Effects of a d-Xylose Preload With or Without Sitagliptin on Gastric Emptying, Glucagon-Like Peptide-1, and Postprandial Glycemia in Type 2 Diabetes

TONGZHI WU, MBBS1,2
MICHIELE J. BOUND, BMed Rad Nuc Med1,2
BEIYI R. ZHAO1,2
SCOTT D. STANDFIELD, BSc1,2
MAX BELLON, Dip Med Tech Ad Nuc Med3
KAREN L. JONES, PhD1,2
MICHAEL H. ROWITZ, MBBS, PhD1,2
CHRISTOPHER K. RAYNER, MBBS, PhD1,2

OBJECTIVE—Macronutrient “preloads” can reduce postprandial glycemia by slowing gastric emptying and stimulating glucagon-like peptide-1 (GLP-1) secretion. An ideal preload would entail minimal additional energy intake and might be optimized by concurrent inhibition of dipeptidyl peptidase-4 (DPP-4). We evaluated the effects of a low-energy d-xylose preload, with or without sitagliptin, on gastric emptying, plasma intact GLP-1 concentrations, and postprandial glycemia in type 2 diabetes.

RESEARCH DESIGN AND METHODS—Twelve type 2 diabetic patients were studied on four occasions each. After 100 mg sitagliptin (S) or placebo (P) and an overnight fast, patients consumed a preload drink containing either 50 g d-xylose (X) or 80 mg sucralose (control (C)), followed after 40 min by a mashed potato meal labeled with 13C-octanoate. Blood was sampled at intervals. Gastric emptying was determined.

RESULTS—Both peak blood glucose and the amplitude of glycemic excursion were lower after PX and SC than PC (P < 0.01 for each) and were lowest after SX (P < 0.05 for each), while overall blood glucose was lower after SX than PC (P < 0.05). The postprandial insulin-to-glucose ratio was attenuated (P < 0.05) and gastric emptying was slower (P < 0.01) after d-xylose, without any effect of sitagliptin. Plasma GLP-1 concentrations were higher after d-xylose than control only before the meal (P < 0.05) but were sustained postprandially when combined with sitagliptin (P < 0.05).

CONCLUSIONS—In type 2 diabetes, acute administration of a d-xylose preload reduces postprandial glycemia and enhances the effect of a DPP-4 inhibitor.

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Theoretical strategies directed at reducing postprandial glycemia are of fundamental importance in the management of type 2 diabetes (1). For patients with mild-to-moderate hyperglycemia, postprandial blood glucose is a better predictor of HbA1c than fasting blood glucose (2).

Both gastric emptying and the action of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are major determinants of postprandial glucose excursions (3). Gastric emptying determines the rate of nutrient delivery to the small intestine, accounting for approximately one-third of the variation in the initial rise in glycemia after oral glucose in both healthy subjects (4) and those with type 2 diabetes (5). GLP-1 and GIP, released predominantly from the distal and proximal gut, respectively, are the known mediators of the incretin effect, whereby much more insulin is stimulated by enteral compared with intravenous glucose (6). In type 2 diabetes, the incretin effect is impaired (7), related at least partly to a diminished insulinoctropic effect of GIP, while that of GLP-1 is preserved (8). In addition, GLP-1 slows gastric emptying (9), suppresses glucagon secretion (10), and reduces energy intake (11). Therefore, incretin-based therapies for diabetes have hitherto focused on GLP-1.

One promising strategy to stimulate endogenous GLP-1 is the “preload” concept, which involves administration of a small load of macronutrient at a fixed interval before a meal so that the presence of nutrients in the small intestine induces the release of gut peptides, including GLP-1, to slow gastric emptying and improve the glycemic response to the subsequent meal. Fat (12) and protein (13) preloads achieve these goals but entail additional energy intake. We recently demonstrated in healthy subjects the potential for poorly absorbed sweeteners, which yield little energy, to stimulate GLP-1 secretion and slow gastric emptying (14).

D-Xylose is a pentose sugar, which is incompletely absorbed by passive diffusion in human duodenum and jejunum (15), with the remainder delivered to the ileum and the colon, where bacterial fermentation occurs, producing hydrogen that can be detected in the breath (16). We recently showed that oral consumption of d-xylose stimulates GLP-1 secretion to a greater and more sustained extent than glucose in healthy older subjects (17), consistent with the principle that the length and region of small intestine exposed to carbohydrate are important determinants of GLP-1 release (18). D-Xylose also slowed gastric emptying compared with water, with efficacy similar to that of the glucose load (17).
Intact GLP-1 is short-lived in the circulation largely because of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) (19), and orally administered DPP-4 inhibitors, such as sitagliptin, increase postprandial plasma concentrations of intact GLP-1 (20). However, the concept of stimulating endogenous GLP-1 with enteral nutrients and then optimizing its action with a DPP-4 inhibitor has received little attention. Moreover, little consideration has been given as to whether the composition of the diet influences the efficacy of DPP-4 inhibition to lower postprandial blood glucose.

