental areas for glucose and insulin from 0 to 120 min were also significantly reduced after both HV-HPMC doses versus control (all $P < 0.01$). The values for glucose and insulin IAUCs from 0 to 180 min were lower after both HV-HPMC tests versus control, but the differences were less pronounced than those during the first 120 min ($P < 0.05$ versus control except IAUC for insulin 0–180 min). An exploratory analysis of glucose and insulin values at each time point showed that levels of both were significantly lower than control in the 4- and 8-g HV-HPMC conditions from 15 through 60 min.

Tolerability

No statistically significant differences were noted across conditions for any of the gastrointestinal tolerability parameters (data not shown).

CONCLUSIONS — The results of the present trial demonstrate that inclusion of 4 or 8 g HV-HPMC in a carbohydrate-rich meal significantly blunted postprandial glucose and insulin excursions in overweight and obese men and women. These effects were most evident during the first 120 min after meal consumption, which is consistent with delayed absorption rather than a reduction in the total quantity of carbohydrate absorbed.

Although a previous trial showed lower peak (24%) and total (15%) postprandial glucose responses in subjects with type 2 diabetes when 10 g HV-HPMC was incorporated into a meal, no significant reductions were observed in subjects without diabetes who had a mean BMI of 30.2 kg/m^2 (20). The explanation for the difference in results for the subjects without diabetes between the present investigation and that of Reppas et al. (20) is not readily apparent. Because the prior trial included a small sample ($n = 10$), the 95% CI for the difference between conditions in peak and total glucose responses was large; thus, the lack of effect may have been a chance finding. The results of the present study are concordant with those of other trials that have shown blunted glucose and insulin responses in insulin-resistant subjects with and without glucose intolerance when viscous fibers such as psyllium, guar, or β-glucan have been included in carbohydrate-rich meals (4,12–15).

No evidence of dose response was present in the current study. In fact, the mean glucose responses were essentially indistinguishable between the 4- and 8-g HV-HPMC conditions, both showing reductions of 14% in the peak postprandial glucose response compared with control. This finding suggests that the acute effects may be maximal at the 4-g dose. Previous research indicates that blunting of postprandial glucose and insulin responses induced by viscous fibers is potentiated after chronic dosing (4,13,15). Therefore, it is possible that clinically important ef-

Table 2—*Insulin and glucose responses by treatment condition*

Parameter	0 g HV-HPMC	4 g HV-HPMC	8 g HV-HPMC	*P**
Peak glucose (mmol/l)	8.6 ± 0.3	7.4 ± 0.2	7.4 ± 0.2	<0.001
Pairwise†		<0.001	<0.001	
Glucose IAUC 0–120 min‡	363 ± 34	235 ± 29	233 ± 24	0.001
Pairwise		0.002	0.004	
Glucose IAUC 0–180 min	521 ± 51	395 ± 50	391 ± 45	0.025
Pairwise		0.025	0.044	
Peak insulin (pmol/l)	473 ± 54	306 ± 41	280 ± 48	<0.001
Pairwise		<0.001	<0.001	
Insulin IAUC 0–120 min	24,003 ± 3,184	16,454 ± 2,827	13,376 ± 2,000	<0.001
Pairwise		0.025	<0.001	
Insulin IAUC 0–180 min	28,090 ± 3,864	22,754 ± 3,964	18,114 ± 2,707	0.010
Pairwise		0.300	0.0120	

Data are means ± SEM. $n = 31$ for each variable. **P* values from repeated-measures ANOVA. †Pairwise comparisons to control were derived by Dunnett's test. ‡Units for glucose IAUC are (millimoles per liter) × minute and for insulin IAUC are (picomoles per liter) × minute.

