# Gastric motor function

# in health and diabetes –

# implications for incretin hormone release and postprandial blood glucose regulation

A thesis submitted by

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# THESIS SUMMARY

This thesis focuses on gastric motor function in patients with longstanding diabetes, and the role of gastric emptying and gastrointestinal hormones in the regulation of glycaemia in health and patients with type 2 diabetes mellitus.

Diabetes is a common chronic disorder worldwide, with the prevalence of type 2 diabetes escalating due to an increasingly sedentary lifestyle and rising rates of obesity. Diabetes is associated with micro- and macrovascular complications, particularly in the context of poor glycaemic control (1993, 1998). Another complication of type 1 and 2 diabetes is gastroparesis (Horowitz et al., 2001, Horowitz M, 1986, Horowitz et al., 1989, Horowitz et al., 1991) (delayed gastric emptying in diabetes) and there is limited information about the natural history and prognosis of this condition. While the prognosis of diabetic gastroparesis has been assumed to be poor, limited data in a small cohort followed for a mean period of 12 years suggest otherwise, with neither deterioration in the rate of gastric emptying (Jones et al., 2002) nor increased mortality due to the condition itself (Kong et al., 1999).

The study reported in Chapter 3 evaluated the longitudinal progression of gastric emptying in patients with longstanding diabetes over a 25 year period to determine if there is a progressive slowing of gastric emptying or whether

gastric emptying is relatively stable with a good prognosis from the outset, and to ascertain the potential impact of glycaemic control and/or autonomic function. The study concludes that gastric emptying and upper gastrointestinal symptoms are relatively stable over 25 years, while there was a deterioration in autonomic function and an improvement in glycaemic control. The study reported in Chapter 4 examined the prognosis of diabetic gastroparesis and its findings highlight that this condition is neither associated with a poor prognosis nor a higher rate of mortality.

There is increasing recognition that glycated haemoglobin (HbA1c), which is a measure of overall glycaemic control, is influenced more by postprandial, rather than fasting, blood glucose levels in the majority of patients with type 2 diabetes. This makes intuitive sense, because the majority of one's time is spent in a postprandial state, digesting the caloric load of the ingested meal, which in healthy subjects empties from the stomach in a tightly regulated process at a rate of 1-4kcal/minute (Khoo et al., 2009). Accordingly, good control of postprandial glucose excursions should be a priority for the treatment of diabetes. The rate of gastric emptying itself influences the magnitude of the initial rise in postprandial glycaemia in health as well as type 1 and 2 diabetes (Jones et al., 1996, Horowitz et al., 1993, Horowitz et al., 1986), whereby slower emptying is associated with diminished postprandial glucose excursions. The overall rate of gastric emptying is dependent on the integration of motor activity in each region of the stomach and slower gastric

emptying is associated with suppression of antral and duodenal contractions, and stimulation of phasic and tonic pyloric pressures, with the latter acting as a brake to gastric outflow (Horowitz et al., 1994).

When glucose is given by the oral/enteral route, the stimulation of insulin is markedly greater than with an isoglycaemic intravenous glucose infusion. This phenomenon is known as the 'incretin effect' and is mediated by the gastrointestinal hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from the small intestine in response to nutrients (Ma et al., 2009a). GLP-1 and GIP both stimulate insulin secretion from the pancreas in the setting of elevated blood glucose levels, and are responsible for ~70% of the postprandial insulin response in healthy humans (Horowitz and Nauck, 2006). GLP-1 analogues, such as exenatide, are now widely used in the management of type 2 diabetes, in whom the response to exogenous GIP is attenuated markedly (Holst and Gromada, 2004) but the insulin response to GLP-1 remains intact (Elahi et al., 1994). It appears that an important action of GLP-1 analogues in reducing postprandial glycaemia is by retardation of small intestinal motility modulating carbohydrate absorption (Linnebjerg et al., 2008, Little et al., 2006).

An alternative to the use of exogenous GLP-1 analogues in the management of type 2 diabetes is to develop dietary strategies which stimulate endogenous

GLP-1 release. Glutamine, which is widely used as a nutritional supplement, appears to be the most potent amino acid in inducing GLP-1 release (Reimann et al., 2004). It has been reported that 30g glutamine, given in 300mL water, stimulates GLP-1 release in both healthy subjects and patients with type 2 diabetes (Greenfield et al., 2009) and Samocha-Bonet et al (Samocha-Bonet et al., 2011) reported that 15g and 30g glutamine when given as a drink, before an oral glucose load in patients with type 2 diabetes, dose-dependently stimulate GLP-1 and diminish subsequent glycaemic excursion. However, the effect of glutamine on the rate of gastric emptying of glucose could potentially influence the observed effect on glycaemia as it is now appreciated that the rate of gastric emptying itself has a major influence on postprandial glucose levels in healthy subjects and patients with type 1 and 2 diabetes (Chang et al., 2010). The study reported in Chapter 5 examined the effects of intraduodenal glutamine on GLP-1, GIP and insulin release and the subsequent glycaemic response to an intraduodenal glucose load, in health and type 2 diabetes, of which the intraduodenal route of delivery of glutamine will bypass the stomach, thus, eliminating any influence of glutamine on the rate of gastric emptying of glucose. This study showed that intraduodenal glutamine has minimal effect on the glycaemic response to intraduodenal glucose, despite its ability to stimulate GLP-1, GIP and insulin release, and stimulate phasic pyloric contractions, suggesting that slowing of gastric emptying may play a major role for the glucose lowering effect seen with oral glutamine.

DECLARATION

Name: Jessica Chang Program: Master of Philosophy

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# PUBLICATIONS ARISING FROM THE THESIS

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Chang J, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis – backwards and forwards. J Gastroenterol Hepatol. 2011 Jan; 26 Suppl 1: 46-57

Chang J, Russo A, Bound M, Rayner CK, Jones KL, Horowitz M. A 25 year longitudinal evaluation of gastric emptying and gastrointestinal symptoms in diabetes mellitus. (Submitted for publication)

Chang J, Rayner CK, Jones KL, Horowitz M. Prognosis of diabetic gastroparesis – a 25 year evaluation. (Submitted for publication)

Chang J, Wu T, Greenfield JR, Samocha-Bonet D, Horowitz M, Rayner CK. Effects of intraduodenal glutamine on incretin hormone release, the glycaemic response to an intraduodenal glucose infusion and antropyloroduodenal motility in health and type 2 diabetes. (Submitted for publication)