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Hydroxypropylmethylcellulose and Methylcellulose Consumption Reduce Postprandial Insulinemia in Overweight and Obese Men and Women[1,2]

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Abstract

Hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC) are modified cellulose dietary fibers that generate viscous solutions in the gastrointestinal (GI) tract. This study assessed the effects of high viscosity (HV) HPMC, ultra-HV (UHV) HPMC, and medium viscosity MC on postprandial glucose and insulin responses in overweight and obese men and women ($n = 50$). After overnight fasts, subjects consumed 5 breakfast meals containing 75 g carbohydrate, each of which contained 1 of the following: 1 g HV-HPMC, 2 g HV-HPMC, 2 g UHV-HPMC, 4 g medium-viscosity MC or control (2 g cellulose). Test sequence was randomized and double-blind, except the MC test, which was last and single-blind (46 subjects completed all 5 tests). Glucose and insulin responses were determined pre-meal and for 120 min postprandially. Median (interquartile limits) peak glucose concentration was lower ($P = 0.001$) after the meal containing 2.0 g UHV-HPMC (7.1, 6.3–8.2 mmol/L) compared with the control meal (7.7, 6.6–8.7 mmol/L). The control did not differ from the other conditions for peak glucose or for any of the HPMC/MC conditions for glucose incremental areas under the curves (IAUC). Peak insulin was reduced ($P < 0.05$) for all HPMC/MC conditions compared with control. Insulin IAUC was lower than control ($P < 0.001$) after meals containing 2 g HV-HPMC, 2 g UHV-HPMC, and 4 g MC. GI symptoms did not differ among treatments. These findings indicate that HV-HPMC (1 and 2 g), UHV-HPMC (2 g), and MC (4 g) consumption reduced postprandial insulin excursions consistent with delayed glucose absorption. J. Nutr. 138: 292–296, 2008.

Introduction

Viscous dietary fibers such as β-glucan, psyllium, pectins, and some gums lower postprandial glucose and insulin excursions when administered with a meal (1–5). The degree of viscosity appears to be inversely related to glycemic response, with the more viscous dietary fibers producing greater effects (2,4,5). These fibers form viscous solutions when mixed with the gastrointestinal (GI)[5] tract contents, slowing gastric emptying and thickening small intestinal contents. This may reduce contact between food and digestive enzymes and interfere with diffusion of nutrients to absorptive surfaces, thus slowing the rate at which glucose molecules become available for absorption at the small-intestinal brush border (2,6).

There is growing interest in therapeutic interventions that modulate glycemic response. It has been suggested that lowering dietary glycemic load may be advantageous for individuals at risk for type 2 diabetes, coronary heart disease, and obesity (7–11). Over time, consumption of a high glycemic load diet by individuals with insulin resistance and compensatory hyperinsulinemia may contribute to pancreatic β-cell exhaustion and the eventual development of glucose intolerance (12,13).

One class of medications, the α-glucosidase inhibitors, delay starch digestion, thereby lowering postprandial glucose and insulin concentrations (14). The Study To Prevent Non-Insulin Dependent Diabetes Mellitus found that using an α-glucosidase inhibitor (acarbose) reduced new onset diabetes by 25%, new onset hypertension by 34%, and the cardiovascular event rate by 49%, compared with placebo, after 3.3 y of follow-up among subjects with impaired glucose tolerance (15,16). In a substudy, the acarbose group also showed less progression of carotid intima-media thickness, a surrogate marker for atherosclerosis, further supporting a possible beneficial effect on cardiovascular health (17). Given that highly viscous dietary fibers exert effects similar to acarbose on the rate of glucose absorption, it is reasonable to hypothesize that they might also have favorable effects on the risks for both diabetes and cardiovascular disease.

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[5] Abbreviations used: Cp, centipoise; GI, gastrointestinal; HPMC, hydroxypropylmethylcellulose; HV, high viscosity; IAUC, incremental area under the curve; MC, methylcellulose; rpm, revolutions per minute; t, time; UHV, ultra-high viscosity.
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Hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC) are modified cellulose fibers that produce viscous solutions in the GI tract (18,19). A previous study showed that 10 g of high viscosity (HV) HPMC consumed as part of a meal reduced peak blood glucose concentrations by 24% in subjects with type 2 diabetes compared with a cellulose control (20). The area under the plasma glucose curve from 0 to 6 h was also reduced by 15% (20). However, there were no significant effects of HV-HPMC on the blood glucose responses following a standard meal in healthy volunteers. More recently, our group showed that inclusion of 4.0 or 8.0 g of HV-HPMC with a breakfast meal significantly lowered peak glucose (14–15%), peak insulin (35–42%), and postprandial incremental areas for glucose (38–42%) and insulin (44–51%) in overweight and obese adults without diabetes (9).

