Glycemic Response to a Food Starch Esterified by 1-Octenyl Succinic Anhydride in Humans

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To evaluate the glycemic response to a food starch esterified by 1-octenyl succinic anhydride (OSA), 30 healthy nondiabetic adult subjects were studied in a double-blind crossover design. After an overnight fast, subjects consumed a product containing either 25 g of glucose or 25 g of OSA-substituted starch. Finger-prick capillary blood was obtained at baseline and 15, 30, 45, 60, 90, and 120 min postprandial for glucose measurement. After OSA treatment, the rise in blood glucose was reduced ($P < 0.05$) at 15 and 30 min and tended ($P < 0.08$) to be lower at 45 min. Mean peak rise in glucose was reduced 19% ($P < 0.01$) by OSA (3.30 ± 0.19 versus 2.66 ± 0.16 mmol/L) compared to glucose, but time to peak did not differ between treatments. Net incremental area under the curve was also lower ($P < 0.05$) on OSA compared to glucose. Minimal effects on gastrointestinal symptoms (intensity and frequency of nausea, cramping, distention, and flatulence) were noted for both products, with no clinically significant difference between products. In conclusion, starch substitution with OSA attenuated the postprandial glycemic excursion compared to an equivalent glucose challenge and was well tolerated by fasting healthy adult subjects.

Keywords: *Glycemic response; humans; 1-octenyl succinic anhydride; modified starch*

INTRODUCTION

The prevalence of physician-diagnosed diabetes in U.S. adults is estimated to be 5.1% (*1*), and it continues to be a major health problem because of the increasing frequency of obesity and sedentary lifestyles. According to the American Diabetes Association, many medical experts believe that there is potential for the long-term management of the complications associated with diabetes through tight glycemic control (*2*). Intensive therapy to control blood glucose has been shown to improve quality of life in people with diabetes (*3*, *4*), and dietary choices can have a profound impact upon glycemic control (*5*). Dietary recommendations have been made to replace saturated fat with complex carbohydrates (e.g., starch); however, the glycemic responses to different dietary carbohydrate sources are not the same (*6*, *7*).

Numerous chemically modified food starches are available as ingredients for processed foods and are used to enhance physical and nutritional stability of the product. Chemical treatments currently allowed and used to produce modified starches for food use in the United States include esterification, etherification, acid modification, bleaching, and oxidation (*8*). Multiple modifications of starch are a common occurrence for making starches with specific applications in the food industry. Wolf et al. (*9*) postulated that the use of these modifications might allow for the production of a slowly digested starch that could be used for the treatment of certain medical modalities (e.g., glycogen storage disease and diabetes mellitus) by improving the postprandial glycemic excursion (i.e., prevention of hyperglycemia and hypoglycemia).

Wolf et al. (*9*) found that the etherification of waxy and high-amylose cornstarch with propylene oxide decreased the extent of starch digestion in vitro. In the case of dextrinization, as the degree of modification increased, the level of digestible starch decreased, suggesting an increase in the amount of resistant starch. They postulated that the use of chemically modified starch should attenuate the glycemic response. In healthy young men, Raben et al. (*10*) evaluated the glycemic response to isocaloric meals containing 50 g of modified potato starch. The glycemic and insulinemic responses were similar between a 1−2% acetylated potato starch and an unmodified potato starch. In contrast, β-cyclodextrin supplementation at 2% flattened the glucose curve and lowered the insulin response. On the basis of these two studies, the glycemic response to modified starch appears to be dependent upon both the type and level of modification.

Starch esterified by octenyl succinic anhydride (OSA) has been used by the food industry for over 30 years. Esterification of starch with OSA provides hydrophobic domains that enhance the emulsifying ability of starch. As a result, OSA-modified starch improves the mixing characteristics and stability of elemental or protein-hydrolysate formulas in which protein is absent or the natural emulsifying properties of milk or vegetable proteins have been destroyed by partial protein hydroly-

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sis (*11*). Toxicology studies have shown that OSA-modified starch is safe when fed at up to 15 g/kg of body weight/day in rats (*12*). Even though OSA-modified starch has been in the food supply for many years, limited clinical data on this ingredient are available (*13*), and the glycemic response of this modified starch is unknown.

