

**RELATIONSHIPS OF GASTRIC EMPTYING  
WITH GLYCAEMIA, INSULIN SECRETION  
AND THE INCRETIN EFFECT IN HEALTH  
AND TYPE 2 DIABETES**

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NOTE: Statements of authorship appear in the print copy of the thesis held in the University of Adelaide Library.

# THESIS ABSTRACT

This thesis focuses on the inter-dependent relationships between gastric emptying, incretin hormones (GIP and GLP-1) and postprandial glycaemic and insulinaemic responses in health and type 2 diabetes.

Key themes relate to:

- 1) Evaluation of the relationships of ‘early’ and ‘late’ glycaemic responses with gastric emptying in subjects with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes.
- 2) Evaluation of the relationships of the insulin secretory response and the oral disposition index with gastric emptying in subjects with normal glucose tolerance.
- 3) Utilisation of intraduodenal glucose infusions to assess the impact of gastric emptying on: a) the incretin effect, gastrointestinal glucose disposal and the glucagon response, b) the oral disposition index, c) the secretion of incretin hormone secretory pattern in Caucasian compared with Han Chinese subjects and d) postprandial blood pressure and heart rate in type 2 diabetes.

Gastric emptying, which regulates the entry of nutrients into the small intestine, is a major determinant of the ‘initial’ glycaemic response (i.e. at 30 min) following an oral glucose tolerance test in health, as well as in type 2 diabetes such that if gastric emptying is more rapid, the initial blood glucose levels are greater. However, the relationships of the 60 min blood glucose (a known predictor of type 2 diabetes) and 120 min blood glucose (used for diagnosis) with gastric emptying during oral glucose tolerance tests have not been studied. My study explored the relationships of 30 min, 60 min and 120 min blood glucose with gastric emptying (measured scintigraphically – the ‘gold standard’ method) in participants with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes.

The relationship between the insulin secretory response (calculated as the ratio of change in insulin at 30 min to the change in glucose at 30 represented as  $\Delta I_{0-30} / \Delta G_{0-30}$ ) and insulin sensitivity (calculated as the reciprocal of fasting insulin and represented as  $1/\text{fasting insulin}$ ) during an oral glucose tolerance test is hyperbolic in subjects with normal glucose tolerance such that their product, referred to as the 'oral disposition index' ( $\Delta I_{0-30} / \Delta G_{0-30} \times 1/\text{fasting insulin}$ ) is always constant. This implies that as long as the pancreatic beta cells are able to compensate adequately (by up-regulating insulin secretion) for any reduction in insulin sensitivity, the oral disposition index remains constant so that the individual has a 'normal glucose tolerance'. It is, therefore, the failure to compensate fully for the reduction in insulin sensitivity (resulting in a lower oral disposition index) that leads to development of impaired glucose tolerance and type 2 diabetes. Oral disposition index is widely used as a predictor of type 2 diabetes. While the relationship of the early glycaemic response ( $\Delta G_{0-30}$ ) with gastric emptying has been characterised, the relationships of the early insulin response ( $\Delta I_{0-30} / \Delta G_{0-30}$ ) and the oral disposition index with gastric emptying are uncertain. My study explored these relationships in subjects with normal glucose tolerance.

There is a wide inter-individual, but relatively little intra-individual variation in the overall rate of gastric emptying (between 1-4 kcal/min in health); this range is even wider in diabetes as a substantial proportion of patients have gastroparesis (i.e. delayed gastric emptying) while in some gastric emptying is abnormally accelerated. This has profound implications for control of glycaemia in diabetes, as even minor variations in the rate of entry of nutrients into the small intestine may be associated with substantial changes in postprandial glycaemic and insulinaemic responses. The incretin hormones, GIP and GLP-1, located in the gut and stimulated by exposure of nutrients to the intestine, play a major role in postprandial glucose metabolism accounting for up to 50% of the post-meal insulin response in health. The incretin hormones are responsible for the so-called 'incretin effect' – the amplified insulin secretory response following oral, compared with intravenous, glucose. The incretin effect is known to

be attenuated in type 2 diabetes. The impact of gut in glucose disposal can also be described by the so-called 'gastrointestinal glucose disposal' (GIGD). GIGD, the amount of glucose required by intravenous infusion to 'copy' the glucose excursions after the oral load, was calculated as follows: if 25g intravenous glucose is required to copy a 75g oral glucose load, the GIGD amounts to  $100 \times (75 - 25)/75 = 66\%$ . GIGD is also reduced in type 2 diabetes.

