Clinical Use of Sorbitol as a Sweetening Agent in Diabetes Mellitus

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SORBITOL is a naturally occurring sugar alcohol found in certain edible fruits, vegetables, and berries. It is manufactured by the hydrogenation of glucose for use as a moistening conditioning agent in certain food and pharmaceutical products. In addition to its ability to retain moisture and improve the durability of various foods, sorbitol is also useful as a sweetening agent. In the latter connection, sorbitol has been recommended for use in dietetic food products to which it lends palatibility and bulk.

Its use as a sweetening agent in diabetic diets has received considerable study since it was first recommended for this purpose in 1929.[1-3] The effect of sorbitol upon the blood glucose in patients with diabetes mellitus has been somewhat controversial. Among the early workers who recommended its use as a sweetening agent, there have been two viewpoints. On the one hand, sorbitol was believed to be converted to glycogen to be slowly liberated as glucose without producing hyperglycemia.[1-4] Furthermore, sorbitol has been shown to have a protein-sparing action[3] and to be potently ketolytic under various experimental conditions. On the other hand, it has been stated that since sorbitol is not directly metabolized it may be employed in the diabetic diet purely as a flavoring agent.[6] Although many investigators have not observed a rise in the blood glucose values in diabetes, Silver and Reiner,[7] and Donhoffer[8] have reported hyperglycemia in diabetic patients following its administration.

In the present study, clinical observations were conducted among several groups of diabetic patients to determine whether or not the feeding of sorbitol in this form would significantly influence their diabetic control and insulin requirements. Sorbitol was used in the preparation of a low fat* "ice cream" replacing sucrose for the sweetening agent. It was felt that the feeding of "ice cream" would represent a practical means of determining the influence of sorbitol upon the metabolic status, since this is a substance that many patients enjoy in their diets.

METHODS AND MATERIALS

In two separate studies, 29 patients were under treatment at Temple University Hospital, and 9 were observed at Philadelphia General Hospital. It was considered important to examine the effect of the sorbitol preparation in patients with varying degrees of severity of diabetes.

Of the Temple University patients seven were new cases under initial stabilization; the remaining 22 had been admitted for medical and surgical complications. In the latter group, control of the metabolic status has not been achieved in 4 instances, and, in addition, there was one young pregnant patient with very unstable diabetes. There were five patients whose blood sugar was controlled with diet alone. On the other hand, the sorbitol prepara-

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* Known in industry as ice milk.

tion was included in the feeding program during the convalescence of nine patients following operative procedures shown in Tables II, III, and IV, because of the increasing insulin requirements frequently observed postoperatively.

During this study 30 of the total of 38 patients in the combined groups were receiving a long-acting insulin (either NPH or Lente) in the treatment of their diabetes. Four were also given regular insulin because of a high post-breakfast blood glucose or a strongly positive morning glycosuria. Appropriate diets were computed for each patient prior to the addition of "ice cream" to the dietary program, and a series of blood glucose determinations were made for 2 or 3 days on the diet-plus-insulin program alone. Following this, the patients were given sorbitol "ice cream" at lunch, supper, and bedtime in amounts of 50 or 100 grams *without* substitution or exchange for equivalent caloric values in the diets which were prepared using the Food Exchange System. During the period of sorbitol administration, the blood glucose determinations were repeated for periods of 3 to 5 days, using the Nelson modification of the Somogyi method,[10] on samples obtained in the fasting state at 7:30 a.m., and at 11:30 a.m. and 3:00 p.m. Fractional urine glucose determinations were obtained at 7:00 a.m., and 11:00 a.m., 4:00 p.m., and 9 p.m.

The sorbitol ice cream was served in two schedules to the patients. It was initially given at lunch, supper and with the bedtime feedings in quantities of 100 grams at each meal. Subsequently, it was given at lunch only in 200-gram quantities which approximate the average serving of ice cream used for dessert. In eight instances, regular ice cream was given in place of the sorbitol preparation in order to compare the influence of each upon the diurnal blood glucose values.