We postulated that OSA substitution should interfere with the binding of α-amylase, thus decreasing the rate and/or extent of starch digestion. The formulation of novel products with carbohydrates of low glycemic index should therefore enhance the use of nutrition as adjunctive therapy for people with diabetes mellitus. The primary objective of this study was to determine the glycemic response to a food starch esterified by OSA in healthy nondiabetic adult subjects. A secondary objective was to evaluate the effects of an acute challenge of 25 g of OSA-substituted starch on subjective gastrointestinal tolerance.

MATERIALS AND METHODS

In Vitro Starch Digestion. Because differences in the glycemic response to dietary starch are directly related to rate of starch digestion (*14*), an in vitro starch digestion method was used to predict the extent of starch digestion over time in the small intestine. The percentage of digestible starch was determined as described by Wolf et al. (*9*), who used a modification of the method of Muir and O'Dea (*15*, *16*; α-amylase and amyloglucosidase enzyme system). A 15-h in vitro incubation has been shown to correlate with the amount of starch escaping digestion in the small intestine (*16*).

The extent of OSA-substituted starch (Capsul, dextrose equivalency ≅ 3, degree of substitution ≅ 0.07; National Starch and Chemical Co., Bridgewater, NJ) hydrolysis over time was compared to the extent of digestion of common cornstarch (Agro, CPC International, Englewood Cliffs, NJ). Both starches were tested in raw and cooked states. For cooking, 0.1 g of carbohydrate was suspended in 1 mL of water and autoclaved for 30 min at 2.1 kg/cm^2 and 121 °C. Immediately after autoclave treatment, starch samples were cooled in a cold water bath for 10 min and then used in the in vitro procedure as described by Wolf et al. (*9*).

Subjects. A total of 30 healthy nondiabetic (fasting plasma glucose value of <6.1 mmol/L; *17*) volunteers (12 men and 18 women) were recruited. Subjects had a mean (±SE) age of 43 ± 3 years (range = 20−74 years), weight of 68 ± 2 kg (range = 50−93 kg), and body mass index of 24.1 ± 0.6 kg/m^2 (range = 19.4−32.2 kg/m^2). Twenty-five were self-described as Caucasian, four as Asian or Pacific Islander, and one as other. Subjects did not have active gastrointestinal or metabolic diseases, a first-degree family history of diabetes mellitus or glucose intolerance, or recent infection, surgery, or corticosteriod treatment. No subjects were receiving oral contraceptives. During subject screening, a fasting blood draw was obtained for determination of routine serum chemistry values (St. Michael's Hospital, Toronto, ON, Canada). All subjects gave written informed consent to the protocol, which was approved by the Western Institutional Review Board (Olympia, WA).

Dietary Treatments. Two dietary treatments were evaluated in the study (Table 1): (1) glucose [25 g of dextrose (Corn Products International Inc., Bedford Park, IL) per 238 g serving] and (2) OSA [25 g of 1-octenyl succinic anhydride-substituted starch (Capsul; National Starch and Chemical Co.) per 241 g serving]. Details regarding the starch processing parameters are proprietary industry trade secrets. Ingredients were made into a 10.4% solution with water, filled into 250-mL glass bottles, and terminally sterilized (Ross Products Division of Abbott Laboratories, Columbus, OH). Sodium citrate and citric acid were added as buffers to both products to prevent the isomerization of glucose in the glucose product.

Table 1. Ingredient Composition of Test Products[a]

	g/100 g	
ingredient	glucose treatment	OSA treatment
dextrose	10.40	0.00
OSA	0.00	10.40
sodium citrate	0.15	0.15
citric acid	0.10	0.10
water	89.35	89.35

[a] Product fill weights were 238 ± 3 and 241 ± 3 g for glucose and OSA, respectively.

