D-Tagatose: A Novel Therapeutic Adjunct for Non-Insulin-Dependent Diabetes

T. Donner, J. Wilber, D. Ostrowski, Baltimore, MD

ABSTRACT

D-tagatose (D-tag), a novel D-hexose sweetener, has a lower energy value and leads to less weight gain than sucrose when fed to rats. Because D-tag blunts the rise in blood glucose (BG) in rats after the administration of oral sucrose, we wondered whether D-tag could exert beneficial effects upon carbohydrate tolerance in man. To investigate this problem, after an overnight fast 6 normal (NL) and 6 non-insulin-dependent diabetic (NIDDM) subjects were administered separate 75 gm, 3-hour oral glucose (GLU) and D-tag tolerance tests, and given 75 gm D-tag immediately preceding a 75 gm GLU load. Oral loading with D-tag itself led to no changes in BG or insulin (INS) in NLs or NIDDMs. Pretreatment with D-tag, however, attenuated the rise in BG from baseline following oral GLU in NLs at 30 min (29±18 vs 63±16 ng/d), and in NIDDMs at 120 min (85±21 vs 180±47 ng/dl, $P<0.05$) and at 180 min (69±26 vs 112±25 ng/dl). Rises in INS levels from baseline after oral GLU in NLs were also blunted by D-tag at 30 min (42±14 vs 63±23 uU/ML) and at 60 min (36±19 vs 63±12 uU/ML).

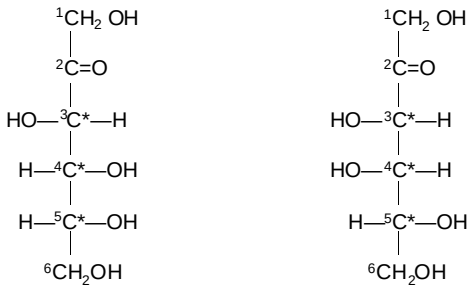
Six NLs were randomized to receive 75 gm D-tag or 75 gm sucrose daily for 8 weeks. No significant changes were seen in either group in fasting BG, INS, glycohemoglobin (HbA_{1C}), blood pressure (BP), weight or lipids. Four NIDDMs received either 75 gm D-tag or no D-tag daily for 8 weeks. Eight weeks of daily D-tag led to a substantial decrease in HbA_{1C} from baseline (8.4 vs 9.5%, but no change in fasting BG, BP, lipids, or weight. Conclusions: (1) Acute or chronic administration of D-tag improves glucose tolerance in NIDDM, (2) Qualitatively similar effects were seen in NLs but were not statistically significant, (3) No adverse metabolic effects were seen in either group with chronic use, (4) D-tag may enhance INS sensitivity, impair gastrointestinal (GI) absorption of GLU, or stimulate GI insulin secretogogues. Speculation: D-tag may be a useful adjunct in the management of NIDDM.

INTRODUCTION:

D-tagatose is a novel hexose bulk sweetener which exhibits 92% of the sweetening activity of sucrose while possessing maximally only 25% on a molar basis of its metabolizable energy. Moreover, the energy yielded is utilized entirely in D-tagatose metabolism, precluding net energy yield. D-tagatose is found in numerous foods including sterilized cow's milk, hot cocoa, various cheeses and yogurt. The administration of D-tagatose to rodents was found to inhibit the rise in plasma glucose after animals were fed sucrose. Additionally, the administration of sucrose to a chow diet, when compared with a similar amount of D-tagatose over a 90 day test period, led to a 228% greater weight gain in the sucrose-fed rats. Importantly, nearly 90% of the final body weight differences between the two groups was attributed to an 814% higher body fat content increment in sucrose-fed compared to the tagatose-fed group.

On the basis of these results in rodents, we sought to determine (1) if D-tagatose could exert beneficial effects upon carbohydrate tolerance and fasting hyperglycemia in type II diabetic subjects, (2) if D-tagatose could attenuate or prevent dietary-associated weight gain in type II diabetic patients with obesity, and (3) if D-tagatose could be administered to diabetic subjects without deleterious effects upon carbohydrate or lipid metabolism.

Comparison of D-Fructose and D-Tagatose Molecular Structures



METHODS:

16 total subjects, 8 normal (NL) and 8 non-insulin-dependent diabetics (NIDDM), were enrolled into the study. After a 12 hour fast, subjects were administered separate 75 gram, 3-hour oral glucose and D-tagatose tolerance tests, and given 75 gram D-tagatose immediately preceding a 75 gram glucose load. Blood was drawn at baseline, 30 60, 120, and 180 minutes for glucose and insulin measurements.

The 8 NLs were randomized to receive either 75 gm D-tagatose (25 gm with each meal) or 75 gm sucrose daily for eight weeks. The 8 NIDDMs received either 75 gm D-tagatose or no D-tagatose daily for eight weeks. Fasting measurements of glucose, insulin, lipids, weight and blood pressure were measured at baseline and bi-weekly for eight weeks. Glycohemoglobin levels were drawn at baseline, four and eight weeks.

