Metabolic Response to Oral Challenge of Hydrogenated Starch Hydrolysate Versus Glucose in Diabetes

Madelyn L. Wheeler, MS, RD, CDE
S. Edwin Fineberg, MD
Reid Gibson, BS
Naomi Fineberg, PhD

Our objective was to determine whether *1*) hydrogenated starch hydrolysates (HSHs), bulking/sweetening agents used in hard candies, produce a diminished postmeal glycemic response relative to glucose in individuals with and without diabetes and *2*) any diminished glycemia is secondary to altered carbohydrate absorption. This study followed a randomized double-blind crossover design and was performed in 12 individuals with diabetes (6 non–insulin dependent, 6 insulin dependent) and 6 nondiabetic individuals. Each group consisted of 3 men and 3 women, none with known neuropathy. After an overnight fast, each subject was challenged with 50 g of glucose, HSH 5875 (7% sorbitol/60% maltitol), and HSH 6075 (14% sorbitol/78% hydrogenated maltooligosaccharides)/1.73 m^2 of body surface area in random order on 3 successive days. Individuals with diabetes were maintained on continuous subcutaneous insulin infusion throughout the study to achieve prechallenge glucose levels between 4.5 and 6.7 mM. For all groups, the order of plasma glucose responses over 5 h postchallenge was glucose>HSH 6075>HSH 5875, $P < 0.001$ (glucose vs. HSH). Pooled data for all groups for areas under the curve confirmed that HSH 6075 resulted in greater glycemia than HSH 5875 ($P < 0.05$). This was reflected in the order of C-peptide responses seen in the nondiabetic and non-insulin-dependent groups (glucose>HSH 6075>HSH 5875, $P < 0.001$). Breath H_2 after glucose was low, whereas HSH 5875 > HSH 6075 ($P = 0.003$). Gastric distress was noticed with all products. HSH ingestion as a single carbohydrate ingredient results in decreased glycemia relative to glucose in individuals with and without diabetes. Decreased glycemia results from altered small intestinal carbohydrate absorption. HSH as a single ingredient appears to be a suitable product for consumption by individuals with diabetes mellitus.
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Candies and gums containing hydrogenated starch hydrolysates (HSHs) are commercially marketed, with a target group being people with diabetes. HSH may constitute up to 70–98% by weight of a product, replacing sucrose and/or corn syrup. As bulking and nonreducing sweetening agents, HSH products have, in recent years, been used in candy under the independent "generally recognized as safe" (GRAS) determination of the manufacturers and distributors. GRAS-affirmation petitions were filed with the Food and Drug Administration in 1984 and 1985, have been accepted for submission, and are under review (1). If petitions were accepted, HSH use would be expanded, particularly to formulate products such as table top sweeteners and syrups.

HSH is produced via a series of chemical reactions, which begins with the partial hydrolysis of cornstarch. This reaction is controlled to produce a desired fixed ratio of glucose to polymers of glucose smaller than starch (maltooligosaccharides) (2). Subsequent hydrogenation of these polymers produces a series of products containing mixtures of polyols (sugar alcohols), each having specific uses in the confectionary industry that depend on functional properties; e.g., tendency to crystalize or hydrate (Lonza, Fair Lawn, NJ; unpublished observations).

Little research has been published concerning blood

From the Diabetes Research and Training Center, Indiana University Medical Center, Indianapolis, Indiana.

Address correspondence and reprint requests to Madelyn L. Wheeler, MS, RD, CDE, Indiana University Medical Center, DRTC, RHC 234, 1001 West 10th Street, Indianapolis, IN 46202.

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glucose and insulin responses of humans or animals to HSH products. In 1971, Bjorling et al. (3) described the effect of hydrogenated maltooligosaccharides on blood glucose concentrations. Their study indicated that, in both diabetic and nondiabetic subjects, blood glucose concentrations rose considerably after consumption of an early HSH formulation. In the rat, Lorenz and Grosklaus (4) compared blood glucose levels after intake of various sweetening agents, including sorbitol, Palatinit, the HSH product Lycasin 80/55, and polydextrose, to sucrose. For all sweeteners, the rise in glucose concentrations over a 180-min period was somewhat less than for sucrose.

We felt it important that an oral-challenge study be done with new formulations to compare the glycemic potential of HSH with glucose in prospective consumers such as people with diabetes. This study was designed to determine the metabolic responses of nondiabetic and diabetic (insulin-dependent [IDDM] and non-insulin-dependent [NIDDM]) subjects to randomly administered single challenges of the HSH products Hystar HSH 5875 and HSH 6075 (Lonza) and glucose. The hypotheses tested were that HSH ingestion would result in diminished postmeal glycemia relative to glucose and that this diminishment of glycemia would be secondary to incomplete small intestinal carbohydrate absorption.