The products were incorporated into pourable solutions that were consumed as a beverage (viscosity < 5 mPa·s).

Experimental Design. The study was a double-blind crossover design in which subjects participated in two 2-h meal glucose tolerance tests on separate occasions. Subjects were randomly assigned to one of two treatment sequences. After an overnight fast, subjects consumed either the glucose or OSA product. To ensure that subjects had similar glycogen stores on the two test days, subjects were instructed to consume a high-carbohydrate diet (goal = 300 g/day, minimum = 150 g/day) for 3 days before each meal glucose tolerance test and also were asked to avoid exercise for 24 h before the experiment. On the evening before each meal glucose tolerance test, all subjects consumed a low-residue dinner consisting of one 8 fl oz (237 mL) can of chocolate Ensure Plus with additional Honey Graham Crunch Ensure Bars to provide one-third of each subject's individual daily caloric requirement as estimated by the Harris−Benedict equation multiplied by an activity factor of 1.3 (*18*). After their low-residue evening meal, subjects were instructed to fast overnight, during which they were allowed to consume only water. Smoking was prohibited. Subjects returned within 14 days (range = 5−14 days) for repeat analysis with the appropriate crossover treatment. Subjects were allowed water (250 mL) during each 2-h test. All subjects were recruited and enrolled from one study site.

Blood Glucose Analysis. A fasting (mean of 13 h, range = 10−14.5 h) finger-prick capillary blood sample was obtained and collected into a fluoro-oxalate tube after 30 min of rest. Subjects then consumed the appropriate test meal within 10 min. Finger-prick capillary blood was obtained at 15, 30, 45, 60, 90, and 120 min postprandial. Samples were stored at −20 °C for a maximum of 3 days until analysis of whole blood glucose. Capillary blood glucose was measured by the glucose oxidase method using a YSI analyzer (model YSI 2300 STAT PLUS, Yellow Springs Instruments, Yellow Springs, OH).

Gastrointestinal Tolerance. Using a questionnaire, subjects were asked to report the frequency and intensity of the following symptoms: nausea, cramping, distention, and flatulence for the 24-h period immediately following consumption of the test material. Intensity and frequency were set to a 100-mm line scale (0 representing "absent" and 100 "severe" and 0 representing "usual" and 100 "more than usual," respectively). Subjects placed a single perpendicular slash mark across the 100-mm horizontal line to indicate their scores for each of these variables of frequency and intensity. A score of 5 or less was considered to be not physiologically meaningful.

Study Variables. The primary variable for this study was incremental (i.e., baseline-adjusted) peak blood glucose response. Secondary variables for this study were net incremental area under the curve (AUC) for blood glucose, relative glycemic response, and subjective gastrointestinal tolerance factors. Exploratory variables for this study were mean incremental change from baseline in blood glucose at 15, 30, 45, 60, 90, and 120 min postprandial.

Calculations. Net incremental AUC (*19*, *20*) for glucose was calculated as (AUC 0−120 min) − (120 × baseline blood glucose concentration at 0 min). The areas after the challenge were calculated with the trapezoid rule. Relative glycemic response was calculated as (net incremental AUC for OSA/net incremental AUC for glucose) × 100 (also known as relative glucose area; *21*).

Statistical Methods. Prior to conducting this experiment, a power analysis was prepared utilizing the data generated

Table 2. In Vitro Hydrolysis of Cornstarch and 1-OSA-Modified Starch Ingredients[a]

	% starch hydrolyzed (dry matter basis)					
ingredient	0 h	0.5 h	1 h	2.5 h	5 h	15 h
OSA, raw	1.1	51.7	55.1	58.2	61.0	67.8
OSA, cooked	1.2	53.4	56.9	61.7	66.5	70.0
cornstarch, raw	2.0	8.5	15.5	26.5	40.3	68.6
cornstarch, cooked	2.5	70.0	81.4	91.0	98.7	99.9

[a] Values are means of triplicate samples. Hydrolyzed starch, expressed as a percentage of ingredient dry matter, was determined according to the method of Muir and O'Dea (*15*, *16*; α-amylase and amyloglucosidase enzyme system); a 15-h in vitro incubation has been shown to correlate with the amount of starch escaping digestion in the small intestine (*16*). Time 0 values represent percent free glucose in samples.

