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## **D-Tagatose, a novel hexose: acute effects on carbohydrate tolerance in subjects with and without type 2 diabetes**

T.W. Donner<sup>1</sup>, J.F. Wilber<sup>1</sup>, and D. Ostrowski<sup>2</sup>

<sup>1</sup> Department of Internal Medicine, University of Maryland Hospital, Baltimore, MD, USA.

<sup>2</sup> Department of Paediatrics, University of Maryland Hospital, Baltimore, MD, USA.

**Aim:** D-Tagatose (D-tag), a hexose bulk sweetener, does not affect plasma glucose levels when orally administered to rodents. Additionally, D-tag attenuates the rise in plasma glucose after mice are administered oral sucrose. The current study was undertaken to investigate the acute glycaemic effects of oral D-tag alone or in combination with oral glucose in human subjects with and without type 2 diabetes mellitus. Glycaemic responses to D-tag also were investigated in subjects after oral sucrose to examine whether the glucose-lowering effects of D-tag in rodents may result from a direct inhibition of intestinal disaccharidases.

**Methods:** Eight normal and eight subjects with diabetes mellitus were administered 75 g of glucose, 75 g of D-tag, or 75 g of D-tag 30 min prior to a 75 g oral glucose tolerance test (OGTT). Five patients with diabetes mellitus were challenged with a 75 g oral sucrose tolerance test (OSTT) with and without oral pre-treatment with 75 g of D-tag. Patients with diabetes mellitus also received separate 0, 10, 15, 20 and 30 g of D-tag 30 min prior to a 75 g OGTT.

**Results:** Oral loading with D-tag alone led to no changes in glucose or insulin levels in either normal patients or those with diabetes mellitus. Pre-OGTT treatment with 75 g D-tag, however, attenuated the rise in glucose levels in patients with diabetes mellitus ( $p < 0.02$  at 60 and 180 min, and  $p < 0.01$  at 120 min). The glucose area under the curve (AUC) was reduced significantly also by pre-treatment with D-tag in a dose-dependent manner in patients with diabetes mellitus ( $p < 0.05$  for 10 g D-tag,  $p < 0.001$  for 20 g D-tag, and  $p = 0.0001$  for 30 g D-tag). In patients with diabetes mellitus 75 g D-tag similarly attenuated the rise in glucose following an OSTT ( $p < 0.01$  at 30 min, and  $p < 0.02$  at 60 min). Pre-treatment with 75 g D-tag also tended to blunt the rise in insulin following an OGTT in normal patients ( $p = 0.07$  for insulin AUC) but not patients with diabetes mellitus ( $p = 0.66$ ). Following 75 g of oral D-tag in four normal patients, plasma D-tag levels rose to a mean peak level of 3.6 mg/dl at 90 min. The administration of 75 g D-tag led to diarrhoea, nausea and/or flatulence in 100% of subjects. When D-tag was administered at lower doses ranging from 10 g to 30 g, only three of 10 patients with diabetes mellitus had gastrointestinal symptoms which were much more mild than those evoked by 75 g D-tag.

**Conclusions:** These results show that oral D-tag significantly blunts the rise in plasma glucose seen after oral glucose in patients with diabetes mellitus in a dose-dependent manner without significantly affecting insulin levels. The minimal elevation of plasma D-tag levels in normal patients and the adverse gastrointestinal effects seen following larger doses of D-tag support poor absorption of this hexose and suggest that D-tag may act by attenuating glucose absorption in the intestine. D-tag may be a useful therapeutic adjunct in the management of type 2 diabetes mellitus.

**Keywords:** D-tagatose, diabetes, glucose tolerance

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### **Correspondence:**

Thomas W. Donner, MD, University of Maryland Hospital, Department of Medicine, Room N3 W50, 22 S. Greene Street, Baltimore, MD 21201, USA.

