

LETTER

The Impact of Pancreatic Enzyme Supplementation on Postprandial Responses of Glucagon-Like Peptide-2 in Patients with Chronic Pancreatitis and Pancreatic Exocrine Insufficiency

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Dear Sir,

We have recently shown that patients with chronic pancreatitis and pancreatic exocrine insufficiency exhibit greater postprandial responses of the intestinal hormone glucagon-like peptide-2 (GLP-2) as compared to healthy control subjects [1]. GLP-2 is a 33-amino acid peptide hormone secreted by the endocrine L cells of the intestinal mucosa following meal ingestion [2]. It acts as a growth factor in the small intestine [3] and, in patients with functional short-bowel syndrome, GLP-2 has been shown to improve intestinal absorption [4]. Furthermore, GLP-2 seems to increase intestinal blood flow [5], including blood flow in the superior mesenteric artery of pigs [6] and humans [7]. Interestingly, our recent observation of increased postprandial GLP-2 responses in patients with chronic pancreatitis and pancreatic exocrine insufficiency correlated with increased postprandial blood flow in the superior mesenteric arteries of these patients [1]. However, the mechanisms behind the increased postprandial GLP-2 response in chronic pancreatitis patients with pancreatic exocrine insufficiency could only be speculated upon, with one explanation being that reduced assimilation of nutrients in the proximal part of the small intestine results in delivery of a larger nutrient load to the distal L cell-rich part of the small

intestine. Reduced assimilation of nutrients in chronic pancreatitis patients with pancreatic exocrine insufficiency can be clinically modulated by the administration of pancreatic enzyme supplementation. In 2007, we reported that pancreatic enzyme supplementation in these patients resulted in increased postprandial secretion of GLP-2's sister peptide, GLP-1, also released from intestinal L cells [8]. In order to investigate potential mechanisms behind exaggerated GLP-2 levels in chronic pancreatitis we evaluated the impact of pancreatic enzyme supplementation on postprandial GLP-2 responses in the chronic pancreatitis patients from our 2007 study [8].

Eight patients with chronic pancreatitis and pancreatic exocrine insufficiency were investigated using two liquid meal tests consumed with and without two capsules of pancreatic enzyme supplementation (Creon[®] 25,000 U, Solvay Pharma, Herlev, Denmark) as previously described [8]. A group of 8 healthy sex-age- and body mass index-matched control subjects was examined using the same meal. Arterialized blood was drawn and distributed into EDTA tubes containing aprotinin and a dipeptidyl peptidase 4 (DPP4) inhibitor as previously described [8]. The tubes were centrifuged for 20 minutes at 1,700 *g* and 4°C, and plasma was stored at -20 °C until analysis. The GLP-2 radioimmunoassay employs antiserum code no. 92160 and standards of human GLP-2 (proglucagon 126-158, a gift from Novo Nordisk A/S, Bagsværd, Denmark) and monoiodinated Tyr-12 GLP-1, specific activity greater than 70 MBq/nmol. The antiserum is directed against the N-terminus of GLP-2 and therefore measures only fully processed intact GLP-2 of intestinal origin. Sensitivity for the assay is below 2 pmol/L and the intra-assay coefficient of variation is below 6% [9]. Data are expressed as mean±SEM and were compared by means of analysis of variance (ANOVA). Area under curve (AUC) values were calculated using the trapezoidal rule.

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Abbreviations GLP: glucagon-like peptide