RESULTS:

Oral loading with D-tagatose itself led to no changes in glucose or insulin in NLs or NIDDMs. Pre-treatment with D-tagatose attenuated the rise in BG from baseline following oral glucose in NLs at 30 min (37 vs. 60 mg/dl) and 60 min (31 vs. 44 mg/dl), and in NIDDMs at 120 min (89 vs. 181 mg/dl, $P<0.05$) and at 180 min (66 vs. 109 mg/dl). Rises in insulin levels from baseline after oral glucose in NLs were also blunted by D-tagatose at 60 min (58 vs. 100 uU/ml) and 120 min (11 vs. 32 uU/ml), and in NIDDMs at 60 min (1 vs. 32 uU/ml), 120 min (10 vs. 22 uU/ml) and 180 min (3 vs. 23 uU/ml).

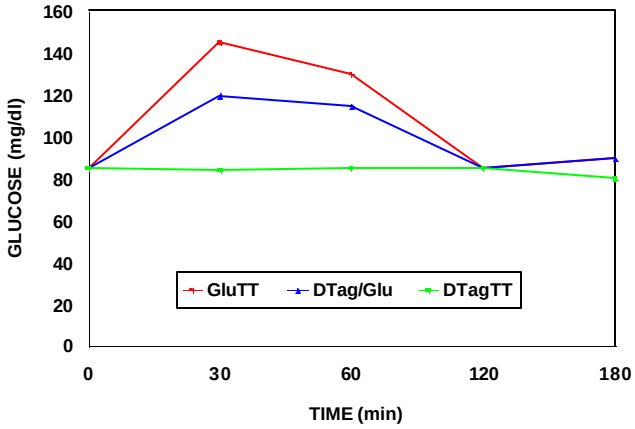
NLs who received either 75 gm D-tagatose or 75 gm sucrose daily for eight weeks showed no significant changes in either fasting glucose, insulin, glycohemoglobin, blood pressure, weight, lipids or LFTs. All four NIDDMs had a decrease in glycohemoglobin on daily D-tagatose at four weeks (9.4 vs. 10.1%). Two of the three NIDDMs who completed eight weeks of D-tagatose had a continued fall in glycohemoglobin. One NIDDM had a 2.4% increase in glycohemoglobin during the last four weeks associated with a five pound weight gain and excessive caloric intake.

Oral loading with 75 grams of D-tagatose in NLs and NIDDMs led to variable adverse G.I. effects, including bloating, flatulence, nausea and diarrhea. These adverse effects did not lead any of the four NLs or NIDDMs to discontinue long term, daily D-tagatose.

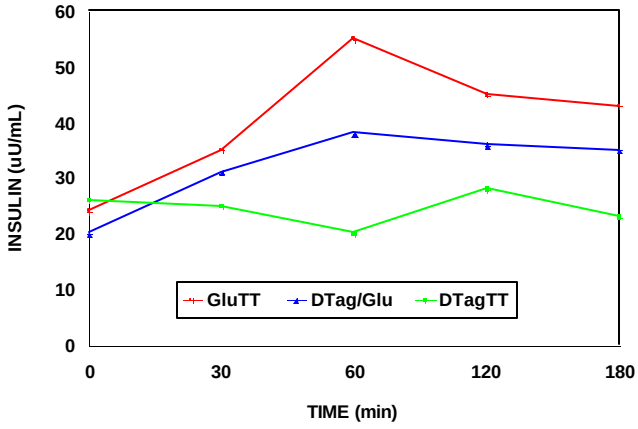
Baseline Characteristics

	Normal Subjects	NIDDM Subjects
Age	43.8	50
Sex (male/female)	4/4	4/4
Weight (lbs)	202	189
FBG	90	165
Insulin (Uu/ml)	19.8	29.5
Glyhgb (%)	6.5	10.1
SBP (mmHg)	119	131
DHP (mmHg)	71.4	78.6
CH (mg/dl)	174	211
TG (mg/dl)	115	208
HDL (mg/dl)	45	39.7
LDL (mg/dl)	103	130

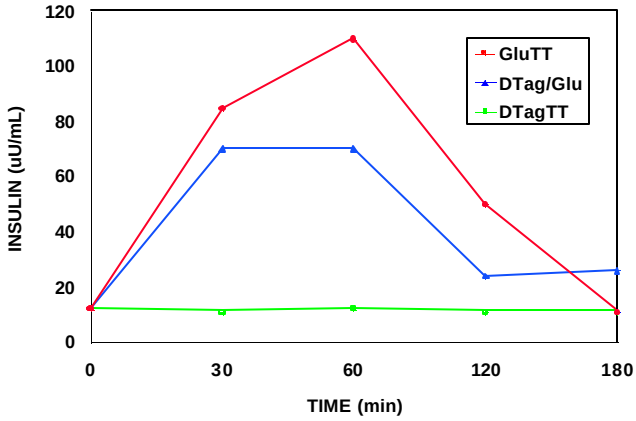
D-Tagatose Blunts the Rise in Plasma Glucose After Oral Glucose in 8 NLs