RESEARCH DESIGN AND METHODS

Participants included 18 individuals (6 IDDM, 6 NIDDM, and 6 nondiabetic; Table 1). All were identified from patient-record files or were university staff volunteers. Individuals with neuropathy were excluded. Subjects were between 31 and 69 yr of age. Each group consisted of 3 men and 3 women. The NIDDM group was heavier than the other groups but did not have HbA_1 significantly different from that seen in the IDDM group (normal range for HbA_1 5.5–8.5%). This study conformed with principles stated in the Declaration of Helsinki and was approved by the institution's Human Subjects Review Committee. Before initiation of the study, written informed consent was obtained from all subjects. Studies were carried out in the General Clinical Research Center (GCRC) of Indiana University Medical Center.

TABLE 1
Subject characteristics by group

	Nondiabetic	NIDDM	IDDM
Age (yr)	40 ± 6	56 ± 8	44 ± 13
n (M/F)	3/3	3/3	3/3
Race (White/Black)	6/0	6/0	5/1
Body mass index (kg/m²)	24.4 ± 3.5	31.7 ± 2.2	23.2 ± 2.7
Body surface area (m²)	1.79 ± 0.15	1.92 ± 0.11	1.82 ± 0.23
HbA_1 (%)	6.1 ± 0.5	8.7 ± 2.3	9.8 ± 2.5
Duration of diabetes (yr)		11 ± 11	21 ± 14
Therapy			
Insulin		4	6
OHA		2	0

Values are means ± SD. NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; OHA, oral hypoglycemic agent.

TABLE 2
Baseline evaluation

	Nondiabetic	IDDM	NIDDM
Glucose (mM)			
Fasting	4.8 ± 0.5	9.4 ± 4.9	8.2 ± 2.9
Peak	8.6 ± 1.0	21.7 ± 3.0	13.5 ± 4.1
Insulin (pM)			
Fasting	43 ± 39	42 ± 31	189 ± 84
Peak	830 ± 461	48 ± 39	522 ± 256
C-peptide (nM)			
Fasting	0.46 ± 0.17	<0.03	0.50 ± 0.43
Peak	2.65 ± 0.99	<0.03	1.49 ± 0.73

Values are means ± SD; *n* = 6 subjects for each group. IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

During a visit before the oral-challenge studies, subjects underwent a baseline evaluation to ensure that they were properly categorized. Subjects treated with insulin or oral hypoglycemic agents omitted their morning doses before testing. After an overnight fast, blood samples were drawn for HbA_1, hematocrit, hemoglobin, fasting blood glucose, insulin, and C-peptide. Then nondiabetic subjects drank 75 g glucose mixed with deionized water, and diabetic subjects ingested 20% of their average daily calories as a nutritionally complete liquid-diet formula (Sustical, Mead Johnson, Evansville, IN) within a 5-min period. Sustical was used for diabetic subjects to provide a maximal insulin secretory challenge (mixed carbohydrate and protein) as reported previously (5). Blood was drawn at 30, 60, 90, and 120 min after the test was begun. Results of the baseline evaluation are given in Table 2. Because of the presence of anti-insulin antibodies in some subjects, C-peptide measurements were also performed. As expected, IDDM subjects were characterized by little, if any, insulin or C-peptide response to a food challenge, whereas NIDDM subjects had significant responses.

On admission to the GCRC, subjects were administered three different oral challenges (glucose and the 2 HSH products). HSH 5875 contains primarily maltitol (60%), the remainder being sorbitol (7%) and reduced maltooligosaccharides (33%). Seventy-eight percent of the HSH 6075 is reduced maltooligosaccharide chains from 3 to 20 U, the remainder being 14% sorbitol and 8% maltitol. The study was a double-blind crossover experimental design, with each person drinking one of the three oral challenges on successive days. The order of treatment was randomized by Latin square.