### **E-Mail:**

tdonner@medicine.ab.umd.edu

### **Introduction**

D-Tagatose (D-tag) is a novel hexose bulk sweetener which exhibits 92% of the sweetening activity of sucrose [1]. It is present in numerous food products, including sterilized and powdered cow's milk (2000-3000 mg/kg and 100-1000 mg/kg, respectively), hot cocoa, numerous cheeses, yogurt, and other dairy products. D-Tag is a component of two medications, Chronulac® and Cephulac® (0.7 weight percentage), which have had broad use in the treatment of constipation and hepatic encephalopathy, respectively, for more than 14 years [1]. On a molecular level, D-tag is structurally identical to D-fructose, except for an inversion of the hydroxyl and hydrogen groups at the fourth carbon atom. Chemically synthesized in a two-step process from lactose, D-tag appears to provide no net metabolizable energy when fed to rats [2]. Administration of D-tag to rodents does not affect plasma glucose levels. Additionally, oral D-tag attenuates the rise in plasma glucose seen after mice are administered oral sucrose, but the mechanism of this effect has not been clarified [3]. These data raise the possibility that D-tag might be a useful therapeutic adjunct in the management of glucose intolerance in type 2 diabetes mellitus in man.

Because the effects of D-tag on blood glucose have not been studied in man, the current study was undertaken to investigate the acute glycaemic effects of D-tag alone and in combination with oral glucose. Glycaemic responses to D-tag also were investigated in a subset of subjects with diabetes mellitus after receiving an oral sucrose load to examine whether the glucose lowering effects of D-tag in rodents may result from a direct inhibition of intestinal disaccharidases.

### **Subjects and Methods**

#### **Subjects**

The initial study group (Study 1) consisted of a normal group (n = 8) and a group with type 2 diabetes mellitus (n = 8). Each group was constituted of four men and four women. A second group of 10 diabetes mellitus subjects (six men and four women) were recruited to study the effects of increasing D-tag dosages (Study 2). The age range for diabetes mellitus subjects was 31-67 years, they had had diabetes for more than 1 year, and had been treated with diet alone, or diet in combination with sulfonylurea therapy. Subjects in each group were matched for age, sex, and weight (table 1). Diabetes mellitus was confirmed with a 75-g oral glucose tolerance test (GTT), according to American Diabetes Association (ADA) criteria[4]. Study participants were healthy apart from having diabetes, and were excluded for any of the following reasons: poorly controlled diabetes or diabetes requiring insulin; known gastrointestinal disorders, including gastroparesis or diarrhoea; treatment with glucocorticoids, other investigational drugs or medications which might affect gastrointestinal mobility and/or absorption. All investigational protocols were approved by the Institutional Review Board of the University of Maryland and participants were enrolled only after giving written informed consent.

#### **Materials**

D-Tagatose was prepared by Biospherics Incorporated [Beltsville, MD, USA]. All samples used were =99% pure by high performance liquid chromatography (HPLC) analysis, and were weighed and packaged in the University of Maryland Pharmacy prior to administration.

## Study Protocol

### Study 1

During a period of 3 days prior to the study period, subjects were adapted to D-tag by receiving 5, 10 and 25 g of D-tag/day sequentially. In rats, a 3-day adaptation period to D-tag has been shown previously to enhance gastrointestinal tolerance [1]. Eight normal and eight diabetes mellitus subjects were administered separate 75-g, 3-h oral glucose and D-tag tolerance tests, and were given also 75 g D-tag 30 min prior to a 75 gm glucose load. Subjects received 10 g D-tag/day between test days. A subset of five patients with diabetes mellitus were given separate 75 gm oral sucrose tolerance tests (OSTTs) alone or 30 min after 75 g of oral D-tag.

Ten diabetes mellitus subjects received separate 0, 10, 15, 20 and 30 g of D-tag 30 min prior to a 75-g OGTT. Tolerance testing was performed at 08.00 h following a 12-h fast. Patients with diabetes mellitus who were under treatment with sulfonyureas ( $n = 2$ ) received their usual morning dose at 07.30 h. Blood samples were obtained at 0, 30, 60, 120 and 180 min for glucose, D-tag, and insulin determinations.

At the end of the initial study period, all 16 subjects were challenged with increasing doses of D-tag with each meal to establish the threshold at which adverse gastrointestinal symptoms first appeared. Subjects received 5 g of D-tag with each meal on Day 1, and dosages were then increased by 5 g/meal on each subsequent day. Testing was discontinued at the onset of any adverse gastrointestinal symptoms, including flatulence, diarrhoea, and/or bloating.