Table 3. Clinical Chemistry Values of Subjects at Time of Screening

	value[a]
Hb A_{1c} (% of total hemoglobin)	5.0 ± 0.1
aspartate aminotransferase (units/L)	25.4 ± 1.2
LDL cholesterol (mmol/L)	2.94 ± 0.14
total cholesterol (mmol/L)	4.86 ± 0.15
chloride (mmol/L)	103 ± 0.3
total CO_2 (mmol/L)	29.3 ± 0.3
creatinine (μmol/L)	80.9 ± 2.5
HDL cholesterol (mmol/L)	1.37 ± 0.07
potassium (mmol/L)	4.3 ± 0.06
sodium (mmol/L)	144 ± 3.3
triglycerides (mmol/L)	1.23 ± 0.10
urea (mmol/L)	5.16 ± 0.28

[a] Mean ± SEM; $n = 30$ except for Hb A_{1c}, for which $n = 28$. Hb A_{1c} normal range = 3.5−6.5%.

in a similar study with healthy subjects (Goetz et al., 1987, unpublished observations). Peak glucose response was used as the variable to calculate power. A conservative estimated difference of 0.75 standard deviation (~20% decrease in peak glucose response) between treatments was used for the power calculation. We determined that a sample size of 30 would give 80% power (significance level of 0.05) to detect differences between treatments.

Data obtained during the two testing days for the glucose parameters and symptoms of gastrointestinal tolerance were fit to a two-period crossover model. The residuals obtained from fitting the two-period crossover model were examined for evidence of a normal distribution with the Shapiro−Wilk test. If the assumption of normality was rejected ($P < 0.05$ for the Shapiro−Wilk test), a nonparametric model was used. The effects of sequence, period, and treatment were examined by two-sided *t* test or two-sided Wilcoxon rank sum test, as appropriate (SAS version 8, SAS Institute, Cary, NC).

RESULTS

The extent of in vitro starch hydrolysis over time is presented in Table 2. Compared to cooked cornstarch, OSA substitution decreased the extent of starch hydrolysis by ~30 percentage units, indicating an increase in the amount of resistant starch. A majority of the digestible component of OSA was hydrolyzed quickly, in contrast to the extent of hydrolysis for raw cornstarch over time. Cooking OSA had minimal effects on its extent of hydrolysis over time. On the other hand, cooking cornstarch dramatically increased its in vitro extent of hydrolysis over time by α-amylase and amyloglucosidase.

Clinical chemistry values of the subjects evaluated in this experiment are presented in Table 3. The mean fasting blood glucose concentrations were not different ($P > 0.20$) between treatments (4.38 ± 0.06 and 4.31 ± 0.07 mmol/L for glucose and OSA, respectively). Table 4 presents data for mean peak incremental change from baseline in blood glucose and net incremental AUC for blood glucose. Mean peak incremental change from baseline and net incremental AUC for blood glucose were lower ($P < 0.01$ and $P < 0.05$, respectively) for the OSA treatment. In addition, the relative glycemic response was calculated to be 93.8 ± 11.6, indicating that OSA-substituted starch has a blunted glycemic response compared to that from glucose. The postprandial incremental change from baseline in blood glucose was reduced ($P < 0.01$) for the OSA treatment at 15 and 30 min and tended ($P < 0.08$) to be lower at 45 min (Figure 1). The postprandial incremental change from baseline in blood glucose did not differ ($P > 0.20$) between treatments at 60 and 90 min but was higher ($P < 0.01$) for the OSA treatment at 120 min.