Of the nine diabetic patients studied at Philadelphia General Hospital three were managed without insulin, while the remainder received from 20 to 55 units of NPH insulin daily. All nine subjects received 100 g of the sorbitol ice cream at lunch following two weeks of observations on a measured diet.

Analysis of the sorbitol ice cream revealed the ingredients, percentage composition, and caloric content per 100 grams shown in Table I.

Based on this analysis, the three feedings provided 12 g fat, 21.84 g milk solids carbohydrates, 13.26 g milk solids protein, and 54 g sorbitol carbohydrates. The single 200-gram serving provided 8.0 g fat, 14.56 g milk solids carbohydrates, 8.84 g milk solids protein, and 36.00 g sorbitol carbohydrate. Similar studies have been conducted using a fat-free sorbitol sherbet. This substance provided 2.8 g milk solids carbohydrates, 1.7 g protein, and 17.09 g sorbitol carbohydrate per 100 grams.

TABLE I

Analysis of Sorbitol Ice Cream

Ingredients	Composition	Calories per 100 grams
	%	
Butterfat	4.00	36.00
Milk solids carbohydrate	7.28	29.12
Milk solids protein	4.42	17.68
Diastab:		
Sorbitol carbohydrate	18.00	72.00
Stabilizer	0.50	00.00
Calcium cyclamate	0.08	00.00
Ash	1.30	00.00
Moisture	64.42	00.00
	100.00	154.80

RESULTS

In Table II are shown the mean blood glucose values obtained in five patients with mild diabetes who had been under treatment for periods of 6 months to 10 years by means of dietary restriction of carbohydrate alone. The diets provided from 120 to 200 g of carbohydrate. There was no alteration of the blood glucose during the time that sorbitol ice cream was given as an extra feeding to these patients.

The majority of the other patients were under control with a depot insulin in doses ranging from 12 to 78 units daily. In four of these, additional unmodified insulin was required to supplement the intermediate action of the depot preparations.

Table III shows the mean blood glucose values obtained during the control and sorbitol feeding periods representing the results of two

TABLE II

Diabetic Patients Controlled by Diet Alone

	Age, years	Duration diabetes	Status	Control period* 1	Control period* 2	Control period* 3	Sorbitol period* 1	Sorbitol period* 2	Sorbitol period* 3
R. L.	62	3 yr.	Undiagnosed abdominal pain	121	138	142	118	114	117
A. M.	52	6 mo.	Kimmelsteil-Wilson syndrome?	94	115	114	101	114	107
H. W.	67	10 yr.	Gangrene of foot; amputation	109	166	131	136	154	182
C. D.	63	6 yr.	Myocardial infarction	98	112	93	110	131	125
A. B.	62	1 yr.	Cerebral thrombosis	142	125	147	123	160	141

* 1—Fasting blood glucose in mg per 100 ml. 2—11 a.m. blood glucose. 3—3:30 p.m. blood glucose.

