Gastric emptying and its relationship with postprandial glycaemic control in young people with cystic fibrosis and type 1 diabetes.

A thesis submitted by

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THESIS AIMS

1. To quantify gastric emptying in adolescents with exocrine pancreatic insufficient cystic fibrosis and examine its relationship with postprandial glycaemia, incretin hormone response, and pancreatic enzyme replacement therapy.

2. To quantify gastric emptying in adolescents with type 1 diabetes and examine its relationship with postprandial glycaemia, gastrointestinal symptoms and autonomic function.

HYPOTHESES

In adolescents with exocrine pancreatic insufficient cystic fibrosis, both with and without cystic fibrosis related diabetes:

i) Gastric emptying of a high fat/carbohydrate meal will be abnormally rapid.

ii) Abnormal emptying will be associated with postprandial hyperglycaemia and deficient GIP, GLP-1 and insulin responses.

iii) These abnormal responses will be ameliorated by pancreatic enzyme

In adolescents with type 1 diabetes

(i) Gastric emptying is slower than in controls

(ii) Cardiac autonomic dysfunction relates to gastric emptying

(iii) Gastrointestinal symptoms are associated with abnormal gastric emptying.

THESIS SUMMARY

This thesis examines gastric emptying and its relationship to postprandial glycaemia in two groups of young people; those with cystic fibrosis (CF) and those with type 1 diabetes (T1D). In particular, the relationship of gastric emptying to postprandial glycaemia, and incretin hormone responses, and the effect of pancreatic enzyme supplementation therapy (PERT) is investigated in CF, while in T1D the relationship of gastric emptying to postprandial glycaemia, gastrointestinal symptoms and autonomic function is investigated.

Optimal glycaemic control, as measured by glycated haemoglobin (HbA1c), is critical in preventing long term micro- and macro-vascular complications of diabetes. Gastric emptying is a major determinant of overall glycaemic control, accounting for at least 30% of the variation in postprandial blood glucose concentrations in adults with diabetes (Monnier et al., 2003, Horowitz et al., 1993). Both the magnitude of postprandial glycaemic excursions and peak postprandial blood glucose relate to the rate of gastric emptying in health and in type 2 diabetes (Horowitz et al., 1993, Jones et al., 1995), so that rapid emptying and delivery of nutrients to the small intestine results in a sharp, early rise in blood glucose.

Gastric emptying is the result of co-ordinated gastric motor activity of the proximal and distal stomach, and is influenced by multiple variables including the neurohumoral axis, in particular the incretin hormones, and the autonomic nervous system. The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), play a critical role in postprandial

glycaemic control, with up to 70% of the total insulin response to oral glucose attributed to their actions in health (Baggio and Drucker, 2007). They are secreted from intestinal enteroendocrine cells in response to nutrient exposure; GLP-1 has both glucose-dependent insulinotropic and glucagonostatic properties, and also plays an important role in the slowing of gastric emptying. GIP predominantly improves postprandial glycaemia through its insulinotropic effects, as it does not appear to influence the rate of gastric emptying, and may stimulate glucagon secretion (Nauck et al., 1997).

While diabetes management has focused on fasting or pre-prandial glycaemia, the contribution of postprandial glycaemia to HbA1c, particularly when the latter is only moderately elevated (HbA1c <7.5%) is being increasingly recognised (Monnier et al., 2003, Horowitz et al., 1993). Consequently, there is now growing interest in dietary and pharmaceutical therapies that modify the rate of gastric emptying for optimising postprandial glycaemic control in diabetes.

