

# Novel Soy Germ Pasta Enriched in Isoflavones Ameliorates Gastroparesis in Type 2 Diabetes

A pilot study

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**OBJECTIVE**—To determine the effect of soy germ pasta enriched in biologically active isoflavone aglycons on gastric emptying in type 2 diabetic patients with gastroparesis.

**RESEARCH DESIGN AND METHODS**—This randomized double-blind, placebo-controlled study compared soy germ pasta with conventional pasta for effects on gastric emptying. Patients ( $n = 10$ ) with delayed gastric emptying consumed one serving per day of each pasta for 8 weeks, with a 4-week washout. Gastric emptying time ( $t_{1/2}$ ) was measured using the [<sup>13</sup>C] octanoic acid breath test at baseline and after each period, and blood glucose and insulin concentrations were determined after oral glucose load.

**RESULTS**—Soy germ pasta significantly accelerated the  $t_{1/2}$  in these patients ( $161.2 \pm 17.5$  min at baseline vs.  $112.6 \pm 11.2$  min after treatment,  $P = 0.009$ ). Such change differed significantly ( $P = 0.009$ ) from that for conventional pasta ( $153.6 \pm 24.2$  vs.  $156.2 \pm 27.4$  min), without affecting glucose or insulin concentrations.

**CONCLUSIONS**—These findings suggest that soy germ pasta may offer a simple dietary approach to managing diabetic gastropathy.

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**G**astroparesis is a symptomatic chronic debilitating disorder of the stomach, characterized by delayed gastric emptying of solid and semi-solid foods in the absence of mechanical obstruction. It affects 30–50% of patients with long-standing type 2 diabetes (T2D) (1,2) and is associated with upper gastrointestinal symptoms. It compromises the pharmacokinetics of orally administered drugs by altering rates of absorption and

can also alter glycemia control. The withdrawal of the prokinetic cisapride (3) has compromised therapeutic options (4,5). Interestingly, dietary modifications have been suggested to potentially represent an alternative to drugs for diabetic gastroparesis (2). Our objective was to evaluate a novel soy germ pasta containing biologically active isoflavone aglycons (6,7) for effects on gastric emptying in T2D patients with gastroparesis.

## RESEARCH DESIGN AND METHODS

This randomized, double-blind, placebo-controlled crossover study enrolled 10 adults (5 male and 5 female; mean  $\pm$  SEM  $62.7 \pm 2.3$  years of age; BMI  $28.8 \pm 1.0$  kg/m<sup>2</sup>; HbA<sub>1c</sub> 64 mmol/mol) with T2D and delayed gastric emptying ( $t_{1/2}$  range 134–253 min; normal range <120 min). None had major complications of diabetes and all were maintained on a standard diabetes diet for >6 months and throughout the study. Prior use of medications that affect gastric emptying, soy-based products, or supplements and a history of gastrointestinal or liver disease were exclusion criteria. The study was conducted with informed consent and approved by the Human Ethics Committee of the University of Perugia School of Medicine.

Patients were randomized to two groups. One group ( $n = 5$ ) consumed one serving per day of soy germ-enriched pasta (80 g) followed by conventional pasta for 8 weeks, with a 4-week washout between. The other group ( $n = 5$ ) consumed these pastas in reverse sequence. The two pastas were indistinguishable. The composition of the soy germ pasta (Aliveris S.r.l., Perugia, Italy), which contained 2% soy germ, delivering 31–33 mg isoflavones per serving, is described elsewhere (6). At baseline, blood was collected after fasting and 30, 60, 90, and 120 min after a standard meal for measurement of plasma glucose and serum insulin by standard methods. The next day, gastric emptying time was measured using the [<sup>13</sup>C]octanoic acid breath test (8,9). These tests were repeated after 8, 12, and 20 weeks, and the severity of symptoms of gastroparesis was also assessed using the Gastroparesis Cardinal Symptom Index (GCSI) questionnaire (10). Methods and data analysis are described in more detail in the Supplementary Data.

**RESULTS**—Compliance to soy germ pasta was confirmed by an elevated mean plasma isoflavone concentration of  $68 \pm 9$  ng/mL (11), and for conventional pasta from counting of returned packages.

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Figure 1 shows individual  $t_{1/2}$  values for gastric emptying measured at baseline and after consuming both pastas. No period, sequence, or washout effects were observed. The inclusion of soy isoflavone-enriched pasta to the standard American Diabetes Association (ADA) diet led to a significant acceleration in mean ( $\pm$ SEM)  $t_{1/2}$  in the 10 patients when compared with baseline values ( $t_{1/2} = 161.2 \pm 17.5$  vs.  $112.6 \pm 11.2$  min,  $P = 0.009$ ;  $P = 0.109$  for the analysis limited to pairwise comparison of data from the end of each period). The regression coefficient for individual  $t_{1/2}$  values before and after soy germ pasta ( $0.478$  [95% CI  $0.134$ – $0.822$ ];  $R^2 = 0.562$ ;  $P < 0.013$ ) lies well below unity, indicating a substantial reduction of the  $t_{1/2}$  (Fig. 1). These findings are consistent with results from the crossover analysis, indicating that soy germ pasta improves gastric emptying time irrespective of the order in which it was given. By contrast, there was no significant

difference in the group mean  $t_{1/2}$  values when conventional pasta lacking isoflavones was consumed ( $153.6 \pm 24.2$  vs.  $156.2 \pm 27.4$  min,  $P = 0.76$ ).

No statistical differences from baseline, or between the two pastas, were observed for the plasma glucose and insulin responses to a standard meal (Supplementary Table 1).