Intraduodenal glucose infusions (via a naso-duodenal catheter) bypass the pylorus and allow glucose to be delivered directly into the small intestine at a pre-determined rate. This model has been employed to study the impact of gastric emptying on postprandial glycaemic and insulinaemic excursions. The outcome of these studies, in which glucose was infused at variable rates within the 'physiological' range of gastric emptying i.e. 1,2,3 and 4 kcal/min, indicate that the relationship between the rise in glycaemia and the rate of small intestinal glucose exposure is non-linear. While the glycaemic response was significantly greater in response to 2 kcal/min intraduodenal infusion than 1 kcal/min, increasing the infusion rate further (i.e. 3 and 4 kcal/min) only resulted in minimal, if any, further increase in blood glucose. Glucagon, the hormone produced by the  $\alpha$  cells of pancreas, is suppressed following ingestion of glucose in health and thus an important determinant of postprandial blood glucose response, although glucagon suppression is impaired in type 2 diabetes. While GLP-1 suppresses glucagon, GIP does not and may, in fact, modestly elevate it. The effect of gastric emptying on glucagon responses in health and type 2 diabetes is not known. My study looked at the impact of variable duodenal glucose load on the incretin effect and GIGD as well as on glucagon responses in health as well as in type 2 diabetes.

There is evidence that East Asians secrete less insulin than Caucasians following oral glucose suggesting that impaired insulin secretion is fundamental to the pathogenesis of type 2 diabetes. However, information about the secretory patterns of GIP and GLP-1, dependent on duodenal glucose load in East Asians, is limited. My study evaluated the glycaemic,

insulinaemic and incretin hormone response to a duodenal glucose load in healthy Han Chinese men compared with healthy Caucasian men.

Postprandial hypotension (PPH), defined as a fall in systolic blood pressure  $\geq 20$  mmHg after a meal, occurs frequently in diabetes and its management remains sub-optimal. As well as influencing postprandial glycaemia, gastric emptying also affects the postprandial hypotensive response in 'healthy' older subjects and type 2 patients, such that when GE is relatively more rapid, the magnitude of fall in systolic blood pressure is greater. In healthy older subjects, when gastric distension – which may influence blood pressure – is 'bypassed' by infusing glucose directly into the duodenum, the fall in systolic blood pressure is greater in response to 2 and 3 kcal/min than 1 kcal/min. It is not known whether duodenal glucose delivery influences blood pressure in type 2 patients. My study evaluated the effects of variations in the intraduodenal glucose load on blood pressure and heart rate in type 2 patients.

## **FORMAT OF THE THESIS**

This thesis consists of chapters adapted from one review and six original manuscripts. The review and the original manuscripts have all been published (except chapter 3, which has been submitted for publication) in peer-reviewed journals. None of these articles were solicited by the journals. All published papers were submitted to appropriate diabetes journals, and underwent peer review by 2-4 reviewers with further revisions until the reviewers and editors were satisfied. Each study is reported “in full” as a chapter, to allow independent review with unavoidable repetition. The methodology is described individually in each chapter. All chapters (and published papers) report on data derived from three main clinical studies.

# THESIS DECLARATION

I, Chinmay Marathe,

- certify that the work is original and has not been accepted for the award of any other degree or diploma in any university or other tertiary institution and contains no material previously published or written by another person, except where due acknowledgement is made in the text
- certify that no part of the work will be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and, where applicable, any partner institution responsible for the joint-award of the degree, except where due reference has been made in the text
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Signed,

Date 14<sup>th</sup> February 2016

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# **RESEARCH PRESENTATIONS ARISING FROM THIS THESIS**

**Marathe CS**, Jones KL, Horowitz M, Rayner CK.

Relationships of early insulin response and oral disposition index with gastric emptying during an oral glucose tolerance test in subjects with normal glucose tolerance.

*Diabetes UK Annual Conference, Glasgow, United Kingdom*

*March 2016 - Oral presentation*

(In Competition for Type 2 Diabetes Research Award)

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

Small intestinal glucose exposure is a determinant of the magnitude of the incretin effect in health and type 2 diabetes.