TABLE III

Patients Wholly or Partially Controlled by Diet and Insulin Therapy

	Age	Duration diabetes	Status	Control Period: Insulin dose[a]	Control Period: Blood glucose 1	Control Period: Blood glucose 2	Control Period: Blood glucose 3[c]	Sorbitol Control: Insulin dose	Sorbitol Control: Blood glucose 1	Sorbitol Control: Blood glucose 2	Sorbitol Control: Blood glucose 3
M. G.	70	New	Cholecystectomy	12	164	170	138	12	130	166	**143**
E. G.	35	New	Small bowel obstruction; lysis of adhesions	16	116	132	136	16	114	144	**129**
R. D.	60	4 yr.	Cerebrovascular accident, convulsive state[b]	66 (Reg. −10)	184	196	142	70 (Reg. −10)	151	252	**170**
J. L.	69	9 yr.	Congestive heart failure	24	119	160	140	20	122	171	**152**
W. S.	54	1 yr.	Massive infection and necrosis of foot; transmetatarsal amputation	40	140	165	147	36	120	128	**112**
E. C.	45	5 yr.	Dental infection; extraction	58	106	155	128	44	88	127	**112**
G. F.	81	6 yr.	Hypertension, renal papillitis; died	56 (Reg. 4)	128	186	160	56 (Reg. 4)	134	230	**183**
E. D.	64	8 yr.	Gangrene of foot; supracondylar amputation	64	106	118	102	64	84	130	**96**
M. B.	22	8 yr.	No complication	48	262	251	162	50	94	183	**142**
J. R.	54	New	Cervical disc	16	145	152	136	18	122	130	**121**
M. B.	26	12 yr.	Pregnancy and vomiting	28	121	240	147	36	84	198	**112**
C. S.	36	12 yr.	Adrenal cortical hyperplasia, Cushing's disease	54 (Reg. 4)	88	141	162	50 (Reg. 4)	70	114	**105**
R. S.	73	10 yr.	Gangrene of leg; amputation	78	142	124	82	74	142	182	**150**
B. H.	60	5 yr.	Arteriosclerotic heart disease, congestive failure	16	177	221	215	20	174	230	**216**
L. P.	58	3 mo.	Cataract extraction	34	92	89	114	30	94	130	**116**
E. L.	67	9 yr.	Gangrene of foot	66	121	169	95	66	119	148	**110**
P. S.	35	New	Pulmonary tuberculosis, diabetic coma	44	120	71	157	40	130	108	**98**
W. G.	29	New	Hepatosplenomegaly	32	132	142	148	32	116	138	**106**
W. P.	40	New	Stabilization	52	148	149	205	56	152	176	**155**
F. M.	52	New	Diabetic coma, mastitis, diabetic ulcer	46	156	195	197	46	128	165	**151**

[a] Units of isophane (NPH) or Lente insulins.
[b] Unmodified insulin.
[c] 1—Fasting blood glucose in mg per 100 ml. 2—11 a.m. blood glucose. 3—3:30 p.m. blood glucose.

to five days of testing for each interval. In 7 of the 20 patients of this group it was possible to lower the insulin dose during the period of sorbitol administration. In fact, patient E. G. received no insulin on the final day of the experimental period, the insulin dose having been decreased from 16 units daily to none. The improvement in the diabetic status of these patients is not attributed to the use of sorbitol supplementation of the diet, but rather represents the lowering of insulin dosages so often observed under carefully controlled conditions operating in the hospital environment, as well as the lowering of insulin needs which accompanies recovery from complicating illnesses necessitating hospitalization. Further inspection of Table III shows that six other patients required slightly higher insulin doses while receiving the sorbitol preparation. Patient M. G. was found to have a relatively normal blood glucose curve with sorbitol while receiving only 2 units more of insulin than during the control period in which the blood glucose values were elevated. In general, the insulin doses are so similar for the two periods that the sorbitol can be regarded as having virtually no effect.

In the poorly controlled patients (Table IV), a persistent glycosuria and hyperglycemia prevailed. In these patients the administration of sorbitol may have been associated with continuing hyperglycemia, although the nature of the complicating factors makes this assumption somewhat tenuous. Patient J. M. sustained a sharp rise in the fasting and postprandial blood glucose following sorbitol administration. It is of interest that this patient was under treatment for advanced decompensated hepatic cirrhosis due to excessive alcohol ingestion. This may have been a factor in the occurrence of hyperglycemia, because the metabolism of sorbitol and its storage as glycogen may be deficient in the presence of liver damage. In the other three patients of this group, the diabetes did not seem worse during the sorbitol feeding. The feeding of regular ice cream produced an increase of the blood glucose levels in the patients receiving it. In the case of the E. S. (Table I), the blood levels were 175, 364 and 331 mg. per 100 ml, respectively, for the usual test periods.