No statistical difference was observed in the GCSI scores between responses to the two pastas at crossover analysis, or in the analysis limited to pairwise comparison of data from the end of each study period. However, the median (range) total GCSI score was 8 (2–13) at baseline, and this significantly decreased to 5 (0–7) ( $P = 0.039$ ) for the soy germ pasta group. The corresponding values for conventional pasta were 7 (0–21) and 6 (0–11) ( $P = 0.289$ ), respectively.

**CONCLUSIONS**—The major findings of this pilot study of T2D patients with gastroparesis were that the inclusion of an

isoflavone-enriched soy germ pasta on the background of an ADA diet led to a significant acceleration in the rate of gastric emptying, whereas conventional pasta lacking isoflavones had no effect.

The gastric emptying time measured on baseline conditions (either before or after the washout period) was longer ( $P = 0.073$ ) than the upper limit of normal (120 min) (8,9) and consistent with delayed gastric emptying, even though the patients reported only mild symptomatology.

Concerns that accelerating gastric emptying could potentially lead to increased glycemia (12–14) were not supported from measurements of plasma glucose or insulin concentrations in response to a standard meal after normalization of the  $t_{1/2}$  by soy germ pasta. This is presumably because these patients adhered to an ADA maintenance diet, were not taking drugs, and were all in good glycemic control.

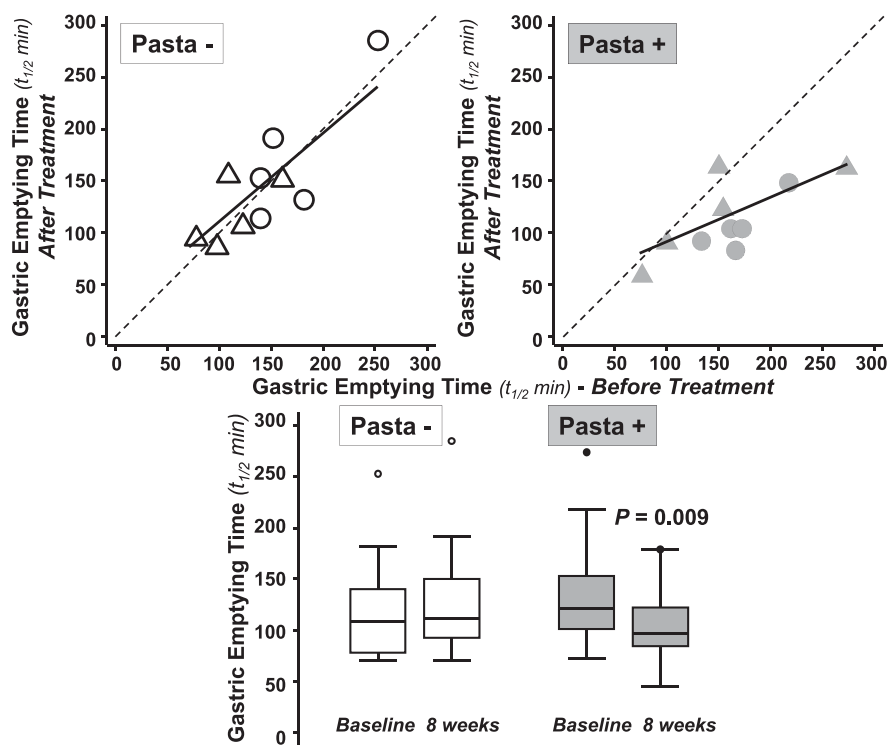
Although not the primary objective of our study, and not surprising given the relatively low baseline GCSI scores and small sample size, we found only a minor improvement in the severity of upper gastrointestinal symptoms after an improvement in  $t_{1/2}$ . A larger study of patients with more severe symptoms would better address the effectiveness of soy germ pasta on symptomatology.

We speculate that isoflavones, when in contact with gastric mucosa, influence prostaglandin synthesis to modulate motility. Gene expression data from gastric mucosal biopsies of healthy adults has shown that soy germ pasta significantly alters the expression of many genes involved in gastric function. *PTDGS*, a gene encoding prostaglandin D2 synthase, the enzyme responsible for prostaglandin F2 $\alpha$  synthesis, was upregulated fivefold by soy germ pasta (S.A., K.D.R.S., C.C., 2012, unpublished data).

In conclusion, pasta enriched with biologically active isoflavone aglycons improved gastric emptying time in T2D patients, warranting consideration of this dietary intervention in the management of diabetic gastroparesis, especially given that there is currently no effective pharmacologic therapy.

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**Figure 1**—Relationship between gastric emptying time ( $t_{1/2}$ ) in 10 patients with documented diabetic gastroparesis measured at baseline and after consuming soy germ pasta containing isoflavone aglycons and conventional pasta lacking isoflavones. The dotted line in the upper plots denotes no change after consuming pasta. Data points below this line indicate reduced gastric emptying time. The solid lines show the regression line of values after treatment on those before treatment during enriched pasta (Pasta+) or control pasta (Pasta-) feeding. Gray and hollow circles denote the data measured on entry into this crossover study and after the first pasta treatment (to be enrolled, these patients had to show a baseline emptying time  $>120$  min); gray and hollow triangles denote values measured after the washout period, i.e., before and after the other pasta treatment. The lower plot (box plots) shows the distribution of gastric emptying times before and after 8-week treatment with the two pastas.

responsible for recruitment, enrollment, and clinical care of the patients and performed the clinical and biochemical tests and data collection and processing. P.-M.B. performed the statistical analysis of data. S.A. performed the clinical and biochemical tests and data collection and processing. All authors reviewed the manuscript. K.D.R.S. and C.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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