Nondiabetic subjects arrived at the GCRC each morning, fasting for the challenge. Subjects with NIDDM and

IDDM were admitted to the GCRC on the afternoon before their first oral challenge. All intermediate- and long-acting insulins were withheld on the afternoon of admission, and oral hypoglycemic agents were withheld for 1 wk before studies. Subjects with diabetes were administered regular human insulin (Humulin BR, Lilly, Indianapolis, IN) via a continuous subcutaneous insulin pump. Initial basal rates of insulin were 0.5 U · kg^{-1}· day^{-1} for those with NIDDM and 0.35 U · kg^{-1} · day^{-1} for those with IDDM. Blood glucose concentrations were monitored at least hourly via a Yellow Springs glucose analyzer (Yellow Springs, OH). The basal insulin subcutaneous infusion was adjusted hourly to maintain the patient within a target blood glucose range of 4.5–6.7 mM until the start of the oral challenge the next morning. This method ensured that prechallenge fasting blood glucose levels were similar in all subjects. Basal insulin delivery was then maintained at the final fasting rate throughout the test. Bolus premeal injections of insulin were given before regular meals and snacks but not before oral challenges. Insulin reservoirs, tubing, and batteries were changed after lunch each day. This procedure was repeated throughout the study.

Evening meals before each challenge day for all subjects consisted of plain meat, rice, bread, margarine, broth, and apple juice. Evening snacks were toast and juice. Meals for the diabetic subjects during the inpatient period simulated, as much as possible, their normal daily pattern.

The oral challenge was 50 g of glucose, HSH 5875, or HSH 6075/1.73 m^2 of body surface area (BSA). The formula used to determine BSA in square meters was $BSA = 0.007184 \times wt\ (kg)^{0.425} \times ht\ (cm)^{0.725}$ (6,7).

Each challenge material was mixed with deionized water to make a final volume of 200 ml for ease of consumption. HSH 5875 (Hystar lot number 377-838) and HSH 6075 (Hystar lot number 373-639) were provided by Lonza.

Peripheral venous blood samples were collected at 0, 15, 30, 45, 90, 120, 150, 180, 240, and 300 min postfeeding. Plasma glucose, insulin, free–fatty acid (FFA) and C-peptide concentrations were measured in each blood sample.

Alveolar samples for breath H_2 analyses were collected (GaSampler system, QuinTron, Milwaukee, WI) at 30-min intervals from baseline to 4 h after the test meal and additionally at the 5th h.

FFA levels were determined with the method of Novak (8). Plasma glucose concentrations were measured by the Somogyi-Nelson colorimetric method with a protein-free filtrate (9). Human C-peptide levels were assayed by a double-antibody procedure with a goat anti-C-peptide antiserum and an antigoat antiserum (10). In control subjects, plasma insulin was determined directly with a guinea pig anti-porcine antibody (no differences between pork and human insulin) and a goat anti-guinea pig second antibody (11). In diabetic subjects, polyethylene glycol–extracted plasma was used in a double-antibody human insulin assay to determine free (antibody-free)-insulin concentrations (11). Percent HbA_1 determinations were done with cation-exchange columns, an aldimine eliminator step, a constant temperature chamber (23°C), and Isolab (Akron, OH) reagents and minicolumns (12). Labile glycosylated hemoglobin was removed during the hemolysis step.

Breath H_2 samples for each subject were processed by a special-purpose gas analyzer (QuinTron model CM2 MicroLyzer) designed to measure small quantities of H_2 in expired air. The method is based on a modified gas-chromatography technique. Manufacturer's instructions were followed for calibration and analyses.

The study was designed as a repeated-measures study with one repeated-measure factor (glucose, HSH 5875, HSH 6075) and one independent factor (nondiabetic, IDDM, NIDDM). Two-way repeated-measures analysis of variance was used to analyze data measurements over the course of oral challenges and areas under the curve (calculated by the trapezoidal rule) (13). This type of analysis compares the three groups of subjects (NIDDM, IDDM, nondiabetic) and the three oral challenges (HSH 6075, HSH 5875, glucose), and an interaction term (IA) indicates if the effects of the oral challenges are parallel in the three groups. In addition, peak glucose and insulin responses were analyzed by analysis of variance. Breath H_2 values were analyzed after square-root transformation to normalize data. Values are means ± SD.

RESULTS

As seen in Fig. 1 for all groups, the order of plasma glucose responses over the 5-h period was glucose >HSH 6075 >HSH 5875. Peak glucose responses were seen earlier in nondiabetic than in diabetic subjects (45 vs. 60–120 min). These differences were observed for all oral challenges, and have been observed previously for glucose for nondiabetic compared with diabetic subjects (14). When comparing the areas under the 5-h curves (Table 3), the nondiabetic group had less glycemia after each type of oral challenge than the diabetic groups ($P < 0.001$). HSH challenges provoked less elevation in glucose than glucose challenges ($P < 0.001$). Furthermore, the patterns of elevation in plasma glucose differed between the HSH products and glucose in that peak responses occurred earlier after HSH consumption ($P < 0.026$; Fig. 1). Subjects with NIDDM had less glycemia after HSH 5875 than HSH 6075, which was not seen in nondiabetic or IDDM subjects (Table 3).