TABLE IV

Patients in whom Diabetes was Poorly Controlled by Diet and Insulin

	Age	Duration diabetes	Status	Control Period				Sorbitol Period			
				Insulin dose[a]	Blood glucose 1	2	3[b]	Insulin dose	Blood glucose 1	2	3
C. McD.	71	1 year	Toe infection	70 (Reg. 20)	208	208	386	100 (Reg. 12)	136	278	256
J. M.	55	2 years	Portal cirrhosis	26	156	259	151	30	214	310	359
E. R.	75	20 years	Plantar ulcer, thrombophlebitis	40	189	263	248	42	167	292	238
G. H.	60	10 years	Herniated intervertebral disc	30	186	275	182	32	180	206	183

[a] Units of isophane (NPH) or Lente insulins.

[b] Time of blood glucose examination as in Tables II and III.

In one patient the feeding of sorbitol ice cream had to be discontinued after the first 24 hours due to diarrhea. This condition disappeared immediately after stopping the sorbitol preparation. In this case, the agent was given in the immediate postoperative period following cholecystectomy. In none of the other patients were diarrhea or other untoward symptoms noted.

Among those patients observed at Philadelphia General Hospital, the 24-hour urine glucose excretion rates were measured before and during sorbitol administration. The mean glycosuria on diet alone was 7.41 g, while on sorbitol it was 6.48 g daily without any change of the insulin dosage or dietary program. In addition, fasting and postcibal blood glucose levels were determined during each period. The results were similar to those reported above, with no increase in postcibal blood glucose following sorbitol feeding.*

* We are indebted to the metabolic services of the Philadelphia General Hospital for permission to study patients in their wards.

DISCUSSION

The metabolism of sorbitol has been studied by many methods. By means of liver homogenates, Breusch[11] was the first to demonstrate sorbitol dehydrogenase in this organ. Blakely[12] has studied this system in liver and kidney slices, demonstrating the specific and reversible action of the enzyme upon sorbitol. The reactions involved in the transformation of sorbitol to glycogen probably proceed through the following pathway:[13]

$$\text{sorbitol} \rightleftharpoons \text{fructose} \rightleftharpoons \text{fructose-6-PO}_4 \rightleftharpoons \text{fructose 1-6 PO}_4 \rightleftharpoons \text{triose PO}_4 \rightleftharpoons \text{glucose 6 PO}_4 \rightleftharpoons \text{glucose 1 PO}_4 \rightleftharpoons \text{glycogen}$$

The initial reaction is mediated by diphosphopyridine nucleotide. The identification of fructose as an intermediate product in the metabolism of sorbitol was suggested by Anschel[14] and Silver and Reiner[7] in fructosuric patients; the work of Blakely[12] and Stetten and Stetten[15] has confirmed these observations. In this connection, Craig *et al.*[16] have demonstrated by hepatic vein catheterization that fructose is metabolized in the liver of diabetic subjects in the absence of insulin just as well as in the normal individual. This may partially account for the absence of a rise in the blood glucose in our diabetic patients following sorbitol feeding. The conversion of sorbitol to glycogen has been convincingly demonstrated by Johnston and Deuel[17] and by Carr and Forman.[18] Wick, Almen, and Joseph[19] have shown that the incorporation of C^{14}-labeled sorbitol into liver glycogen is equal to that of labeled glucose. Their studies showed that the total oxidation of C^{14}-labeled sorbitol approached that of glucose in normal rats but proceeded at a much slower rate. Stetten and Stetten,[15] using a similar technique with C^{14}-labeled sorbitol in diabetic rats, showed that this hexitol was strongly glycogenic; the major portion of the administered sorbitol was excreted in the urine and only small amounts appeared as labeled carbon dioxide. Wick and Drury[20] administered C^{14}-labeled sorbitol to nephrectomized eviscerated rabbits, demonstrating that this substance was distributed in the extracellular compartment and that the volume of distribution was not increased by insulin. The failure of these animals to eliminate labeled carbon dioxide in the expired air is confirmatory of the findings of Blakely.[12]