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No significant difference between the baseline values of GLP-2 during the two meal tests was observed in patients with chronic pancreatitis and pancreatic exocrine insufficiency ($P=0.253$). Chronic pancreatitis patients had higher mean baseline values as compared to control subjects (28 ± 3 vs. 19 ± 3 pmol/L; $P=0.041$). As illustrated in Figure 1, patients with chronic pancreatitis and pancreatic exocrine insufficiency exhibited steeper rises in plasma GLP-2 concentrations and reached significantly higher peak concentrations (89 ± 16 pmol/L with pancreatic enzyme supplementation and 80 ± 12 pmol/L without pancreatic enzyme supplementation; $P=0.498$ between the two meal tests) following meal ingestion as compared to control subjects (51 ± 4 pmol/L; $P=0.034$ and $P=0.037$ with and without pancreatic enzyme supplementation, respectively). Likewise, patients with chronic pancreatitis and pancreatic exocrine insufficiency exhibited significantly higher postprandial GLP-2 responses (as assessed by AUC) after pancreatic enzyme administration as compared to control subjects (11.7 ± 1.3 vs. 8.5 ± 0.7 nmol/L x 240 min; $P=0.043$). However, neither the difference between the patients without enzyme supplementation and the controls (10.1 ± 1.0 vs. 8.5 ± 0.7 nmol/L x 240 min) ($P=0.204$) or the difference between the two meal tests in the chronic pancreatitis patients reached statistical significance (11.7 ± 1.3 vs. 10.1 ± 1.0 nmol/L x 240 min, with vs. without pancreatic enzyme supplementation, respectively; $P=0.112$). Repeated measure ANOVA did not show significant different time courses between the two meal tests (with and without pancreatic enzyme supplementation) in the chronic pancreatitis patients ($P=0.935$).

The observation of elevated postprandial GLP-2 levels in patients with chronic pancreatitis and pancreatic exocrine insufficiency as compared to control subjects [1] prompted us to investigate whether GLP-2 secretion in these patients could be modulated by pancreatic

enzyme supplementation (increasing the digestive capacity supported by increased plasma concentrations of triglycerides and glucagon) as described for GLP-1 [8]. GLP-2 is secreted in response to the intraluminal presence of the nutritional components, but the exact mechanisms behind GLP-2 secretion are poorly understood. For instance, the separate effects of digested and undigested nutrients on GLP-2 secretion have not been investigated. As mentioned, GLP-2 secreting L cells are most abundant in the distal part of the small intestine, and in patients with chronic pancreatitis and pancreatic exocrine insufficiency, the L cells are thought to be exposed to larger amounts of nutrients due to 1) attenuated assimilation in the 'foregut' [10] and/or 2) accelerated gastrointestinal transit [11]. In the present study, we aimed to evaluate the role of the former by evaluating GLP-2 responses to a liquid meal test with and without pancreatic enzyme supplementation in chronic pancreatitis patients with pancreatic exocrine insufficiency. First, the present data confirm our recent finding of increased postprandial GLP-2 responses in patients with chronic pancreatitis and pancreatic exocrine insufficiency and, second, they suggest that the administration of pancreatic enzymes has a limited impact on postprandial GLP-2 responses. Therefore, we hypothesize that the elevated GLP-2 responses in patients with chronic pancreatitis and pancreatic exocrine insufficiency may reflect accelerated gastrointestinal transit time, resulting in the increased delivery of nutrients to the L cell-rich distal part of the small intestine.

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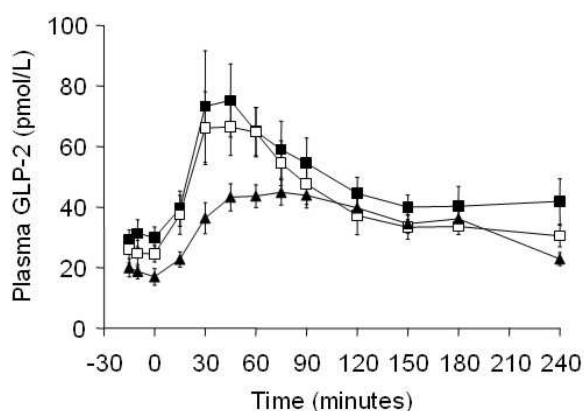


Figure 1. Plasma concentrations of glucagon-like peptide-2 (GLP-2) during liquid meal test in eight patients with chronic pancreatitis and pancreatic exocrine insufficiency treated with (black squares) and without (open squares) pancreatic enzyme supplementation and in eight sex- age- and body mass index-matched healthy control subjects (black triangles). Data are mean values $\pm$ SEM.

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