Virtually no plasma immunoreactive insulin responses were seen in subjects with IDDM (Fig. 2). Subjects with NIDDM had the greatest insulin responses after each challenge, and groups differed significantly ($P = 0.016$; Table 3). Nondiabetic subjects and those with NIDDM had significantly less insulin release in response to the HSH products than to glucose ($P < 0.014$), with the insulin response after HSH 5875 being similar to the response to HSH 6075. Because measurement of immunoreactive insulin is affected by the presence of in-

sulin antibodies, C-peptide responses were assessed in the nondiabetic and NIDDM groups (Table 3). The order of responses was glucose>HSH 6075>HSH 5875. This reflects differences in glucose levels resulting from small intestinal absorption of glucose among the three products. There were no differences between NIDDM and nondiabetic subjects.

Baseline FFA levels were equivalent in all groups (Fig. 3). Reductions of FFA were greater with the glucose challenge than with the HSH challenges (IA = $P < 0.008$). Breath H_2 levels are shown in Fig. 4. Glucose produced no H_2 increase, whereas there were increases after HSH (HSH 5875>HSH 6075, $P = 0.003$). This indicated small intestinal absorption of carbohydrate in the order glucose>HSH 6075>HSH 5875.

Three subjects complained of gastric distress during the 5 h after ingesting the glucose, eight after ingesting the HSH 5875, and six after ingesting the HSH 6075. There were no differences between groups.

TABLE 3
Area under 5-h response curve

	Nondiabetic	NIDDM	IDDM
Glucose (mM/h)*			
Glucose	30.2 ± 2.4	60.1 ± 7.6	62.5 ± 15.2
HSH 6075	28.6 ± 3.5	47.6 ± 5.2	46.6 ± 10.5
HSH 5875	27.9 ± 2.0	37.4 ± 5.3	43.6 ± 14.5
Insulin (pM/h)†			
Glucose	1109 ± 1004	2013 ± 1326	348 ± 247
HSH 6075	451 ± 388	1544 ± 1011	330 ± 234
HSH 5875	301 ± 269	1759 ± 1451	362 ± 294
C-peptide (nM/h)‡			
Glucose	7.48 ± 4.44	7.20 ± 3.87	
HSH 6075	5.27 ± 3.28	5.32 ± 3.14	
HSH 5875	4.46 ± 2.53	4.21 ± 3.48	

Values are means ± SD; $n = 6$ subjects for each group. NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus. Repeated-measures analysis of variance gives rise to 3 significance tests.

*Group comparison indicates whether at least 1 of 3 subject groups (nondiabetic, NIDDM, IDDM) differs; group $P < 0.001$. Carbohydrate (CHO) comparison indicates whether at least 1 of 3 CHOs has different effect than other two; CHO $P < 0.001$. Interaction term (IA) indicates if effects of 3 CHOs differ in subject groups; IA $P = 0.026$.

†Group comparison indicates whether at least 1 of 3 subject groups (nondiabetic, NIDDM, IDDM) differs; group $P = 0.016$. CHO comparison indicates whether at least 1 of 3 CHOs has different effect than other two; CHO $P = 0.014$. IA indicates if effects of 3 CHOs differ in subject groups; IA $P = 0.117$.

‡Group comparison indicates whether at least 1 of 3 subject groups (nondiabetic, NIDDM, IDDM) differs; group $P = 0.937$. CHO comparison indicates whether at least 1 of 3 CHOs has different effect than other two; CHO $P < 0.001$. IA indicates if effects of 3 CHOs differ in subject groups; IA $P = 0.903$.

DISCUSSION

The HSHs are produced by reduction of syrups containing mixtures of glucose and various maltooligosaccharides (chains of glucose units derived from starch). Thus, an HSH may contain sorbitol and the various short chains of glucose units terminated at the reducing end with a sorbitol unit (the reduction product of the disaccharide maltose being termed *maltitol*, etc). Products containing a larger proportion of the longer hydrogenated-saccharide chains (e.g., HSH 6075) should be more available to the digestive enzymes in the small intestine, whereas products containing larger amounts of short chains (HSH 5875) should be less available. For example, only 10% of maltitol may be converted into monosaccharides that are absorbed through the intestinal mucosa (15). Studies done to examine intestinal absorption of monosaccharides in ketotic rats have indicated that the presence of free sorbitol and glucose together impairs glucose absorption by approximately a third (16). From these properties, it would appear that, relative to glucose, both HSH products should produce less glucose absorbed in the small intestine, with that from HSH 5875 being less than that from HSH 6075.