### Laboratory Evaluations

Glycosylated hemoglobin (GlyHb) values were measured by the affinity column method (Helena Glyco-Tek, Beaumont, TX, USA) which has a normal range of 4.4%-7.7% and a mean intra-assay coefficient of variation of 2.95%. Plasma glucoses were measured by the glucose oxidase method. Insulin levels were measured by the Coates-A-Count RIA method (Diagnostics Products Corporation, Los Angeles, CA, USA). Plasma D-tag was analysed by capillary gas chromatography [5] (Medi-Lab, Copenhagen, Denmark).

### Statistical Analyses

Glucose and insulin areas under the curve were calculated after baseline values were subtracted from each subsequent measurement using the trapezoidal method [6]. Two treatments (GTT with and without D-tag pretreatment) were examined statistically using paired *t*-tests. To statistically compare more than two doses of D-tag we used mixed effects regression models. Data are presented as means  $\pm$  s.e.. The level of statistical significance was set at a value of  $P < 0.05$ .

## Results

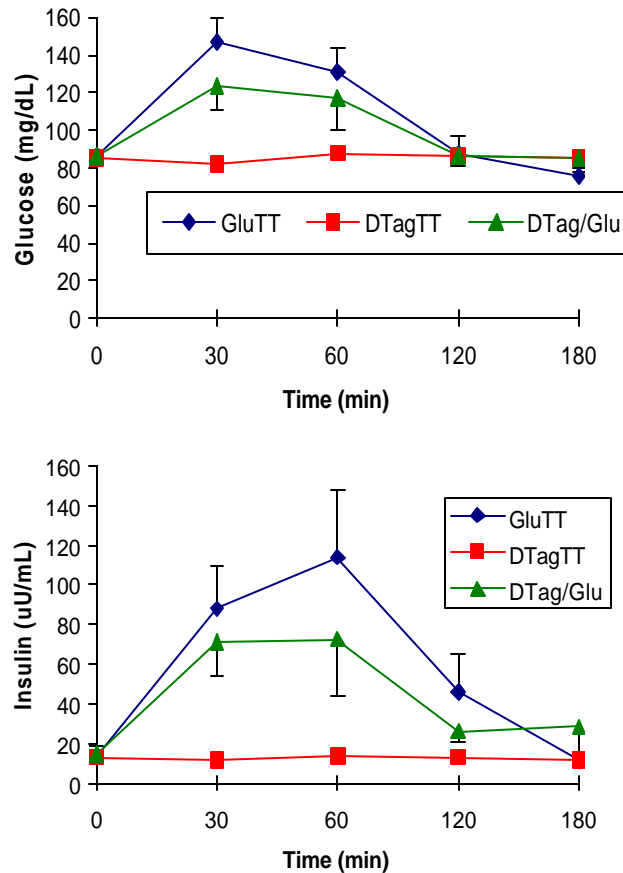
### Study 1

The normal subjects and diabetes mellitus group were very similar in age, weight and gender proportions (table 1). However, diabetes mellitus subjects had significantly greater fasting plasma glucoses ( $164 \pm 14$  vs.  $90 \pm 3$  mg/dl,  $p < 0.001$ ) and GlyHb ( $10.1 \pm 0.5$  vs.  $6.5 \pm 0.5$ ,  $p < 0.001$ ).

