GLYCAEMIA AND UPPER GASTROINTESTINAL FUNCTION IN HEALTH AND CRITICAL ILLNESS

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

in the Discipline of Acute Care Medicine, School of Medicine,

Faculty of Health Sciences

University of Adelaide

by

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Abstract

This thesis comprises four distinct but complementary chapters with a broad focus of glycaemia and upper gastrointestinal function in health and critical illness, encompassing four literature reviews, two epidemiological-observational and two interventional studies in the critically ill and three proof-of-principle studies in healthy volunteers.

Hyperglycaemia occurs frequently in the critically ill, both in patients with diabetes, and in those with previously normal glucose tolerance. The literature is reviewed on the impact of dysglycaemia in the patient with sepsis, emphasising the interaction between acute dysglycaemia, chronic hyperglycaemia and outcomes (*chapter 1.2*). Observational studies were performed to estimate the prevalence of stress induced hyperglycaemia in the critically ill and to evaluate the subsequent risk of diabetes. I established that: (i) stress induced hyperglycaemia occurs in ~50% of patients, and (ii) peak blood glucose concentrations are associated with greater mortality in patients with adequate premorbid glycaemic control but not in those with chronic hyperglycaemia (*chapter 1.3*). In a large, state-wide retrospective observational study I established that stress induced hyperglycaemia doubles the risk for subsequent type 2 diabetes (*chapter 1.4*).

Dysregulated enterohormone secretion is thought to mediate critical illness induced abnormalities of glycaemia and upper gastrointestinal function. A review of the literature is presented on the clinically relevant enterohormone disturbances (*chapter 2.2*). In a prospective comparative study of critically ill patients and healthy volunteers, I quantified gallbladder dysmotility in critical illness, a phenomenon that was independent of plasma concentrations of the enterohormone cholecystokinin (*chapter 2.3*).

The therapeutic potential for the incretin enterohormones in the management of stress induced hyperglycaemia is reviewed in detail with a focus on glucagon-like peptide 1 (GLP-1) (*chapter 3.2*). Upper gastrointestinal function and glycaemia are inextricably linked and in healthy volunteer studies I examined the effect of GLP-1 on gastric emptying during extremes of glycaemia. I demonstrated that GLP-1 attenuated the acceleration of gastric emptying engendered by hypoglycaemia (*chapter 3.3*) and that

the slowing of gastric emptying induced by hyperglycaemia is potentiated by GLP-1 (*chapter 3.4*). In a study investigating the islet cell effects of GLP-1 I demonstrated that intravenous pulsatile delivery of GLP-1 has an equivalent insulinotropic effect to continuous delivery in healthy volunteers (*chapter 3.5*).

Prophylactic administration of proton pump inhibitors for the prevention of gastric stress related mucosal injury is widely prescribed yet has the potential to cause harm and has been inadequately evaluated in the critically ill. A review of the literature highlighting this paradox is presented in *chapter 4.2*. In a prospective, double-blind randomised, placebo-controlled trial I demonstrated that prophylactic administration of a proton pump inhibitor was neither superior nor inferior to placebo in preventing clinically significant upper gastrointestinal bleeding during critical illness (*chapter 4.3*).

In summary, these studies have yielded a number of important insights including; the incidence of stress induced hyperglycaemia and the subsequent risk of diabetes, quantification of gallbladder motility in critical illness, the gastrokinetic effects of GLP-1 during extremes of glycaemia, the insulinotropic effects of pulsatile GLP-1 delivery, and an evaluation of stress ulcer prophylaxis in the critically ill.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name 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 this degree.

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Mark Philip Plummer

08 January 2016

Acknowledgements

I entered into this doctoral programme completely naïve to the challenges of clinical research and have been grateful for the mentoring and encouragement that I have received from my collaborators. The publications that make up this thesis represent only a fraction of my overall experience and none of the successes, or the enjoyment I have had achieving them, would have been possible without a number of key individuals.

First and foremost, I am indebted to Associate Professor Adam Deane (Deano), my primary supervisor and close friend, who took me under his wing as a very green junior registrar and has now shaped my career path in critical care and research. He has been the driving force behind every ethics application, grant, manuscript, abstract presentation and award, and has mentored me through each process with humour, patience and enormous generosity of his time. I greatly admire his integrity, commitment to family and skills as a clinician-scientist and I look forward to our ongoing collaborations in the future.