The current study was designed to determine, in patients with type 2 diabetes, whether a D-xylose preload would slow gastric emptying, stimulate GLP-1 secretion, and improve postprandial glycemia and whether these effects could be enhanced by DPP-4 inhibition.

**RESEARCH DESIGN AND METHODS**—Twelve patients with type 2 diabetes (9 males and 3 females), managed by diet alone, were studied after type 2 diabetes (9 males and 3 females), managed by diet alone, were studied after.

**METHODS**

D-Xylose preload and sitagliptin have received little attention. Moreover, whether the composition of the diet influences the efficacy of DPP-4 inhibition to lower postprandial blood glucose.

The current study was designed to determine, in patients with type 2 diabetes, whether a D-xylose preload would slow gastric emptying, stimulate GLP-1 secretion, and improve postprandial glycemia and whether these effects could be enhanced by DPP-4 inhibition.

Blood samples for insulin were collected in serum tubes. For the measurement of intact GLP-1, venous blood was collected into ice-chilled EDTA tubes containing DPP-4 inhibitor (DPP4-010; Linco Research, St. Charles, MO) (10 μU/mL blood). Samples were mixed six times by gentle inversion and stored on ice before centrifugation at 3,200 rpm for 15 min at 4°C within 15 min of collection. Serum and plasma were separated and stored at −70°C for subsequent analysis.

**Blood glucose, serum insulin, and intact GLP-1**

Blood glucose concentrations were measured immediately using a glucometer (Medisense Precision QID; Abbott Laboratories, Bedford, MA). The accuracy of the method has been validated against the hexokinase technique (4).

Serum insulin was measured by ELISA immunoassay (cat. no. 10-1113; Mercodia, Uppsala, Sweden). The sensitivity of the assay was 1.0 mU/L and the coefficient of variation was 2.1% within assays and 6.6% between assays.

Plasma intact GLP-1 was measured by radioimmunoassay using a commercially available kit (GLP1A-35HK; Millipore, Billerica, MA), which allows quantification of biologically active forms of GLP-1 (i.e., 7-36 amide and 7-37) in plasma and other biological media. The sensitivity was 3 pmol/L, and intra- and interassay coefficients of variation were 3.4 and 9.1%, respectively.

**Gastric emptying**

Breath hydrogen concentrations in breath samples were measured by an isotope ratio mass spectrometer (ABCA 2020; Europa Scientific, Crewe, U.K.) with an online gas chromatographic purification system. The half-emptying time (T50) was calculated, using the formula described by Ghoos et al. (23). This method has been validated against scintigraphy for the measurement of gastric emptying (24).

**Breath hydrogen**

Hydrogen concentrations in breath samples were measured using Quinton MicroLyzer SC (Quinton Instrument, Milwaukee, WI) and were corrected for CO2 levels (25).

**Statistical analysis**

The incremental areas under the curve (AUCs) were calculated using the trapezoidal rule (26) for blood glucose, serum insulin, plasma intact GLP-1, and breath hydrogen and analyzed using one-factor repeated-measures ANOVA. These variables were also assessed by repeated-measures ANOVA, with treatment and time as factors. The amplitude of glycemic excursion (AGE) (postprandial glycemic peak minus the nadir) and J index [J = 0.324 × (mean blood glucose + SD)3] were calculated as measures of glycemic variability, as previously described (27), and these together with gastric emptying (T50) were compared using one-factor ANOVA. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni-Holm correction, were performed if ANOVAs showed significant effects. Relationships between variables were assessed using linear regression analysis. All analyses were performed with SPSS Statistics (version 19.0; IBM, Armonk, NY). Data are presented as means ± SE; P < 0.05 was considered statistically significant.

**RESULTS**—All subjects tolerated the study well. Three subjects reported mild transient loose stools after completion of the study on the D-xylose days.