This study evaluated the influences of lower doses of HV-HPMC (1 and 2 g) than have been previously studied on postprandial glucose and insulin responses in subjects at risk for diabetes. In addition, the effects of 2 g of ultra-HV (UHV) HPMC and 4 g of moderate viscosity MC on postprandial glucose and insulin responses were assessed.

Materials and Methods

Study design. This was a controlled crossover clinical trial conducted at a single clinical research site (Provident Clinical Research, Bloomington, IN). Four of the 5 test conditions were administered in a randomized, double-blind manner. The 5th test condition (MC) was considered secondary, so it was administered last in the sequence, in a single-blind manner, to minimize the potential influence of subject attrition on the other test conditions. This study was conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and US 21 CFR. An institutional review board (Schulman Associates Institutional Review Board, Inc., Cincinnati, OH) approved the protocol before initiation of the study. Written informed consent was obtained from all subjects before protocol-specific procedures were carried out and subjects were informed of their right to withdraw from the study at any time.

Subject selection. Subjects were men and women (18–64 y of age) required to have a BMI $\geq$ 27.0 kg/m^2 and $<$ 40.0 kg/m^2, to have good or excellent classification on a Vein Access Scale, and to be in apparent good health, as indicated by medical history and routine laboratory tests.

Subjects were excluded if they had diagnosed diabetes mellitus, fasting plasma glucose $\geq$ 7.0 mmol/L, or fasting plasma triglycerides $\geq$ 5.7 mmol/L. Subjects were also excluded if they had abnormal laboratory test results of clinical relevance, history of surgery for weight-reducing purposes, or a GI condition that could interfere with study product absorption. Subjects with uncontrolled hypertension or women who were pregnant or planning to be pregnant during the study period were not allowed to participate in the study. Subjects were also excluded if they took medications known to influence carbohydrate metabolism, including adrenergic blockers, diuretics, thiazolidinediones, systemic corticosteroids, or any class of hypoglycemic drug.

Clinic visits. Subjects had a screening visit and 5 test visits, each separated by at least 48 h. Informed consent and medical history were obtained at screening along with height and weight. Chemistry and hematology measurements were also taken at screening to assess general health status and an in-clinic urine pregnancy test was administered for all women $<$56 y of age.

For each test day, subjects reported to the clinic after a fast of at least 10 h. Body weight, vital signs, a 24-h diet recall (utilized to verify that the subject's usual diet contained at least 150 g of carbohydrate daily), and a meal tolerance test were completed at all test visits. For the meal tests, a venous catheter was inserted for collection of samples for measurement of plasma glucose and serum insulin concentrations pre-meal and at time (t) = 15, 30, 45, 60, 90, and 120 min, where t = 0 was the start of test meal consumption. A GI tolerability questionnaire was administered via telephone ~24 h after the start of each meal tolerance test.

Test meals and experimental treatment. Qualified subjects were randomized to a treatment sequence by study staff who were unaware of the study treatments. Test articles were prepackaged and labeled with a test sequence, so neither the staff nor subjects knew what was consumed on each of the first 4 test days. Staff members, but not subjects, were aware that the final test product was MC.

Each test meal consisted of a bagel, butter, 23 g anhydrous glucose, and a powdered beverage mix (sugar-free Crystal Light lemonade) into which the HPMC or control had been incorporated (**Table 1**).

Test articles. The HPMC was Fortefiber (Dow Chemical Company). Fortefiber was manufactured according to the United States Pharmacopoeia (USP 27 NF22 S1 for Hypromellose, USP substitution 2208) with nominal viscosity measured in a 1% aqueous solution at 20°C using a Brookfield digital viscometer. The calculated viscosities for the HPMC products were as follows: HV-HPMC = 5 Pa · s and UHV-HPMC = 7.5 Pa · s (20 revolutions per minute (rpm), spindle 4, using a Brookfield RVT). The MC sample was from Dow Chemical Company, manufactured to food grade specifications. The viscosity of the MC was 0.022 Pa · s (12 RPM, spindle 3, Brookfield LVT). Using the United States Pharmacopeia method for Procedure for Cellulose Derivatives under Viscosity method 911, the nominal viscosities of the treatments measured in 2% aqueous solutions were as follows: HV-HPMC = 100,000 centipoise (Cp), UHV-HPMC = 250,000 and MC = 4,000 cP. The HPMC and MC utilized were derived from cotton and/or wood pulp.