**Table 1: Baseline Characteristics of Normal and Diabetic Subjects**

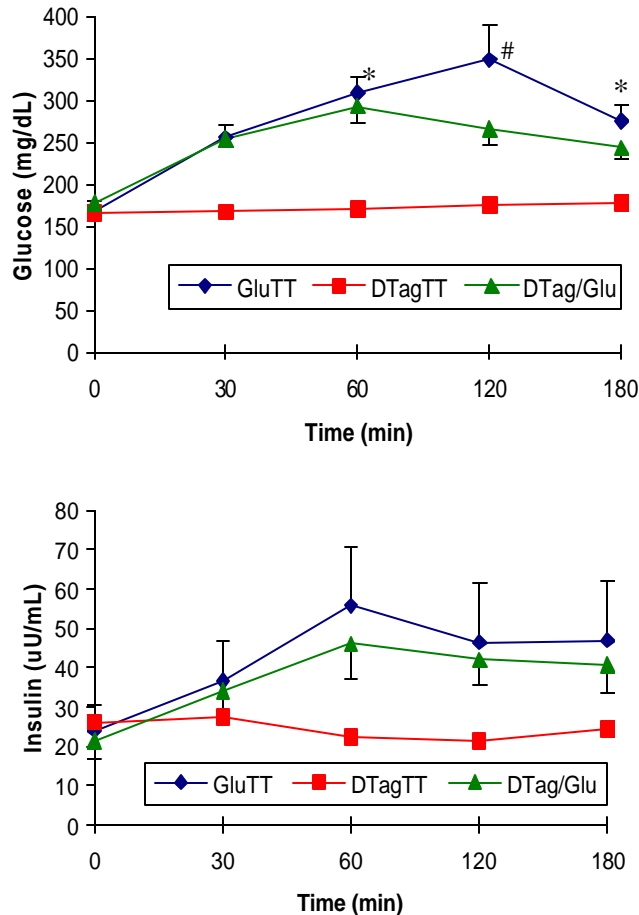
Variable	NLs	DMs
n	8	8
Male:female	4/4	4/4
Age	43.8 ± 1.9	50.0 ± 3.9
Weight (kg)	91.8 ± 8.0	85.9 ± 5.4
Fasting Glu (mg/dl)	90 ± 4	165 ± 14*
Fasting Ins (µU/ml)	19.8 ± 7.3	29.5 ± 6.8
Gly Hgb (%)	6.5 ± 0.2	10.1 ± 0.5*

Oral loading with 75 g of D-tag alone caused no changes in glucose or insulin concentrations in either normal or diabetes mellitus subjects (figures 1,2). Pre-treatment with 75 g of D-tag attenuated the rise in plasma glucose from baseline following oral glucose in normal subjects at 30 min ( $37 \pm 13$  vs.  $60 \pm 13$  mg/dl) and 60 min ( $31 \pm 16$  vs.  $44 \pm 13$  mg/dl) (figure 1A). These glucose lowering effects did not reach statistical significance in normal subjects ( $p = 0.12$  and  $0.1$  at 30 min and 60 min, respectively). In contrast, in diabetes mellitus subjects, elevations in glucose were attenuated significantly by pretreatment with D-tag at 60 min ( $116 \pm 19$  vs.  $142 \pm 19$  mg/dl,  $p < 0.02$ ), 120 min ( $89 \pm 19$  vs.  $172 \pm 42$  mg/dl,  $p < 0.01$ ), and 180 min ( $66 \pm 13$  vs.  $109 \pm 19$  mg/dl,  $p < 0.02$ ) (figure 2A).



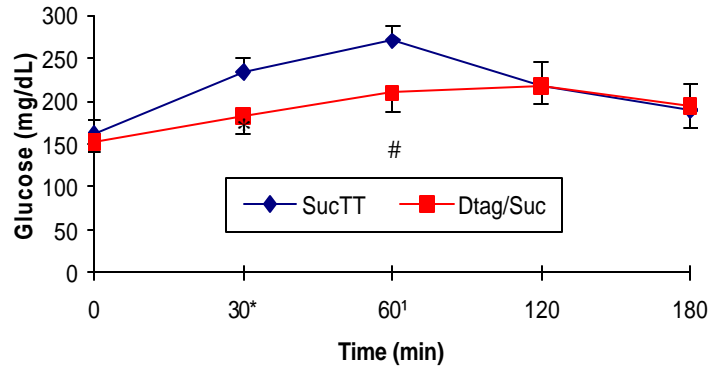
**Fig. 1** (A) Mean ( $\pm$  s.e.) plasma glucose concentrations in eight normal subjects following 75 g oral glucose (GluTT), 75 g oral D-tagatose (DtagTT), or 75 g oral D-tagatose preceding 75 g of oral glucose (Dtag/Glu).  $p = 0.25$  for glucose AUC for Dtag/Glu vs. GluTT. (B) Mean ( $\pm$  s.e.) serum insulin concentrations in eight normal subjects following 75 g oral glucose (GluTT), 75 g oral D-tagatose, or 75 g oral D-tagatose preceding 75 g oral glucose (Dtag/Glu).  $p = 0.07$  for insulin AUC for Dtag/Glu vs. GluTT.