The mean life expectancy for patients with CF is improving, and with this has come the increasing clinical challenge of managing the associated long term co-morbidities, in particular CF related diabetes (CFRD)(Lanng et al., 1994). CFRD is associated with worsening nutritional state and pulmonary function, and increased mortality. Abnormalities of carbohydrate metabolism in CF represent a continuum from normal, through pre-diabetes, to overt diabetes, with CFRD characterised by postprandial, rather than fasting or pre-prandial, hyperglycaemia. Insulin is currently recommended to treat CFRD; however, it is a demanding treatment for patients who already require other complex and time consuming regimens, and is associated with

a risk of hypoglycaemia. Exocrine pancreatic insufficiency with associated fat malabsorption affects approximately 80% of CF patients, and fat digestion often remains abnormal despite PERT (Baker et al., 2005, Symonds et al., 2003). Lipolytic products in the small intestine induce both release of the incretin hormones, and other neurohumoral feedback that slows gastric emptying (Borovicka et al., 2000, Heddle et al., 1989). Fat malabsorption in adults is, therefore, associated with abnormally rapid gastric emptying of high fat meals and accelerated absorption of carbohydrates, resulting in postprandial hyperglycaemia (Carney et al., 1995, Kuo et al., 2010). Few studies have assessed gastric emptying and/or incretin responses in CF patients, with inconsistent observations (Pauwels et al., 2011, Cucchiara et al., 1996, Kuo et al., 2011, Collins et al., 1997). An initial pilot study in 5 adults indicated that PERT slows gastric emptying of a high fat/high carbohydrate meal, with enhanced incretin hormone secretion, and a reduction in postprandial glycaemia (Kuo et al., 2011).

The study reported in Chapter 5 aimed to assess whether PERT slowed gastric emptying, increased incretin secretion and improved postprandial glycaemia in adolescents with CF. This study showed that in adolescents with pancreatic insufficient CF, PERT markedly attenuates postprandial hyperglycaemia by slowing gastric emptying and augmenting incretin hormone secretion. It illustrates the importance of adequate and timely PERT, not just for fat absorption, but also in the management of postprandial hyperglycaemia, which has not been a focus of clinical management.

The prevalence of T1D in children under 15 years has doubled over the last 20 years in Australia , with 2 young people diagnosed each day (Guariguata et al., 2013). Evidence for altered gastric emptying in adults with diabetes is abundant, with delayed gastric emptying more commonly reported, often in association with autonomic dysfunction (Rayner et al., 2001, Jones et al., 2002). Gastrointestinal symptoms can suggest the presence of abnormal gastric emptying, however the correlation between the two is relatively poor (Samsom et al., 2003, Bharucha et al., 2009). Abnormal autonomic function is implicated in the pathogenesis of delayed gastric emptying in patients with long standing diabetes. Abnormalities of heart rate variability (HRV), a measure of cardiovascular autonomic function, can be detected in adolescents with T1D before the appearance of symptoms (Pfeifer et al., 1984, Wawryk et al., 1997). Gastric emptying and its relationship to postprandial glycaemia, gastrointestinal symptoms, and autonomic function, has not been assessed in young people with T1D.

The study in Chapter 6 aimed to assess gastric emptying in adolescents with T1D, and its relationship with postprandial glycaemia, gastrointestinal symptoms and autonomic function. This study showed that adolescents with T1D have rapid gastric emptying compared with healthy controls, and that this is associated with large postprandial glycaemic excursions. Fasting hyperglycaemia is, however, associated with slower gastric emptying and gastrointestinal symptoms in this group. This raises the question of the potential benefit of therapies that modify gastric emptying in the management of postprandial glycaemia in T1D.

DECLARATION

Name: Shiree Perano Program: Master of Philosophy

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PUBLICATIONS ARISING FROM THE THESIS

Perano S J, Rayner C K, Couper J J, Martin A J, Horowitz M. Cystic fibrosis related diabetes- a new perspective on the optimal management of postprandial glycaemia. J Diabetes Complicat 2014; 28: 904-911. (THESIS CHAPTER 2)

Perano S J, Couper J J, Horowitz M, Martin, A J, Kritas S, Sullivan T, Rayner C K. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycaemia in adolescents with cystic fibrosis: a randomised crossover trial. JCEM 2014; 99:2486-93 (THESIS CHAPTER 5)

Perano S, Rayner C, Horowitz M, Kritas S, Donaghue K, Mpundu-Kaambwa C, Giles L, Couper J. Gastric emptying is rapid in adolescents with type 1 diabetes and impacts on postprandial glycaemia. J Clin Endocrinol Metab 2015;100 (6):2248-53 (THESIS CHAPTER 6)