Study product tolerance. Approximately 24 h after the start of each test meal, subjects were contacted by telephone for administration of the GI Tolerance Questionnaire. Subjects were asked to rate the presence and severity of 6 GI symptoms over the prior 24-h period, including gas/bloating, cramping, flatulence, nausea, constipation, and diarrhea/loose stool (21). These symptoms were measured on a 5-point scale: 0 = absent, 1 = much less than usual, 2 = somewhat less than usual, 3 = usual, 4 = somewhat more than usual, and 5 = much more than usual.

Laboratory measurements. Elmhurst Memorial Hospital (Elmhurst, IL) conducted all laboratory analyses utilizing Beckman instruments except where otherwise noted. Serum chemistry analysis was conducted on the LX20 and hematology (performed on EDTA whole blood) testing employed the 750. Urinalysis was completed using the IRIS/200 (IRIS International). The glucose oxidase method was used to measure plasma glucose (22) and a chemiluminescent immunoassay was utilized to determine serum insulin (23).

Statistical analyses. An evaluable sample of 42 subjects was expected to provide 80% power (nominal α = 0.0106, 2-sided, to account for 10 comparisons) to detect differences in response of 0.55 SD in the incremental areas under the curves (IAUC) for glucose (24). A sample of 50 subjects was randomized to allow for attrition and noncompliance.

Statistical analyses were generated using SAS version 9.2 (SAS Institute). All data are reported as means ± SEM unless noted otherwise.

TABLE 1 Nutrient composition of test meal[1]

	Energy[2]	Carbohydrate	Protein	Fat
	kcal		*g*	
Plain bagel	251	51.5	9.0	1.0
Salted butter pats	73	0.0	0.1	8.1
Sugar-free powdered lemonade mix	5	0.6	0.6	0.0
Anhydrous glucose	92	23.0	0.0	0.0
400 mL water	0	0.0	0.0	0.0
Totals	421	75.1	9.7	9.1

[1] Nutrient composition values were obtained from Food Processor Nutrition Analysis and Fitness Software (Version 8.5.0, Salem, OR).
[2] 1 kcal = 4.1868 kJ.

The primary efficacy analysis was completed on an efficacy evaluable population that included all subjects who consumed the control product and at least 1 of the active products (HPMC or MC) and had 120 min of valid postprandial glucose and insulin values for both of these test conditions. The glucose and insulin IAUC from 0 to 120 min (where t = 0 was the start of the test meal) were calculated as described by Wolever et al. (6).

The Shapiro-Wilk test (25) was used to assess normality of the distribution of response variables. Where the normality assumption was rejected, rank transformations were employed. Glucose and insulin responses are expressed as medians and interquartile limits, because the normality assumptions were rejected ($P < 0.05$) for the distributions of these variables.

Repeated measures ANOVA was used to assess possible differences among test conditions. Paired *t* tests were used for pairwise comparisons for models where a significant F-ratio was present. All *P*-values reported for response variables are 2-sided and those <0.20 have been adjusted for multiple comparisons by multiplying by 4.717 to maintain the family-wise error rate at 0.05 (0.05/0.0106 = 4.717; 25).

Results

Subject characteristics. Recruitment occurred from December 2006 to January 2007 and the last subject exited the study on February 16, 2007. We screened 81 subjects, 50 of whom were randomized. Forty-nine subjects, 24 men, 25 women, 87.8% non-Hispanic White, and 8.2% African-American with a mean age of age of 36.6 ± 1.9 y and BMI 30.8 ± 0.5 kg/m^2 completed a control test plus at least 1 other condition and thus were included in the efficacy evaluable sample. Forty-six subjects consumed all 5 of the test meals. One subject withdrew because of difficulty with maintenance of adequate venous access for testing and 3 withdrew consent without completing all treatment conditions.

Glucose and insulin responses. The peak glucose concentration was lower ($P < 0.001$) after the meal containing 2.0 g UHV-HPMC (median, interquartile limits: 7.1, 6.3–8.2 mmol/L) compared with the control meal (7.7, 6.6–8.7 mmol/L; **Fig. 1***A*). No other test conditions differed for peak glucose concentrations or glucose IAUC values (**Table 2**).