Glucose was used as the comparator with HSH because it is totally absorbed in the small intestine. Because HSH products, by weight, are the major constituent of foods in which they are used, identical grams per square meter of BSA of glucose and HSH products were used as oral challenges. As we predicted, glucose levels after glucose were greater in all groups than after the HSH products. However, the peak glucose level occurred earlier with the HSH products than with glucose, suggesting that either small amounts of glucose resulting from hydrolysis are more rapidly absorbed than large amounts of monosaccharides or that the osmotic environment (HSH being osmotically less active by weight) alters absorption rates. Glycemia resulting from HSH 5875 was somewhat less in the NIDDM group than glycemia resulting from HSH 6075 (Fig. 1; Table 3), whereas glycemia resulting from the HSH products was similar in each of the other groups. The reason for these group differences in HSH effects on glycemia is not known. However, when all groups were pooled, HSH 6075 ingestion produced greater plasma glucose responses than did HSH 5875 (HSH 6075 vs. HSH 5875 40.9 ± 11.1 vs. 36.3 ± 10.8 mM/h, $P < 0.05$ [corrected for multiple comparisons]). This would be expected because HSH 5875 is less likely to be available for hydrolysis to glucose and sorbitol than HSH 6075. In both the NIDDM and the nondiabetic subjects, the rise in plasma C-peptide levels (Table 3), which is unaffected by the presence of insulin antibodies and changes in FFA levels (Fig. 3), further confirms the relative glycemic and insulinogenic differences among the HSH products and glucose.

Evidence for incomplete intestinal carbohydrate digestion and absorption from HSH is shown by the breath H_2 test (17). The breath H_2 test is based on the