**Blood glucose concentrations**

Fasting blood glucose concentrations did not differ between the four study days (PC 7.4 ± 0.3 mmol/L, PX 7.5 ± 0.3 mmol/L, SC 7.1 ± 0.3 mmol/L, and SX 7.5 ± 0.4 mmol/L). Before the meal, blood glucose concentrations increased slightly when
the p-xylose preload was given (i.e., PX and SX) in contrast to the control days, so that the iAUC (−40 to 0 min) was greater for PX and SX than for PC and SC (P < 0.05 for each) (Table 1). After the meal, blood glucose concentrations increased on each day before returning to baseline. The postprandial glycemic peak, AGE, and J index were all lower after PX and SC than PC (P < 0.01 for each) and were lowest after SX (P < 0.05 for each) (Table 1). There was a significant treatment effect on the overall iAUC for blood glucose (P = 0.008) (Table 1), such that blood glucose was lower after SX compared with PC (P < 0.05) (Fig. 1A).

Serum insulin
Fasting serum insulin concentrations did not differ between the four study days. Before the meal, the insulin concentrations increased slightly when p-xylose was given (i.e., PX and SX) in contrast to the control days, so that the iAUC (−40 to 0 min) was greater for PX and SX than for PC and SC (P < 0.05 for each) (Table 1). After the meal, serum insulin concentrations increased on each day, but p-xylose and sitagliptin alone and in combination resulted in a lower postprandial serum insulin than PC (P = 0.000 for treatment × time interaction, with significant differences at t = 30, 60, and 90 min for PX vs. PC and SX vs. PC; t = 90 min for SC vs. PC; and t = 30 min for SX vs. SC [P < 0.05 for each]). There was also a significant treatment effect on the overall iAUC for serum insulin (P = 0.009) (Table 1), such that insulin concentrations were lower after SX than PC (P < 0.05) (Fig. 1B).

Before the meal, the insulin-to-glucose ratio (Fig. 1C) remained unchanged after both p-xylose and control preloads, but the ratio increased after the meal and was lower from t = 30 to 90 min after the p-xylose preload compared with control (P = 0.000 for a treatment × time interaction: PX vs. PC and SX vs. SC [P < 0.05 for each]) without any effect of sitagliptin.

Plasma intact GLP-1
Fasting plasma intact GLP-1 concentrations did not differ between the four study days. Before the meal, GLP-1 concentrations increased when the p-xylose preload was given, so that the iAUC (−40 to 0 min) was greater for SX than for PC and SC (P < 0.05 for each) (Table 1), although the difference between PX and PC was not significant. After the meal, intact GLP-1 increased on the control days, but the combination of the p-xylose preload with sitagliptin resulted in a more sustained elevation of plasma intact GLP-1 than on the other days (P = 0.000 for a treatment × time interaction, with significant differences at t = 15, 60, 90, and 120 min for SX vs. PC and during t = 30–120 for SX vs. PX [P < 0.05 for each]). There was also a treatment effect on the overall iAUC for plasma intact GLP-1 (P = 0.003) (Table 1), such that GLP-1 was greatest after SX (SX vs. PC, PX, and SC, P < 0.05 for each) (Fig. 1D).

Breath hydrogen production
Fasting breath hydrogen approximated 0 ppm and did not differ between the four study days. After the p-xylose drink, breath hydrogen increased slightly before the meal (t = −40 to 0 min) and continued to rise to a plateau afterward, while it remained unchanged after the control preload and was unaffected by sitagliptin (P = 0.000 for a treatment × time interaction) (Fig. 2).

Gastric emptying
There was a treatment effect for gastric emptying (P = 0.000), such that the half-emptying time was greater after p-xylose than control (T50 for PX 238.2 ± 26.4 min and SX 256.9 ± 23.1 min vs. PC 152.3 ± 6.0 min and SC 166.3 ± 11.0 min [P < 0.01 for each]) without any effect of sitagliptin (Fig. 3).

Relationships between blood glucose and gastric emptying, plasma intact GLP-1, and breath hydrogen production
When data from the four study visits were pooled, the magnitude of the postprandial rise in blood glucose from baseline at t = 30, 60, and 90 min was inversely related to the T50 (P < 0.01 for each) and at t = 240 min directly related to the T50 (P = 0.001).

Given that plasma intact GLP-1 would be more sensitive as a measure of GLP-1 secretion when DPP-4 was inhibited, data from the SX day alone were examined for a relationship between breath hydrogen production and GLP-1 secretion. Intact GLP-1 concentrations were found to be related directly to breath hydrogen production (for iAUC−40 to 0, r = 0.72, P = 0.009; for iAUC−40 to 240, r = 0.74, P = 0.006).