Median peak insulin concentrations were reduced after all HPMC (−9 to −26%) and MC (−10%) conditions compared with the control meal (Table 2). Insulin IAUC were lower than the control meal ($P < 0.001$) for the 2 g HV-HPMC (−24%), 2 g UHV-HPMC (−33%), and 4 g MC (−20%) conditions (Table 2; Fig. 1*B*). The median insulin IAUC was also significantly lower during the 2 g UHV-HPMC meal than for the 1 g HV-HPMC and 4 g MC meals ($P < 0.001$).

Tolerability. Adverse events overall, or by body system (body as a whole; central and peripheral nervous system; GI system; respiratory system; skin and appendages) did not differ after the various meals nor did any of the variables assessed with the GI tolerability questionnaire (data not shown).

Discussion

The results of this trial extend those from earlier work (9), which demonstrated that inclusion of 4 or 8 g of HV-HPMC in a carbohydrate-rich meal significantly blunted postprandial glucose and insulin excursions in overweight and obese men and women. In this study, all of the HPMC/MC formulations investigated were associated with reductions in peak (9–26%) and incremental (8–33%) insulin responses. However, only UHV-HPMC significantly blunted the peak glucose level (7%) and IAUC for glucose did not differ significantly from control for any of the HPMC/MC test conditions. The observed reductions in postprandial insulin responses are consistent with modest slowing of the rate of glucose absorption and suggest that postprandial insulin response may be a more sensitive indicator of the rate of glucose absorption than postprandial glucose.

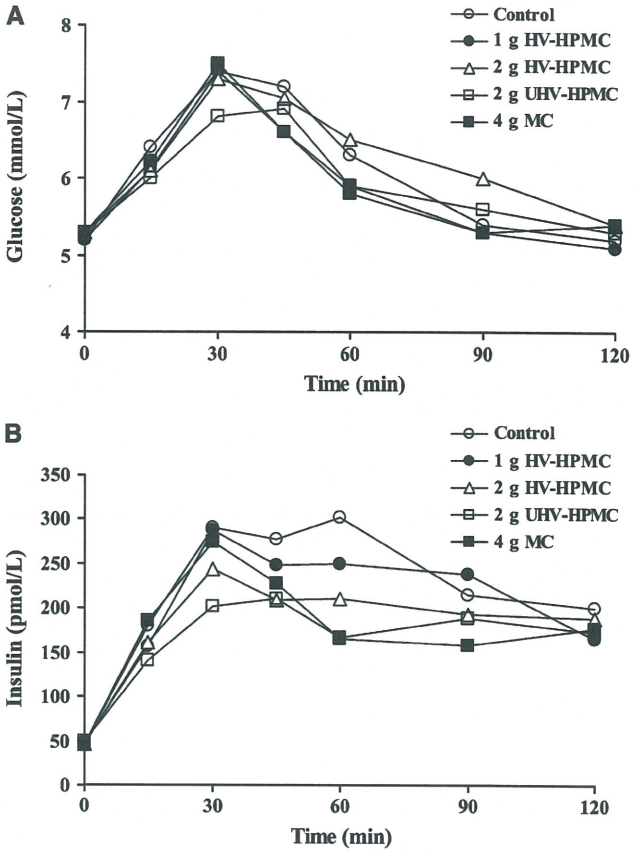

FIGURE 1 Postprandial plasma glucose (*A*) and serum insulin (*B*) concentrations in overweight and obese men and women after consuming a standardized 75-g carbohydrate breakfast containing various cellulose fibers. Values are medians, $n = 49$, and are shown as indicators of central tendency because glucose and insulin peak concentrations and IAUC data were not normally distributed. Data at individual time.

In this trial, peak insulin concentrations were reduced by 9% with 1 g and 21% with 2 g of HV-HPMC. In a prior study, peak insulin concentrations were reduced by 35% (4 g HV-HPMC) and 42% (8 g HV-HPMC) vs. control. Taken together, the results from these 2 investigations are suggestive of a dose-response effect.

Studies in animals have shown that the effect of HV-HPMC and MC on glucose absorption is dependent upon the viscosity of the solution administered (19,26,27). In this study, the most viscous treatment, UHV-HPMC, tended to have the largest effect to blunt peak (−26%) and incremental (−33%) insulin responses and was the only condition for which peak glucose concentration was reduced (−7%) vs. control. Similar results have been reported for other viscous dietary fibers (2,4,5). For example, Leclere et al. (5) observed attenuated glucose and insulin responses following starch meals containing highly viscous guar gum compared with equal amounts of low-viscosity guar gum. Thus, it appears likely that both dose and the ability to form viscosity when hydrated are important determinants of the effects of a dietary fiber on postprandial glucose and insulin responses.