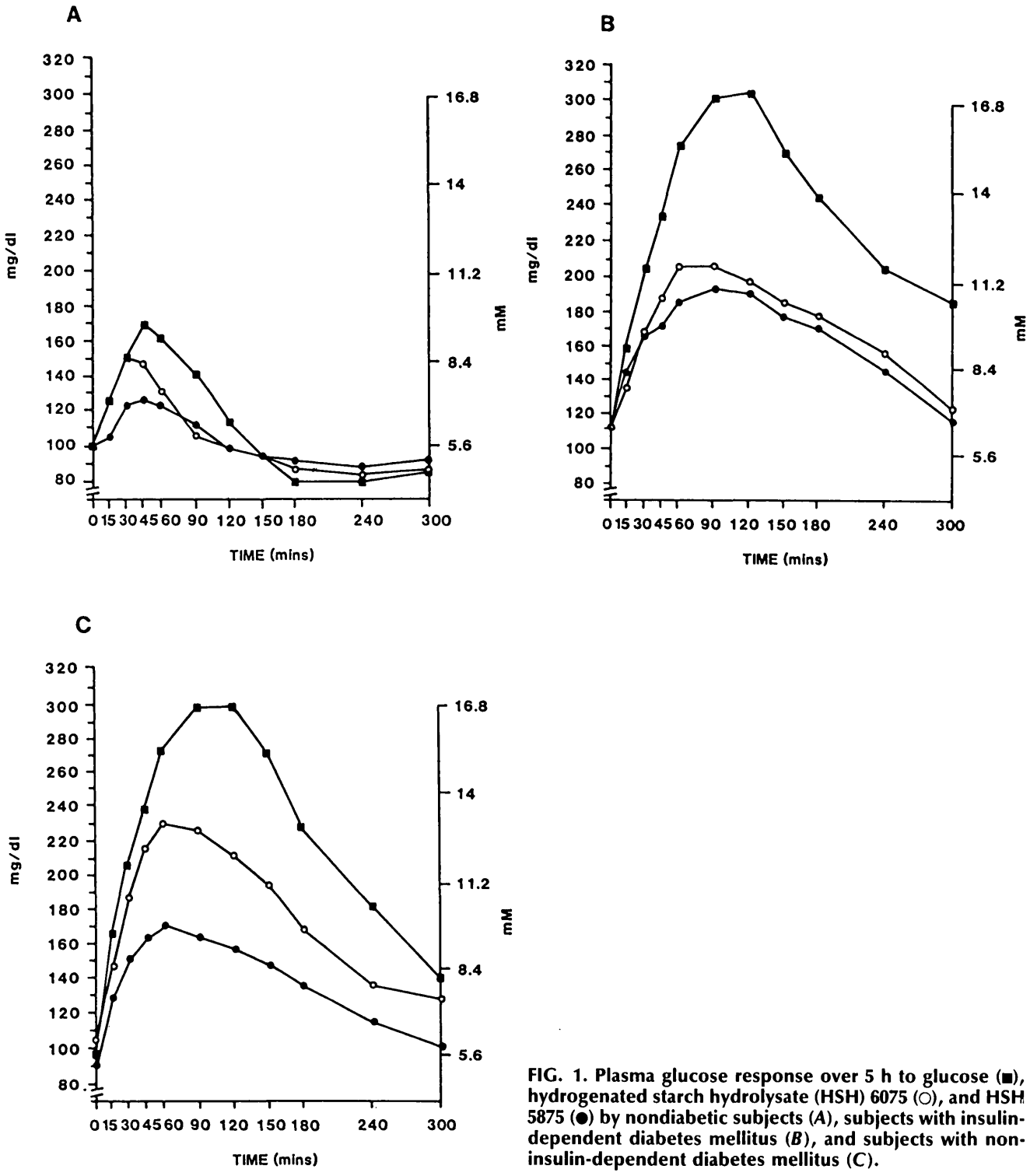

FIG. 1. Plasma glucose response over 5 h to glucose (■), hydrogenated starch hydrolysate (HSH) 6075 (○), and HSH 5875 (●) by nondiabetic subjects (*A*), subjects with insulin-dependent diabetes mellitus (*B*), and subjects with non-insulin-dependent diabetes mellitus (*C*).

principle that carbohydrate fermentation produces H_2, which is partly eliminated by respiratory exchange. Under usual conditions, readily absorbed carbohydrate is removed from the small intestine before reaching the colon, the principal fermentation site. If small intestinal carbohydrate absorption (or hydrolysis) is incomplete, fermentation will occur, and breath H_2 will be released. A positive result is defined as H_2 levels rising >20 ppm above the baseline reading or a >20-ppm rise at any sampling interval (17).