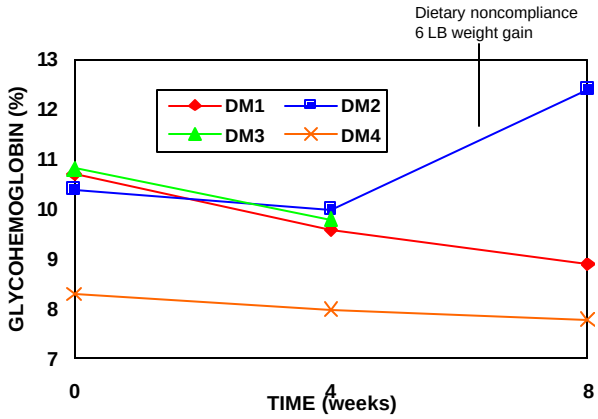
D-Tagatose Blunts the Rise in Insulin After Oral Glucose in 8 Diabetics



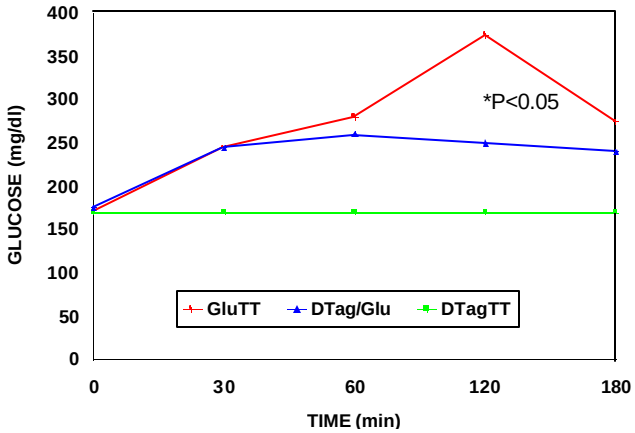
D-Tagatose Blunts the Rise in Serum Insulin After Oral Glucose in 8 Normals



Glycohemoglobin Falls in 4 Diabetics on D-Tagatose



D-Tagatose Blunts the Rise in Plasma Glucose After Oral Glucose in 8 Diabetics



Metabolic Parameters During Eight Weeks of Daily (75 gm) D-Tagatose or Sucrose in Normals

n=3	Week # D-Tagatose				
	0	2	4	6	8
Weight	203.8	202.8	203.8	205.2	205.3
FBG	88	84	84	85	89
Insulin	13.8	16.4	18.5	13.0	14.4
GlyHGB	6.4	--------	6.9	---------	6.7
SBP	124	130	115	127	130
DBP	77	72	68	73	78
CH	182	190	198	201	204
TG	130	191	162	142	131
HDL	41	39	42	44	49
LDL	115	112	124	128	128

n=4	Week # Sucrose				
	0	2	4	6	8
Weight	191	190	191	191	190
FBG	89	80	78	79	80
Insulin	24.3	15.9	14.5	18	20.5
GlyHGB	6.6	---------	6.2	--------	6.6
SBP	113	112	116	110	115
DBP	65	67	65	63	69
CH	168	179	178	171	169
TG	104	99	118	101	107
HDL	48	47	48	50	48
LDL	94	112	106	101	100

Metabolic Parameters During Eight Weeks of Daily (75 gm) D-Tagatose or No D-Tagatose in NIDDM's

n=3	Week # D-Tagatose				
	0	2	4	6	8
Weight	178	178.1	179.2	178.6	181
FBG	186	151	159	161	190
Insulin	29.8	23.2	17.7	18.4	21.7
GlyHGB	9.8	--------	9.2	---------	9.7
SBP	141	138	154	156	161
DBP	79	80	82	87	88
CH	202	203	207	195	228
TG	201	182	167	141	205
HDL	38	38	37	38	40
LDL	124	128	136	129	147

n=4	Week # No D-Tagatose				
	0	2	4	6	8
Weight	190.8	190.9	191.2	192	193.4
FBG	140	160	138	194	173
Insulin	24.2	24.7	23.2	21.9	25.3
GlyHGB	10.1	---------	9.7	--------	10.1
SBP	119	117	118	124	114
DBP	78	75	72	80	76
CH	218	210	223	200	201
TG	213	146	161	180	165
HDL	41	46	50	43	50
LDL	134	135	141	121	119

CONCLUSIONS:

(1) Acute administration of oral D-tagatose alone leads to no changes in serum insulin or plasma glucose in NLs or NIDDMs.

(2) Oral D-tagatose blunts the rise in serum insulin and plasma glucose seen after oral glucose in NLs and NIDDMs.

(3) Daily administration of D-tagatose for four weeks in NIDDMs leads to a 0.7% decline in glycohemoglobin, a change similar to that seen with acarbose.

(4) No adverse metabolic effects were seen in NLs or NIDDMs with chronic D-tagatose use.

SPECULATION:

(1) The improved glucose tolerance seen after D-tagatose may be due to enhanced insulin sensitivity, impaired gastrointestinal absorption of glucose or stimulation of G.I. insulin secretogogues.

(2) D-tagatose may be a useful adjunct in the management of NIDDM.

457
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