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Format of Thesis

This thesis is by publication, supplemented by narrative, as per University of Adelaide Guidelines. The thesis comprises four distinct chapters each with a brief narrative introduction followed by a published literature review and clinical trials. In total the thesis comprises eleven manuscripts; 4 reviews of the literature and 7 clinical trials. At the time of submission of this body of work, ten of the manuscripts have been published or accepted for publication. The manuscript that comprises chapter 1.4 is currently under review with *Intensive Care Medicine*. None of the manuscripts were solicited. Each of the four chapters are followed by a narrative conclusion of the major findings and future directions.

The eleven manuscripts are presented in the style of the publication to which they were submitted, accounting for the heterogeneity in American and UK English, and the variance in referencing style and manuscript structure. The references for the 11 publications are included in each respective manuscript and, for consistency, references for the introductions, conclusions and future directions of each chapter follow each section.

The publications are as follows.

Plummer MP, Deane AM. Dysglycemia and glucose control during sepsis. *Clinics in Chest Medicine* [accepted for publication] (IF 2.1). Relevant section in this thesis; Chapter 1.2.

Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, Raj JP, Chapman MJ, Horowitz M, Deane AM. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Medicine* 2014, 40(7):973-980. (IF 5.3). Relevant section in this thesis; Chapter 1.3.

Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, Moodie S, Horowitz M, Shaw JE, Deane AM: Stress induced hyperglycaemia and the subsequent risk of type 2 diabetes in survivors of critical illness. [under review with *Intensive Care Medicine*]. Relevant section in this thesis; Chapter 1.4.

Plummer MP, Reintam Blaser A, Deane AM: Enterohormones and the response to critical illness. Book Chapter: *The Stress Response of Critical Illness: Metabolic and Hormonal Aspects*. Springer. [accepted for publication]. Relevant section in this thesis; Chapter 2.2.

Plummer MP, Kar P, Cousins CE, Hausken T, Lange K, Chapman MJ, Jones KL, Horowitz M, Deane AM: Critical illness is associated with impaired gallbladder emptying as assessed by 3D ultrasound. *Critical Care Medicine* [accepted for publication] (IF 6.3). Relevant section in this thesis; Chapter 2.3.

Plummer MP, Horowitz M, Deane AM: Incretins and the intensivist: what are they and what does an intensivist need to know about them? *Critical Care* 2014, 18(1):205.(IF 4.7). Relevant section in this thesis; Chapter 3.2.

Plummer MP, Jones KL, Annink CE, Cousins CE, Meier JJ, Chapman MJ, Horowitz M, Deane AM: Glucagon-like peptide 1 attenuates the acceleration of gastric emptying induced by hypoglycemia in healthy subjects. *Diabetes Care* 2014, 37(6):1509-1515.(IF 8.1). Relevant section in this thesis; Chapter 3.3.

Plummer MP, Jones KL, Cousins CE, Trahair LG, Meier JJ, Chapman MJ, Horowitz M, Deane AM: Hyperglycaemia potentiates the slowing of gastric emptying induced by exogenous GLP-1. *Diabetes Care* 2015, 38(6):1123-9. (IF 8.1). Relevant section in this thesis; Chapter 3.4.

Plummer MP, Kar P, Cousins CE, Lange K, Chapman MJ, Nauck MA, Horowitz M, Meier JJ, Deane AM: The insulinotropic effect of pulsatile compared with continuous intravenous delivery of GLP-1. *Diabetologia* [accepted for publication] (IF 6.7). Relevant section in this thesis; Chapter 3.5.

Plummer MP, Reintam Blaser A, Deane AM: Stress Ulceration: prevalence, pathology and assocation with adverse outcomes. *Critical Care 2014* 18;18(2):213. (IF 4.7). Relevant section in this thesis; Chapter 4.2.

Selvanderan SP, Summers MJ, Finnis ME, **Plummer MP**, Ali Abdelhamid Y, Anderson MB, Chapman MJ, Rayner CK, Deane AM: Pantoprazole or Placebo for stress Ulcer Prophylaxis (POPUP): Randomized double blind exploratory study. *Critical Care Medicine* [accepted pending minor edits] (IF 6.3). Relevant section in this thesis; Chapter 4.3.