Table 4. Incremental Change from Baseline in Peak Blood Glucose Concentration and Net Incremental Area under the Blood Glucose Curve (AUC) for Subjects Consuming 25 g of Glucose or 1-OSA-Substituted Starch[a]

item	glucose	OSA
incremental peak glucose (mmol/L)	3.30 ± 0.19	2.66 ± 0.16[b]
net incremental AUC (mmol·min/L)	127 ± 14	107 ± 14[c]

[a] Mean ± SEM, $n = 30$. Fasting blood glucose concentrations were 4.38 ± 0.06 and 4.31 ± 0.07 mmol/L for subjects consuming glucose and OSA, respectively. To convert glucose mmol/L to mg/dL, multiply mmol/L by 18.01 (glucose of 5.0 mmol/L = 90 mg/dL). [b] Different from glucose, $P < 0.01$. [c] Different from glucose, $P < 0.05$.

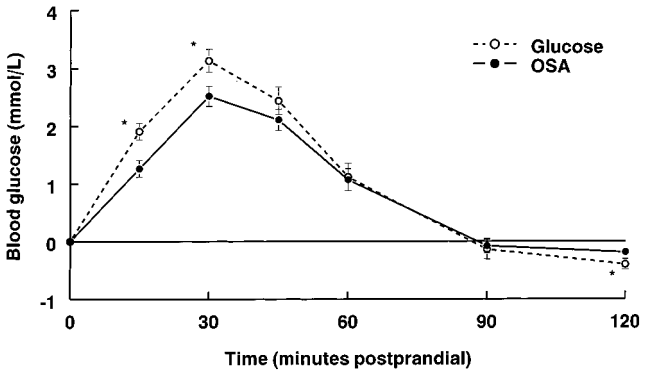

Figure 1. Incremental change from baseline in capillary blood glucose response for 30 subjects consuming 25 g of glucose or OSA. Values are mean ± SEM. Fasting blood glucose concentrations were 4.38 ± 0.06 and 4.31 ± 0.07 mmol/L for subjects consuming glucose and OSA, respectively. To convert glucose mmol/L to mg/dL, multiply mmol/L by 18.01 (glucose of 5.0 mmol/L = 90 mg/dL). *, $P < 0.05$.

Minimal effects on gastrointestinal symptoms (intensity and frequency of nausea, cramping, distention, and flatulence) were noted for both products, with no clinically significant differences between products (data not shown). No adverse events were documented for subjects consuming either product. These data document the excellent tolerance of healthy nondiabetic adult subjects given an acute challenge of 25 g of OSA.

DISCUSSION

Starch digestion primarily occurs within the lumen of the small intestine. Pancreatic amylase is present in the small intestinal lumen in large amounts such that substrate rather than activity limits digestion (*22*). It was once assumed that all starch was hydrolyzed and absorbed within the small intestine. However, it is now

known that a substantial amount of starch escapes digestion in the small intestine (*23*, *24*). Starch that escapes digestion in the small intestine enters the colon, where, through fermentation by the colonic microflora, it may influence large bowel physiology. The rate and extent of starch digestion in the small intestine are dependent upon several intrinsic and extrinsic factors (reviewed in ref *25*).

Processing treatments, storage conditions, chemical modification, and genetic breeding influence the digestibility of starch (*9*, *26*). For example, as the amount of amylose increases, the extent of in vitro hydrolysis decreases (*9*) and the glycemic response is improved (*27*, *28*). Limited data are available on the effects of these parameters on the rate of starch digestion. This topic is of nutritional importance because the rate of starch digestion may have therapeutic application. For example, individuals with type 2 diabetes mellitus could benefit from a foodstuff that contains slowly digested starch in order to improve the postprandial glycemic response (i.e., prevention of hyperglycemia and hypoglycemia).