Moreover, the glucose AUC was significantly less in subjects with diabetes mellitus pretreated with 75 g of D-tag ( $46\,751 \pm 2559$  vs.  $53\,278 \pm 4108$  mg/dl/min,  $p < 0.002$ ) (figure 2A). The insulin AUC tended to be less following pretreatment with D-tag in NLs ( $p = 0.07$ ) (figure 1B), but not in diabetes mellitus subjects ( $p = 0.66$ ; figure 2B).



**Fig. 2** (A) Mean ( $\pm$  s.e.) plasma glucose concentrations in eight normal subjects following 75 g oral glucose (GluTT), 75 g oral D-tagatose (DtagTT), or 75 g oral D-tagatose preceding 75 g of oral glucose (Dtag/Glu). \* $p < 0.02$  vs. Dtag/Glu; # $p < 0.01$  vs. Dtag/Glu.  $p < 0.002$  for glucose AUC for Dtag/Glu vs. GluTT. (B) Mean ( $\pm$  s.e.) serum insulin concentrations in eight diabetes mellitus subjects following 75 g oral glucose (GluTT), 75 g oral D-tagatose (DtagTT), or 75 g oral D-tagatose preceding 75 g oral glucose (Dtag/Glu).  $p = 0.66$  for insulin AUC for Dtag/Glu vs. GluTT.

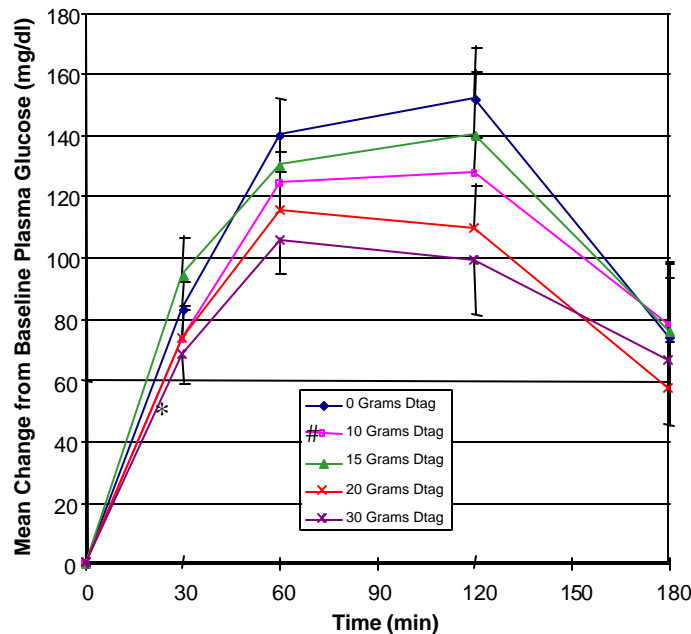
Pretreatment with D-tag also attenuated the rise in plasma glucose from baseline following oral sucrose in diabetes mellitus subjects ( $n = 5$ ) at 30 min ( $30 \pm 20$  vs.  $72 \pm 17$  mg/dl,  $p < 0.01$ ) and at 60 min ( $57 \pm 23$  vs.  $108 \pm 18$  mg/dl,  $p < 0.02$ ) (figure 3). No significant differences were seen in the glucose or insulin AUC in diabetes mellitus subjects who received an OSTT, whether or not D-tag was administered (data not shown). Although pretreatment with D-tag did not lead to a statistically different glucose AUC, this was likely due to the lower power of this comparison ( $n = 5$ ), as reductions in the glucose curve did display the expected pattern consistent with our hypothesis. Insulin values following 75 g oral sucrose or glucose in diabetes mellitus subjects ( $n = 5$ ) were not different statistically, but a greater glucose AUC occurred in diabetes mellitus subjects after oral glucose compared to oral sucrose ( $p < 0.05$ ). A greater decrement in plasma glucose was seen in diabetes mellitus subjects ( $n = 5$ ) during an OGTT compared with an OSTT at 120 min ( $p < 0.05$ ) and at 180 min ( $p < 0.05$ ).



**Fig. 3** Mean ( $\pm$  s.e.) plasma glucose concentrations in five subjects with diabetes mellitus following 75 g oral sucrose (SucTT), or 75 g oral D-tagatose preceding 75 g oral sucrose (Dtag/Suc). \* $p < 0.01$  vs. Dtag/Suc and # $p < 0.02$  vs. Dtag/Suc.