CONCLUSIONS—The main observations made in this study of patients with type 2 diabetes managed by diet were that 1) consumption of the low-energy pentose p-xylose in advance of a high-carbohydrate meal attenuates the postprandial glycemic excursion in association with stimulation of GLP-1 secretion before the meal and slowing of gastric emptying, 2) a single dose of the DPP-4 inhibitor sitagliptin increases postprandial intact GLP-1

Table 1—Postprandial glycemic peak, J index, AGE, iAUC for blood glucose, serum insulin, and GLP-1 in response to a carbohydrate meal after a preload of either p-xylose or sucralfose (control) with or without 100 mg sitagliptin (n = 12)

|                          | PC  | PX  | SC  | SX  | P          |
|--------------------------|-----|-----|-----|-----|------------|
| Glycemic peak (mmol/L)    | 14.8±0.6 | 13.3±0.64 | 13.2±0.6b | 12.3±0.6cde | 0.000 |
| J index (mmol²/L²)        | 54.7±4.5 | 46.7±3.8a | 44.1±3.9b | 39.2±3.4cde | 0.000 |
| AGE (mmol/L)              | 8.7±0.5 | 6.5±0.5a | 7.3±0.5b | 5.5±0.5cde | 0.000 |
| Glucose iAUC−40 to 0 (mmol/L × min) | 3.8±1.4 | 15.3±4.5a | 3.1±2.0 | 12.2±3.8c | 0.010 |
| Glucose iAUC−40 to 240 (mmol/L × min) | 872.6±101.4 | 797.1±68.1 | 717.5±103.8 | 630.7±86.8c | 0.008 |
| Insulin iAUC−40 to 0 (mU/L × min) | 11.3±5.0 | 54.7±10.8a | 17.3±6.2 | 53.7±17.9c | 0.006 |
| Insulin iAUC−40 to 240 (mU/L × min) | 6,715.2±1,701.8 | 5,343.4±1,203.0 | 5,754.1±1,230.0 | 3,972.9±563.2c | 0.009 |
| Intact GLP-1 iAUC−40 to 0 (pmol/L × min) | 14.3±6.7 | 52.2±20.5 | 8.3±3.3 | 86.8±28.9ce | 0.004 |
| Intact GLP-1 iAUC−40 to 240 (pmol/L × min) | 135.8±36.7 | 125.0±39.1 | 130.5±38.5 | 492.1±161.4cde | 0.003 |

Data are means ± SEM. One-factor repeated-measures ANOVA was used to determine statistical difference. Post hoc comparisons were adjusted by Bonferroni-Holm correction. *P < 0.05, PX vs. PC; **P < 0.05, SC vs. PC; ***P < 0.05, SX vs. PC; ****P < 0.05, SX vs. PX; *****P < 0.05, SX vs. SC.
concentrations and reduces postprandial
glycemia without slowing gastric empty-
ing or stimulating postprandial insulin
secretion, and 3) the combination of a
D-xylose preload with sitagliptin reduces
the postprandial glycemic excursion more
than either treatment alone. The magnitude
of the reduction in postprandial blood
glucose achieved by the combination
of D-xylose preload and sitagliptin in
our group of patients with well-con-
trolled type 2 diabetes was substantial
(i.e., reduction in peak blood glucose of
~2.5 mmol/L), and moreover, there was a
marked reduction in indices of glycemic
variability; the latter is associated with ox-
idative stress and may independently in-
crease cardiovascular risk (27).

We chose D-xylose as the preload,
since it is incompletely absorbed and
poorly metabolized (16) and, accord-
ingly, additional energy intake is mini-
mized in contrast to preloads such as fat
(12) and protein (13). Consistent with
our previous report in healthy older sub-
jects (17), ingestion of D-xylose resulted
in a modest increase in blood glucose and
serum insulin, possibly as a result of en-
hanced gluconeogenesis. Sucralose was
selected as a sweet-tasting negative con-
trol, since we have shown that this arti-
cficial sweetener when given acutely has no
effect on either the secretion of GLP-1 or
the slowing of gastric emptying induced
by the D-xylose preload may well have at-
tenuated the component of the postpran-
dial GLP-1 response attributable to the meal.

We observed that the magnitude of the
initial postprandial glycemic excursi-
on was inversely related to the gastric
half-emptying time, consistent with evi-
dence that the rate of gastric emptying
is a major determinant of postprandial
glycemia (4, 5). In the absence of
sitagliptin, the reduction in postprandial
glycemia by D-xylose is probably attrib-
utable mainly to the slowing of gastric
emptying, since postprandial intact GLP-1
concentrations were no greater than on
the control day. The observed decrease
in postprandial insulin concentrations af-
ter D-xylose in contrast to control, partic-
ularly when corrected for differences in
blood glucose (i.e., the insulin-to-glucose
ratio), is consistent with what would be
expected when gastric emptying of the
potato meal is slower (12).