Wootton and Chaudhry (*29*) found that starch substitution with hydroxypropyl or acetate (degree of substitution = 0.06 and 0.07, respectively) reduces the hydrolysis of gelatinized modified wheat starch by pancreatic amylase. We hypothesized that OSA substitution would decrease the extent and/or rate of starch digestion and thus attenuate the postprandial glycemic response. Our in vitro digestion data support the hypothesis that OSA will attenuate the postprandial glycemic response, but appropriate clinical studies are necessary to validate this hypothesis. The present clinical study was initiated to test this hypothesis with a food starch esterified with OSA in comparison to glucose in an oral meal glucose tolerance test in nondiabetic healthy adult subjects. The present experiment found that the postprandial glycemic excursion following a challenge with OSA-substituted starch is lower than that from glucose. Times to peak glucose concentration were similar between treatments; however, baseline-adjusted peak glucose response was reduced 19% ($P < 0.01$) by OSA. The lack of change in the time to peak glucose concentration may suggest that the difference in glycemic response is due to an overall decrease in the extent of digestion. Our in vitro data show that OSA substitution has a minimal effect on the extent of starch hydrolysis over time compared to raw cornstarch [a clinically effective slowly digested starch (*30*−*32*)]. These data may suggest that OSA substitution does not decrease the rate of starch digestion, but it decreases the extent of starch digestion. Our in vitro digestion data that show that extent (15 h) of OSA digestion is decreased compared to cooked cornstarch support this hypothesis. Using our in vitro data, we would predict that 7.5 g of the 25 g OSA challenge would be resistant to digestion in the small intestine and would become available for fermentation in the large bowel. Because fermentation of carbohydrate contributes fewer calories to the host (*33*), foodstuffs containing OSA would have a reduced caloric density. Starch substituted with OSA may enable the formulation of a product that could be used in weight management as well as improving glycemic control in people with diabetes mellitus. On the other hand, no difference in symptoms of gastrointestinal intolerance (a subjective measure of malabsorption) was noted in this double-blind study. In addition, the postprandial blood glucose response at 120 min was higher ($P < 0.05$) for OSA compared to glucose. This difference may indicate a slow, prolonged absorption rather than malabsorption of the OSA starch. Kelley (*13*) has shown that infants fed formula containing OSA-substituted starch excrete OSA and its metabolites in the urine, which suggests that the substituted units of the starch are at least partially hydrolyzed and absorbed in the small intestine. Jenkins et al. (*35*) found that the addition of 14.5 g of guar gum (a soluble, viscous dietary fiber) to a 50-g glucose tolerance test improved the postprandial glycemic excursion. This effect was attributed to a delayed mouth-to-cecum transit (measured by breath hydrogen concentration) and delayed absorption (measured by urine xylose excretion). They documented a higher blood glucose concentration at 120 min postprandial, which may be another marker of slower, prolonged absorption.

Furthermore, Jenkins et al. (*35*) conducted a clinical study in healthy volunteers to specifically evaluate the rate of glucose absorption on postprandial metabolic effects. Nine subjects consumed a 50-g bolus of glucose or sipped 50 g of glucose (3.57 g/0.25 h over 3.5 h) in a crossover design. The blood glucose concentration was higher at 120 and 180 min postprandial when subjects sipped the glucose meal (simulating a slow rate of glucose absorption). Lower doses of a carbohydrate challenge, which would be the same situation as malabsorption, correspond to a quicker decrease in blood glucose, as shown in healthy volunteers (*36*, *37*) and subjects with slightly impaired glucose tolerance (*38*). These data support the hypothesis that at least part of the OSA is slowly digested. Perhaps some of the OSA is malabsorbed, but a concurrent breath hydrogen test should be conducted to test this hypothesis.

In conclusion, starch substitution with OSA attenuated the postprandial glycemic excursion compared to an equivalent glucose challenge. Because of its lower relative glycemic response, OSA-substituted starch may serve as a carbohydrate source in a medical nutritional product developed for people with diabetes. An acute challenge of 25 g of OSA was well tolerated (i.e., no clinically significant gastrointestinal discomfort) by fasting healthy adult subjects. The nutritional use of OSA-substituted starch should attenuate the postprandial glycemic response and may decrease the caloric density of food containing it.

ABBREVIATIONS USED

OSA, 1-octenyl succinic anhydride; AUC, area under the curve; SEM, standard error of the mean.

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