## Study 2

A dose-related attenuation of the increments in plasma glucose concentrations were found when 10 diabetes mellitus subjects were pretreated with graded doses of D-tag prior to a 75-g OGTT (figure 4). Compared with a mean 3-h glucose AUC of  $20\,152 \pm 6125$  mg/dl/min following a 75-g OGTT, pretreatment with D-tag reduced the glucose AUC to  $17\,510 \pm 4811$  mg/min/dl with 20 g D-tag ( $p < 0.05$ ), to  $15\,779 \pm 5703$  mg/min/dl with 20 g D-tag ( $p < 0.001$ ) and to  $15018 \pm 5461$  mg/min/dl with 30 g D-tag ( $p = 0.0001$ ). The reduction in plasma glucose was most marked at 120 min for all doses of D-tag.



**Fig. 4** Mean ( $\pm$  s.e.) change from baseline plasma glucose concentrations in 10 subjects with diabetes mellitus given 0, 10, 15, 20, or 30 g oral D-tag followed by 75 g oral glucose. \* $p < 0.05$  for 10 g D-tag,  $p < 0.001$  for 20 g D-tag, and  $p = 0.0001$  for 30 g D-tag for glucose AUC vs. 0 g D-tag.

Plasma D-tag levels were measured in four normal subjects who were given 75 g of oral D-tag 30 min before a 75-g OGTT. Mean levels reached their peak value at 90 min ( $3.6 \pm 0.7$  mg/dl). Plasma D-tag levels did not rise to a level  $>5$  mg/dl in any subject.

## Adverse Effects

Gastrointestinal side-effects following 75 g D-tag occurred in 100% of subjects, and were similar in normal subjects and those with diabetes mellitus. Symptoms included diarrhoea (81%), nausea (44%), flatulence (19%), bloating (31%), crampy abdominal pain (25%), and headache (12%, table 2). Diarrhoea occurred most commonly 2-3 h after D-tag and resolved typically after 4 h. Several subjects experienced diarrhoea and flatulence for up to 15 h following 75 g oral D-tag. Bloating and nausea began as soon as 30 min after D-tag administration. Several subjects were observed to have more diarrhoea when D-tag was given with an OGTT or OSTT than with D-tag alone. Lightheadedness was reported in two normal subjects during OGTTs. Adverse effects experienced by the 10 diabetes mellitus subjects pretreated with 10, 15, 20 and 30 g D-tag occurred infrequently, were mild and transient (table 2).

**Table 2: Number of Subjects Experiencing Adverse Effects Following Single Oral Doses of D-Tag**

Adverse effect	Dose (g) of D-tag					
	0	10	15	20	30	75
Diarrhoea	0	0	0	0	0	13/16
Nausea	0	0	1/10	1/10	1/10	7/16
Flatulence	0	0	0	0	0	3/16
Bloating	0	0	0	0	1/10	5/16
Abdominal pain	0	0	0	0	0	4/16
Headache	0	0	0	0	0	2/16

Data are presented as number of subjects/total number tested.

When eight normal and eight diabetes mellitus subjects were challenged with increasing doses of D-tag at meal-times at the end of Study 1, mild gastrointestinal symptoms appeared initially at doses of 10-25 g/meal. The first symptom to appear was mild flatulence, diarrhoea, or bloating. The mean daily dose of D-tag at which symptoms first appeared was 53 g. No differences in the side-effect thresholds were noted between normal and diabetes mellitus subjects.

## Discussion

This study demonstrates that the administration of D-tag can blunt hyperglycaemia significantly following oral glucose in a dose-dependent manner in diabetes mellitus subjects without significantly affecting insulin levels. D-tag also tended to blunt the rise in plasma glucose following oral glucose in normal subjects. The failure of this inhibition to reach statistical significance may reflect either the small number of subjects or the modest rise in postprandial glucose typically seen in normal subjects who exhibit a normal insulin secretory response.