The slowing of gastric emptying after
the D-xylose preload was associated with
stimulation of GLP-1 in advance of the
meal, although postprandial intact GLP-1
concentrations were not increased in the
absence of sitagliptin. Since endogenous

Figure 1—Effects of D-xylose or sucralose (control) with or without sitagliptin on blood glucose (A), serum insulin (B), insulin-to-glucose ratio (C), and plasma intact GLP-1 (D) in response to a carbohydrate meal (n = 12). The four treatments were SX, SC, PX, and PC. Repeated-measures ANOVA was used to determine statistical difference. Post hoc comparisons were adjusted by Bonferroni-Holm correction. P = 0.000 for each treatment × time interaction; *P < 0.05, PX vs. PC; #P < 0.05, SC vs. PC; αP < 0.05, SX vs. PC; βP < 0.05, SX vs. PX; eP < 0.05, SX vs. SC. Data are means ± SEM.

Figure 2—Effects of D-xylose or sucralose (control) with or without sitagliptin on breath hydrogen production in response to a carbohydrate meal (n = 12). The four treatments were SX (▪), SC (○), PX (□), and PC (○). Repeated-measures ANOVA was used to determine statistical difference. *P = 0.000, PX vs. PC and SC; #P = 0.000, SX vs. PC and SC. Data are means ± SEM.
GLP-1 is known to slow gastric emptying (9), the elevated GLP-1 may have contributed to the slower gastric emptying after D-xylose, at least during the initial phase. Nevertheless, the combination with sitagliptin, which increased plasma concentrations of intact GLP-1, had no additional effect on the rate of gastric emptying—a finding that is consistent with our recent report of the lack of effect of 2-day dosing with sitagliptin on gastric emptying (33). This is likely to be because gastric emptying is modulated by multiple mechanisms. For example, acute hyperglycemia, even within the physiological range, is known to slow gastric emptying (34), and sitagliptin, particularly when combined with D-xylose, potently decreased postprandial glycemia. Moreover, peptide YY (PYY), which is cosecreted with GLP-1 from enteroendocrine L cells, has the capacity to slow gastric emptying. PYY 1-36 and 3-36 are the predominant biologically active forms in the circulation; the latter is formed from degradation of PYY 1-36 by DPP-4 and is reported to be more potent at retarding emptying (35). Therefore, DPP-4 inhibition might, to some extent, blunt PYY-mediated slowing of gastric emptying.

In contrast, addition of sitagliptin did not affect gastric emptying but was associated with lowering of postprandial glycemia. Despite the fact that plasma intact GLP-1 concentrations were increased after sitagliptin, particularly when given in combination with D-xylose, the insulin response to the meal did not increase in parallel. This is partly accounted for by the fact that the insulinovert effect of GLP-1 is glucose dependent (36), but there is also evidence that mechanisms other than insulin secretion are likely to be important in mediating the glucose-lowering effect of GLP-1; the latter include suppression of both glucagon secretion and endogenous glucose production (37,38) and enhancement of peripheral glucose uptake (39).

It is noteworthy that there has been little consideration of how dietary intake interacts with the actions of DPP-4 inhibitors. The current study is therefore novel in demonstrating how consumption of a specific nutrient can improve the efficacy of a DPP-4 inhibitor for reducing postprandial glycemia. Although the number of subjects studied was relatively small, the observed effects were consistent between subjects and were in keeping with previous observations relating to the slowing of gastric emptying by D-xylose (17) and glucose lowering by sitagliptin (20). Our study represents an acute intervention in a relatively well-controlled group of patients with type 2 diabetes managed by diet alone. In view of the positive outcomes, it would be of particular interest to investigate this approach in type 2 diabetic patients taking metformin, given the synergistic effect of DPP-4 inhibitors with metformin for increasing intact GLP-1 and improving glycemia (40), and to extend our observations to larger and more diverse groups of type 2 diabetic patients over a longer duration.

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T.W. was involved in study design and coordination, subject recruitment, data collection and interpretation, statistical analysis, and drafting of the manuscript; critically reviewed the manuscript; and approved the publication of the final version of the manuscript. M.J.B. assisted with data collection and breath hydrogen analysis, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. S.D.S. performed insulin and intact GLP-1 assays, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. S.D.S. performed insulin and intact GLP-1 assays, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. M.B. performed the gastric emptying analysis, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. K.L.J. and M.H. were involved in conception of the study and data interpretation, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. C.K.R. was involved in conception and design of the study and data analysis and interpretation, had overall responsibility for the study, critically reviewed the manuscript, and approved the publication of the final version of the manuscript. C.K.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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