Ellis and Krantz[21] found that the administration of sorbitol to normal human subjects increased the respiratory quotient equivalent, over a two-hour period, to the rise obtained with an equal quantity of glucose. The blood glucose values were not increased by sorbitol but rose following glucose administration. In 13 moderately severe diabetic subjects, there was no rise in the respiratory quotient nor in the blood glucose values following the administration of 50 g of sorbitol. Glucose, on the other hand, produced a sharp rise in the blood glucose values, with a significant rise in the respiratory quotient. In a review by Carr and Krantz[22] it is stated that the value of sorbitol in diabetic subjects lies in the storage of this compound as glycogen, so that "its subsequent depolymerization and utilization fails to supply the blood with a plethora of glucose which would produce hyperglycemia." In addition, it has been shown that the intestinal absorption of sorbitol is delayed—an important factor in its slow rate of oxidation.[19]

In addition to sorbitol, the "ice cream" preparation employed in the present study contained a small quantity of lactose together with protein, as lactalbumen, and fat. Previous observations made on stabilized patients receiving insulin have shown that variation in the dietary protein and fat allowances with a constant carbohydrate intake has not significantly influenced their insulin requirements. These findings have been made repeatedly on diabetic patients with nutritional problems involving hypoproteinemia and underweight during periods of preparation for surgery, or in the course of convalescence from operations or complicating illnesses. In studies by Wohl, *et al.*[23] and Gubbay[24] it has been shown that increasing protein intakes in diabetic patients has not altered the metabolic status.

The observations reported here demonstrate that there is no significant rise in the blood sugar of mild or moderately severe diabetic patients during a relatively brief period of daily additions of sorbitol ice cream. In one patient

a prompt laxative action of the compound was observed. In one group of patients it was noted that the insulin dosages were reduced and the blood glucose curves were lower while they received the sorbitol preparation. This improvement was attributed to the benefits derived from careful metabolic supervision, rather than to the effect of sorbitol feeding. In the poorly controlled diabetics, sorbitol ice cream feeding was accompanied by an increasing hyperglycemia in one of three such patients. In spite of the lack of effect upon the blood glucose levels in the majority of our patients, the data on sorbitol metabolism clearly show that its utilization proceeds ultimately through glucose, which suggests that it should be classified as an available carbohydrate.[25] Further studies on this aspect of the effect of sorbitol in human diabetics are required.

SUMMARY

A palatable "ice cream" preparation in which sorbitol has been used as the sweetening agent in place of sucrose has been fed to 38 diabetic patients. The slow absorption of sorbitol, and its conversion to fructose and glycogen prior to its availability as glucose, has led to consideration of this substance for use as an adjunct in diabetic diets. In mild and moderately severe diabetic patients, the feeding of sorbitol ice cream as an addition to the usual diet did not significantly alter the diurnal blood glucose values.

If further studies support these findings, it is possible that sorbitol ice cream may be permitted in the diet of the diabetic without substitution for its caloric equivalent. Additional data are required concerning its effect upon colonic bacterial population with reference to its laxative action, and upon its metabolic effects following long-term feeding programs. At present, sorbitol may be regarded as an available carbohydrate until additional studies further delineate its position in human metabolism and in the diabetic patient.

ADDENDUM

Since submitting this paper for publication, twelve additional diabetic patients have been given the sorbitol dessert preparation after periods of observation while on diet and insulin therapy. The results obtained are similar to those reported above. There were eight patients in whom the disorder was controlled satisfactorily. In this group, the fasting and postprandial blood sugars were not significantly changed after sorbitol feeding added to the diets for periods up to 10 days. The remaining four patients were poorly controlled due to the presence of infection. In two patients of this group, the feeding of sorbitol resulted in an elevation of blood sugar, both fasting and postprandial. The other two patients remained unchanged with respect to the levels of diabetic control following sorbitol. These findings support the belief that the sorbitol preparation can be added to the dietary program of controlled diabetic patients in the amount described without influencing the blood sugar; however, in uncontrolled patients, it may produce a rise in blood glucose levels.

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