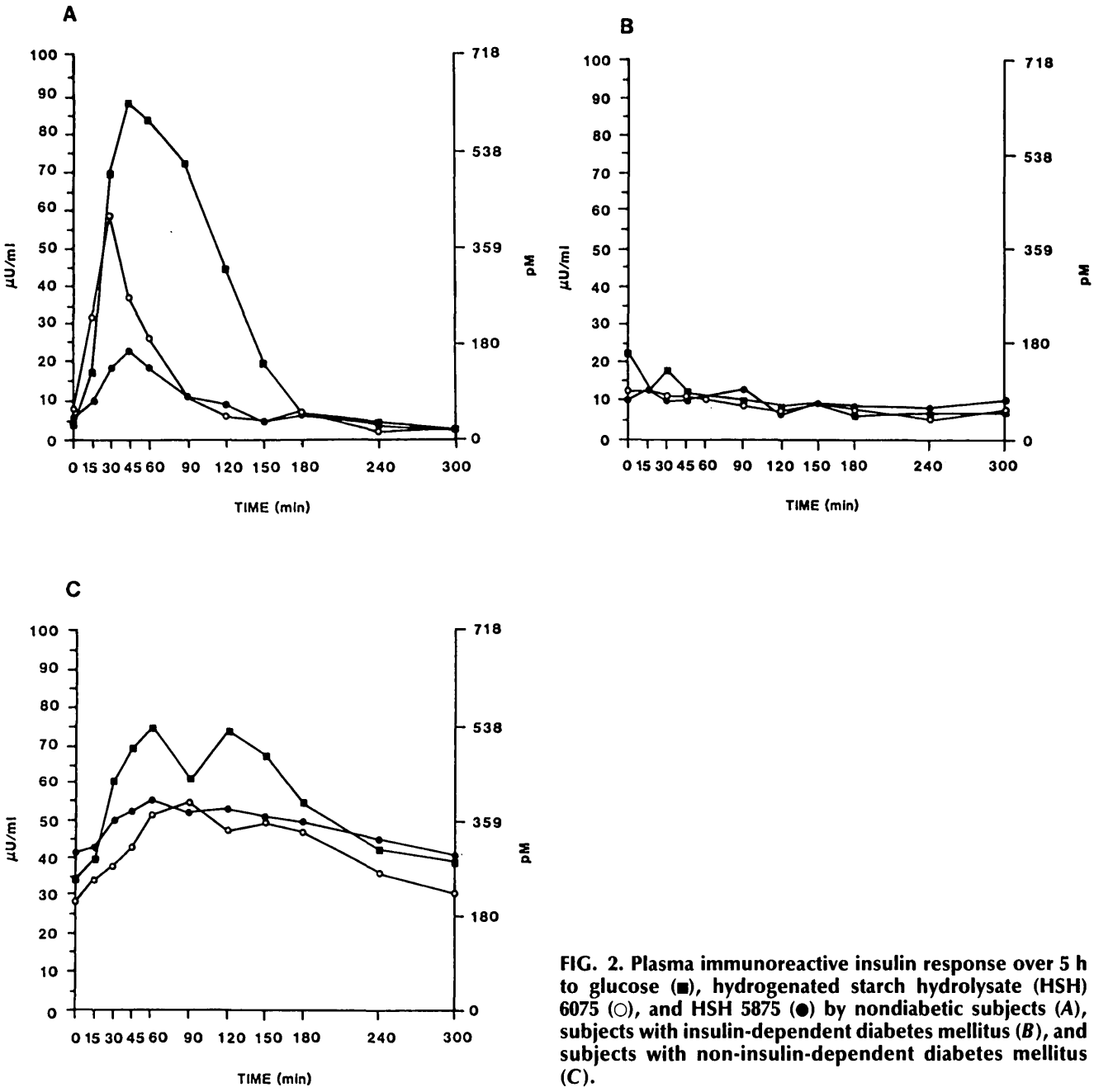

FIG. 2. Plasma immunoreactive insulin response over 5 h to glucose (■), hydrogenated starch hydrolysate (HSH) 6075 (○), and HSH 5875 (●) by nondiabetic subjects (*A*), subjects with insulin-dependent diabetes mellitus (*B*), and subjects with non-insulin-dependent diabetes mellitus (*C*).

Breath H_2 results are inversely proportional to the glycemia and insulin responses, and indicate increased degradation of carbohydrates by colonic bacteria for the two HSH products. In contrast to HSH, glucose ingestion does not result in increased breath H_2, indicating virtually complete absorption in the small intestine in all groups. H_2 levels after ingestion were HSH 5875>HSH 6075> glucose. Breath H_2 levels had not returned to baseline by 5 h after ingestion of the HSH products, indicating their continued presence in the large intestine and continued breakdown by bacterial flora.

Compared with pooled data for glucose levels (100% absorption = 50.9 ± 17.8 mM/h), HSH 5875 produced 71% as much elevation in plasma glucose and HSH 6075 80% as much over a 5-h period. Because some carbohydrate, which escapes digestion and absorption in the human small intestine, is metabolized to volatile fatty acids (18), we cannot comment on the calorie yield of HSH products. Our results do indicate that individuals with and without diabetes react similarly in terms of decreased glycemic availability of HSH products relative to glucose. One study found that an HSH product from another manufacturer (Lycasin 80/55, structurally similar to HSH 5875) was digested in the small intestine, and the products were absorbed (19). The conclusion