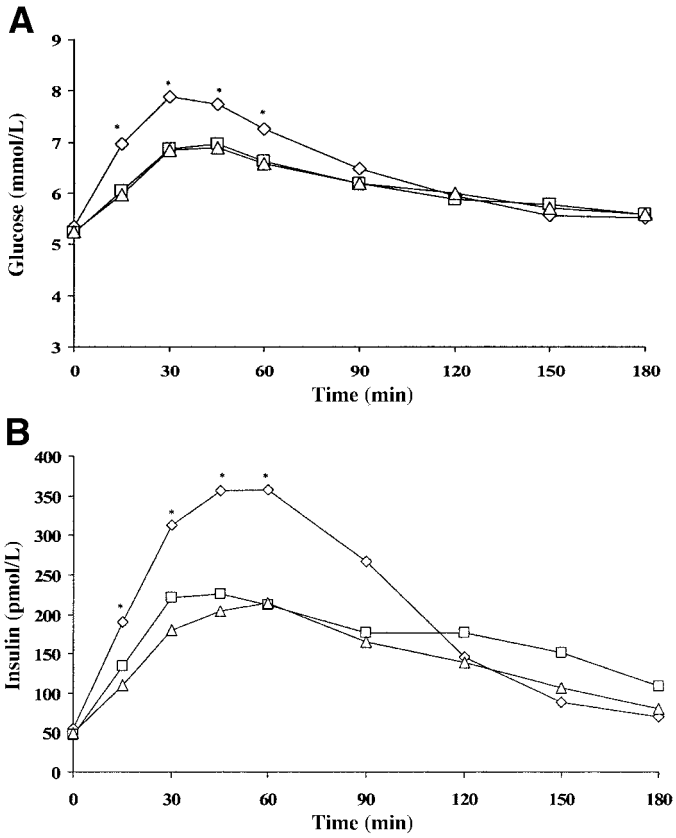

Figure 1—A: *Mean plasma glucose values during meal tolerance tests by treatment condition.* ○, *control;* □, *4 g HV-HPMC;* △, *8 g HV-HPMC.* *P < *0.05 vs. the 4- and 8-g HV-HPMC conditions.* B: *Mean serum insulin values during meal tolerance tests by treatment condition.* ○, *control;* □, *4 g HV-HPMC;* △, *8 g HV-HPMC.* *P < *0.05 vs. the 4- and 8-g HV-HPMC conditions.*

fects may be produced by chronic consumption of HV-HPMC at intakes lower than those used in the present trial.

Inclusion of HV-HPMC reduced the mean IAUCs from 0 to 120 min for glucose by ~35% and for insulin by 35–44%, thus, effectively lowering the dietary "glycemic load" (22). Although still the subject of controversy, data from clinical and epidemiological investigations (6,22,23) support the concept that reducing dietary glycemic load may lower risks for diabetes and cardiovascular disease, lending support to the beneficial effects suggested by results from trials with acarbose (9,10).

A recently published study (24) showed that, although acarbose significantly reduced postprandial hyperglycemia versus placebo in subjects with a baseline fasting plasma glucose between 5.5 and 7.8 mmol/l, there was no difference in the cumulative rate of conversion to frank fasting hyperglycemia with fasting glucose >7.8 mmol/l (29% with acarbose vs. 34% with placebo, $P = 0.65$). A post hoc analysis of the subset who entered with a fasting plasma glucose <7.0 mmol/l showed that the rate of progression to fasting plasma glucose ≥7.0 mmol/l may have been reduced by acarbose ($P = 0.04$). This finding suggests that to see a benefit from delayed glucose absorption, it may be necessary to intervene before β-cell dysfunction is too advanced.

The cellulose backbone of HV-HPMC is resistant to fermentation by the intestinal flora in humans, which may be an advantage regarding the likelihood of producing gastrointestinal side effects (25). The present trial confirmed that HV-HPMC was well tolerated and did not significantly increase the frequency of gastrointestinal complaints compared with the cellulose control. These findings are consistent with results from studies in which subjects consumed HV-HPMC daily for several weeks (17,18). Gastrointestinal complaints are reported by a substantial minority of individuals who use therapeutic doses of α-glucosidase inhibitors (7) and more fermentable viscous fibers such as β-glucan and guar (13,14), which can be significant barriers to long-term adherence with the use of these products.

The National Cholesterol Education Program Adult Treatment Panel III guidelines recommend incorporation of 10–25 g/day of viscous fiber into the diet as an adjunct to Therapeutic Lifestyle Changes for management of hypercholesterolemia (26). In prior studies, consumption of 5.0–30.0 g/day HPMC lowered LDL cholesterol by 12–38% (17,18).

In summary, consumption of 4 or 8 g HV-HPMC with a meal significantly blunted postprandial glucose and insulin excursions in overweight and obese men and women. These findings, along with those from previous studies showing hypocholesterolemic effects, suggest that daily HV-HPMC consumption may prove useful as an adjunct to weight management and physical activity for reducing risks for diabetes and cardiovascular disease. Additional research is warranted to assess the dose-response characteristics of HV-HPMC and to evaluate longer-term effects on glucose homeostasis.

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