*Royal Australasian College of Physicians Annual Scientific Sessions, Cairns*

*2015 – Oral presentation*

(RACP Trainee Research Award for Excellence – South Australia)

**Marathe CS**, Horowitz M, Bound M, Lange K, Rayner CK, Jones KL.

Relationships of early and late glycaemic responses with gastric emptying during an oral glucose tolerance test.

*Australian Diabetes Society Annual Meeting, Adelaide, Australia*

*2015 – Poster presentation*

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

Ethnic variation in insulin and incretin responses to intraduodenal glucose in healthy humans.

*American Diabetes Association Annual Scientific Sessions, San Francisco*

*2014 – Poster presentation*

**Marathe CS, Rayner CK, Jones KL, Horowitz M.**

The magnitude of the incretin effect is dependent on the small intestinal glucose load in type 2 diabetes.

*American Diabetes Association Annual Scientific Sessions, Chicago*

*2013 – Poster presentation*

**Marathe CS, Feinle –Bisset C, Bound M, Standfield S, Jones KL, Horowitz M & Rayner CK.**

The effect of intraduodenal glucose delivery on the oral disposition index in health and type 2 diabetes.

*American Diabetes Association Annual Scientific Sessions, Chicago*

*2013 – Poster presentation*

**Marathe CS, Rayner CK, Jones KL, Horowitz M.**

The size of the incretin effect is dependent on the small intestinal glucose load in health.

*American Diabetes Association Annual Scientific Sessions, Philadelphia*

*2012 – Oral presentation*

**Marathe CS, Horowitz M, Rayner CK, Lange K, Jones KL.**

Biphasic relationship between oral glucose tolerance and gastric emptying in healthy subjects.

*European Association for the Study of Diabetes, Lisbon, Portugal*

*2011 – Poster Presentation*

(Recipient of EASD Travel Grant Award)

## LIST OF PUBLICATIONS ARISING FROM THIS THESIS

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

*Novel insights into the effects of diabetes on gastric motility.*

**Expert Reviews in Gastroenterology and Hepatology**. 2016 Jan 28:1-13.

PMID: 26647088

**Marathe CS**, Horowitz M, Trahair LG, Wishart JM, Bound M, Lange K, Rayner CK, Jones KL.

*Relationships of early and late glycemic responses with gastric emptying during an oral glucose tolerance.*

**Journal of Clinical Endocrinology and Metabolism**. 2015 Sep;100(9):3565-71. doi:

10.1210/JC.2015-2482.

PMID: 26171801

**Marathe CS**, Feinle-Bisset C, Pilichiewicz A, Lange K, Jones KL, Rayner CK, Kahn SE, Horowitz M.

*The duodenal glucose load impacts the oral disposition index in healthy subjects.*

**Diabetic Medicine**. 2015 Nov;32(11):1500-3. doi: 10.1111/dme.12802.

PMID: 25981372

**Marathe CS**, Bound M, Lange K, Jones KL, Rayner CK, Horowitz M.

*Ethnic disparities in insulin and glucose-dependent insulinotropic peptide (GIP) responses to intraduodenal glucose in health.*

**Acta Diabetologica**. 2015 Aug;52(4):817-9. doi: 10.1007/s00592-014-0684-x.

PMID: 25399343

**Marathe CS**, Rayner CK, Bound M, Checklin H, Standfield S, Wishart J, Lange K, Jones KL, Horowitz M.

*Small intestinal glucose exposure determines the magnitude of the incretin effect in health and type 2 diabetes.*

**Diabetes.** 2014 Aug;63(8):2668-75. doi: 10.2337/db13-1757.

PMID: 24696447

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

*Relationships between gastric emptying, postprandial glycemia, and incretin hormones.*

**Diabetes Care.** 2013 May;36(5):1396-405. doi: 10.2337/dc12-1609.

PMID: 23613599

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

*Glucagon-like peptides 1 and 2 in health and disease: a review.*

**Peptides.** 2013 Jun; 44:75-86. doi: 10.1016/j.peptides.2013.01.014.

PMID: 23523778

**Marathe CS**, Rayner CK, Jones KL, Horowitz M.

*Effects of GLP-1 and incretin-based therapies on gastrointestinal motor function.*

**Experimental Diabetes Research.** 2011; 2011:279530. doi: 10.1155/2011/279530.

PMID: 21747825