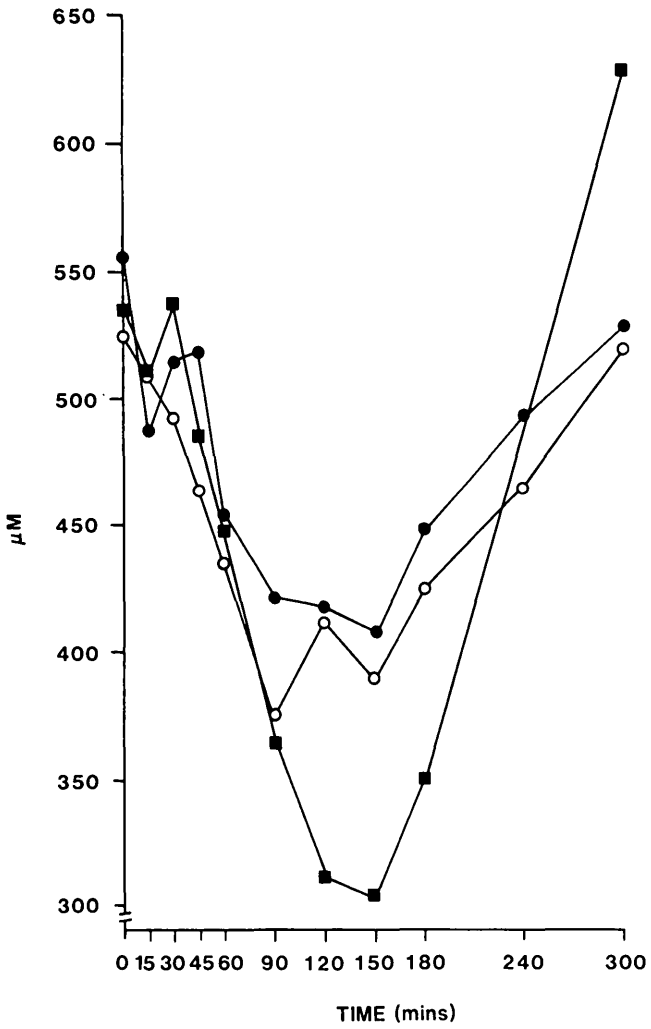

FIG. 3. Plasma free-fatty acid response over 5 h for insulin-dependent and non-insulin-dependent diabetic and nondiabetic groups combined to glucose (■), hydrogenated starch hydrolysate (HSH) 6075 (○), and HSH 5875 (●).

was that the calorie savings expected with polyols in sugar-free products seemed to be low. In contrast, our breath H_2 evidence indicates that there is increased colonic fermentation and decreased small bowel absorption of glucose. The rest of the energy resulting from either HSH 5875 or HSH 6075 would have to result from utilization of volatile fatty acids.

Polyol sorbitol is poorly absorbed in the small intestine and may produce osmotic diarrhea if ingested in large amounts. A safe dose of sorbitol is 50 g, indicated in the *Code of Federal Regulations* (20). The carbohydrate dose we used for each HSH product and for glucose was 50 g/1.73 m^2 BSA (with 50 g of HSH 5875 initially containing 3.5 g sorbitol and 50 g HSH 6075 containing 7 g sorbitol). Our subjects did not have osmotic diarrhea, but some complained of gastrointestinal symptoms for glucose and HSH.

In this clinical study, only single ingredients were tested. Thus, our results are directly applicable only to the pure form of two types of HSH. If HSH 5875 or HSH 6075 were mixed with flavoring or essential oils and noncaloric sweeteners, as they usually are, and made into hard candy, the response would probably differ little from our test results. We do not know, with certainty, if this response would be modified when mixed with other ingredients (e.g., protein and/or fat, such as chocolate) (21–24). Heating is also known to produce physical change in carbohydrate, which may increase glycemic response (25–28); however, this change is most notable after long heating (28).

Our study provides evidence that both HSH 5875 and HSH 6075 have decreased glycemic potential relative to glucose for individuals with and without diabetes. This decreased glycemia probably results from incomplete small intestinal hydrolysis and interactions of sorbitol with glucose. HSH as a single ingredient appears to be a suitable product for consumption by individuals with diabetes mellitus.

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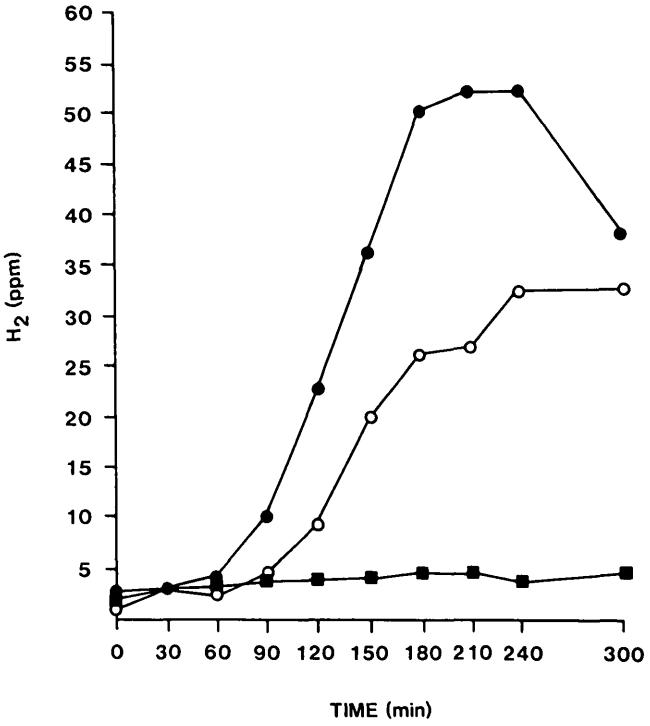

FIG. 4. Breath H_2 response over 5 h for insulin-dependent and non-insulin-dependent diabetic and nondiabetic groups combined to glucose (■), hydrogenated starch hydrolysate (HSH) 6075 (○), and HSH 5875 (●).

(IU), Indianapolis, Indiana (PHS-MO1-RR750); and Lonza, Inc., Fair Lawn, NJ.

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