TABLE 2 Postprandial peak plasma glucose and serum insulin concentrations and IAUC in overweight and obese men and women after consuming a 75-g carbohydrate breakfast containing various cellulose fibers[1]

Variable	Control (2 g cellulose)	1 g HV-HPMC	2 g HV-HPMC	2 g UHV-HPMC	4 g MC
Peak glucose, *mmol/L*	7.7 (6.6–8.7)	7.6 (6.7–8.6)	7.7 (6.6–8.0)	7.1* (6.3–8.2)	7.5 (6.6–8.6)
Glucose IAUC, *mmol·min/L*	100 (59–184)	102 (54–160)	103 (48–162)	79 (52–139)	87 (48–146)
Peak insulin, *pmol/L*	369 (259–574)	338* (217–490)	292* (222–429)	274*,** (181–400)	331* (224–494)
Insulin IAUC, *nmol·min/L*	21.1 (16.1–35.1)	19.5 (13.0–28.0)	16.1* (12.1–22.7)	14.1*,*** (11.3–23.2)	16.8* (12.4–25.0)

[1] Values are medians (interquartile limits), $n = 46$–49. *Different from control, $P < 0.05$; **Different from 1 g HV-HPMC and 4 g MC conditions, $P < 0.001$; ***Different from 1 g UHV-HPMC conditions, $P = 0.015$.

The intermediate response of the lower viscosity, higher dose MC on postprandial insulin in this study is consistent with this hypothesis.

To the best of our knowledge, this study is one of very few trials to test the effects of MC on postprandial glucose and insulin responses. Previously, Jenkins et al. (2) provided small groups of healthy subjects ($n = 5$ or 6) different dietary fiber sources, including 14.5 g of low viscosity MC as part of a 50-g glucose tolerance test. Venous glucose and insulin concentrations were measured for 120 min. MC reduced the IAUC for glucose by 29% during the first hour. However, there were no differences in postprandial insulin concentrations. Our study in overweight and obese subjects utilized a lower dose of a more viscous formulation of MC, provided as part of a high-carbohydrate (75 g) meal. In contrast to the findings of Jenkins et al. (28), we observed a blunting of postprandial insulin levels but not of the postprandial glucose response.

Although still controversial, there is a growing body of literature supporting the concept that prolonging carbohydrate absorption may lower risks for diabetes and cardiovascular disease (8,15,16,28). The potential for such interventions to prevent or delay the onset of type 2 diabetes may be most pronounced for individuals with insulin resistance and/or mild glucose intolerance, before β-cell dysfunction is too advanced (15,29). Given the high prevalence of conditions such as impaired fasting glucose, impaired glucose tolerance, and the cardiometabolic syndrome in the U.S. population (30,31), if consumption of viscous dietary fiber proves to be efficacious for diabetes prevention, the public health implications would be substantial. Moreover, viscous fibers, including HPMC, have been found to effectively lower total and LDL cholesterol levels (32–36). Consumption of 10–25 g/d of viscous fiber is recommended as an adjunct to a diet low in saturated fat and cholesterol by the National Cholesterol Education Program (37).

A majority of published studies on viscous fibers has utilized acute doses of 5–15 g (2–5) to assess effects on postprandial glucose and insulin concentrations in subjects with and without diabetes. However, incorporation of such quantities of viscous fiber into a single serving of a palatable food product is challenging (38). Therefore, it is important to establish the lower limits of intake that might be expected to provide beneficial effects. In addition, many viscous fibers, such as β-glucan, pectin, and guar gum, are partially fermentable, which may produce GI symptoms such as bloating, cramping, and flatulence (39). Because HPMC and MC are resistant to fermentation by intestinal flora (40), they may be less likely to produce such side effects. In this study, the frequency and severity of GI complaints did not differ between the control and HPMC/MC treatment conditions, consistent with findings from studies in which HPMC has been consumed for periods of several weeks (34–36).

In summary, consumption of HV-HPMC, UHV-HPMC, and MC with a meal significantly blunted postprandial insulin excursions and was well tolerated in overweight and obese men and women. These findings add to those from prior studies suggesting that consumption of HPMC has potential therapeutic value in the management of risk factors for type 2 diabetes and cardiovascular disease.

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