The administration of D-tag alone did not cause alterations in either plasma glucose or insulin levels in normal or diabetes mellitus subjects. Low plasma levels of D-tag in normal subjects following a 75-g oral load suggest that this hexose is either poorly absorbed or rapidly metabolized. Studies in pigs have shown that D-tag is poorly absorbed (0-26%) in the small intestine [7]. The appearance of diarrhoea, flatulence and bloating after large oral D-tag doses in this study supports poor absorption. Such malabsorption would lead to the delivery of D-tag more distally in the gastrointestinal tract where it would be exposed to bacterial fermentation and cause adverse abdominal effects similar to those seen in our subjects who received larger doses of D-tag. Augmented hydrogen production has previously been demonstrated in humans given 30 g oral doses of D-tag [8]. The finding that D-tag has no net metabolizable energy when fed to rats [2] may also be due to poor absorption though energy-inefficient metabolism and/or

excretion has not been ruled out. Since D-tag was well tolerated in humans in this study at doses up to 30 g, it may have a role not only as a low energy bulk sweetener, but as an adjunctive therapeutic agent in the treatment of postprandial hyperglycemia in type 2 diabetes mellitus, since doses as low as 10 g were efficacious.

Post-prandial hyperglycaemia occurs in diabetes because of impaired endogenous insulin secretion, impaired insulin-mediated glucose disposal or imperfect exogenous insulin replacement. Recently, several therapeutic agents have been introduced to lower postprandial hyperglycemia specifically. Acarbose [9-11] and miglitol [12,13]—intestinal  $\alpha_1$ -glucosidase inhibitors—have been shown to reduce both postprandial hyperglycemia and GlyHb in patients with type 2 diabetes mellitus. Repaglinide, a rapid-acting stimulator of insulin secretion, has been shown to effectively lower hyperglycemia associated with meals, in addition to elevations in fasting glucose and GlyHb [14,15]. The rapid acting insulin 'lispro' also can reduce postprandial glucose levels in patients with both type 1 and type 2 diabetes [16-18]. The reduction of postprandial hyperglycaemia has received increased attention since recent studies have shown that even small improvements in glycaemic control can reduce the risk of the development and progression of microvascular complications [19-21].

The mechanism by which D-tag blunts the rise in plasma glucose following oral carbohydrates has not been established. Since D-tag appears to be poorly absorbed, one potential mechanism is D-tag-mediated inhibition of gastrointestinal glucose absorption. The glycaemic effects of D-tag may reflect competition with or partial inhibition of glucose transporters in the small intestine, leading to delayed glucose absorption. The observed dose-related decrement in glucose following an oral GTT with D-tag pretreatment supports competitive inhibition of glucose transport. However, a reduction in glucose transport by D-tag has not been shown in animal models. In isolated rat brush border membranes, high concentrations of D-tag led to no inhibition of glucose transport [22].

A reduction of hepatic glycogenolysis by D-tag has been demonstrated in animals and may be responsible, in part, for the blunting of OGTT glucose excursions in the type 2 diabetes mellitus subjects. Treatment of rats [23] or isolated rat hepatocytes [24] with D-tag completely blocks the glycogenolytic response to glucagon. The slow metabolism of hepatic tagatose 1-phosphate was proposed to mediate this effect. Additionally, in rat hepatocytes, D-tag has also been shown to stimulate glucokinase [25], an effect which could have led to improved hepatic glucose uptake in our subjects given an OGTT.

The lack of an insulin or hypoglycaemic response to oral D-tag does not support a role for this hexose as a stimulator of insulin secretion directly or indirectly through secretagogues, such as glucagon-like peptide, or glucose-dependent insulinotropic peptides. A direct effect of D-tag on intestinal  $\alpha_1$ -glucosidase activity, as seen with acarbose, appears unlikely, since the reduced hyperglycaemic response after D-tag was actually more pronounced following oral glucose than following sucrose. However, an inhibition of sucrase activity by D-tag has been demonstrated in rabbit small intestine [3]. Moreover, direct effects of D-tag on insulin sensitivity are also unlikely, since the beneficial glycaemic effects occur within an hour following its administration.

Preliminary studies at our institution in normal and diabetes mellitus subjects who were administered 75 g of D-tag daily for 8 weeks have shown no adverse effects on hepatic function, lipids, or blood pressure, and no consistent effects on body weight [26]. The study herein has revealed that mild gastrointestinal symptoms did not appear until relatively large doses of D-tag were administered—53 g/day on average. Studies to investigate the long-term effects of daily D-tag administration to patients with diabetes mellitus are in progress to determine whether D-tag, at doses that are well tolerated, may be useful as an alternative sweetener and whether it will improve diabetic control.

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