

Reducing the postprandial glycaemic impact of dietary protein in type 1 diabetes mellitus

Megan Anne Paterson

(BNursing, Charles Sturt University; Grad Cert Diabetes Education, Deakin
University)

A thesis submitted in fulfilment of the requirements for the degree Doctor of
Philosophy in Medicine

Faculty of Health and Medicine

University of Newcastle

October 2019

This research was supported by an Australian Government Research Training Program (RTP)
Scholarship.

Statement of Originality

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision.

The thesis contains no material which has been accepted, or is being examined, 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. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

Megan Paterson

Thesis by Publication

I hereby certify that the work embodied in this thesis is in the form of a series of papers. I have included as part of the thesis a written declaration from each co-author, endorsed in writing by the Faculty Assistant Dean (Research Training), attesting to my contribution to any jointly authored papers.

Megan Paterson

Acknowledgements

To begin, I would like to acknowledge and thank my PhD supervisors, Professor Bruce King, Dr Carmel Smart, Laureate Professor John Attia, Professor Patrick McElduff and A/Professor Peter Howley, for their support, guidance and expertise. Bruce, I am especially grateful to you for believing in me from the very beginning and giving me the opportunity to even contemplate doing a PhD. Carmel, thank you for your time and for sharing your wisdom. The studies in this PhD exist because of you both; I was just fortunate enough to be part of it.

Thank you to the paediatric diabetes and endocrine team at the John Hunter Children's Hospital. You have all been a wonderful support to me during this PhD and I feel very blessed to work with you all. Special thanks to Dr Prue Lopez, with whom I was lucky enough to share this PhD journey from day 1. Prue, I am so grateful for your support and value your friendship immensely.

To my parents Alan and Glenda, I thank you for choosing to be my Mum and Dad. I would not be who I am today without you and I am so thankful that I got to grow up with you both for my parents. Dad, I miss you every day and wish you were here to see me finally finish this.

To my husband Brendan, thank you for your unwavering support, your humour when I need it and for staying home at the end to make sure I finished. I could not have done this without you, I love you lots and look forward to having time now to enjoy with you!

To my children, Nathan and Jessica. You both have taught me so much and shown me that the most important job in the world is being your Mum. I love you both so very much and could not be more proud of the people you have both become.

Finally, to Jess. I fell into this work in my quest to try and make sense of type 1 diabetes and why it was dealt to you. I wish every day that I could take it away and I just hope in some small way that this research makes a difference to you and all people who live with type 1 diabetes.

Copyediting was provided by Matthew Sidebotham in accordance with university policy and the university-endorsed Guidelines for Editing Research Theses.

List of Publications

List of publications included as part of this thesis

Paterson MA, Smart CE, Lopez PE, McElduff P, Attia J, Morbey C, King BR. Influence of dietary protein on postprandial blood glucose levels in individuals with Type 1 diabetes mellitus using intensive insulin therapy. *Diabetic Medicine* 2016; 33(5): 592–98

Paterson MA, Smart CEM, Lopez PE, Howley P, McElduff P, Attia J, Morbey C, King BR. Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels in individuals with Type 1 diabetes mellitus. *Diabetic Medicine* 2017; 34(6): 851–4

Paterson MA, King BR, Smart CE, Smith T, Rafferty J, Lopez, P. Impact of dietary protein on postprandial glycaemic control and insulin requirements in type 1 diabetes: A systematic review. *Diabetic Medicine* 2019; DOI: 10.1111/dme.14119.

Paterson MA, Smart CEM, Howley P, Foskett D, Price D, King BR. High protein meals require 30% additional insulin to prevent delayed hyperglycemia. (Manuscript in preparation)

List of additional publications relevant to the thesis

Lopez P, Smart C, Morbey C, McElduff P, Paterson MA, King, BR. Extended insulin boluses cannot control postprandial glycemia as well as a standard bolus in children and adults using insulin pump therapy. *BMJ Open Diabetes Research and Care* 2014; 2:e000050

Paterson MA, Bell K, O’Connell S, Smart C, Shafat A, King B. The role of dietary protein and fat in Glycaemic Control in type 1 diabetes: Implications for Intensive Diabetes Management. *Current Diabetes Reports* 2015; 15: 61. DOI 10.1007/s13300-015-0630-5.

Lopez P, Smart CE, McElduff P, Foskett D, Price DA, Paterson MA, King BR. Optimising the combination insulin bolus split for children and young people with type 1 diabetes mellitus using insulin pump therapy for a high fat, high protein meal. *Diabetic Medicine* 2017; 34(10): 1380–84

Paterson M. The glycaemic impact of dietary protein in Type 1 diabetes: Implications for glycaemic control and insulin requirements. *The Australian Diabetes Educator* 2016; 19(3).

Paterson M, Smith T, Smart CM. Managing the ups and downs of dietary protein and fat: The John Hunter Children’s Hospital Approach in type 1 diabetes care. *The Australian Diabetes Educator* 2019; 22(3).

List of conference presentations of relevance to the thesis

Paterson MA, Smart C, Lopez P, Morbey C, McElduff P, King B. The effect of pure protein on postprandial blood glucose levels in individuals with type 1 diabetes. American Diabetes Association 74th Annual Scientific Sessions, San Francisco, CA USA, June 2014.

Paterson MA, Smart C, Lopez P, Morbey C, McElduff P, King B. The effect of pure protein on postprandial blood glucose levels in individuals with type 1 diabetes. APPES and Australian Paediatric Endocrine Group (APEG) meeting, Darwin Australia, November 2014.

Paterson MA, Smart C, Lopez P, McElduff P, Morbey C, King B. The effect of protein plus carbohydrate with no fat on postprandial glycaemia in individuals with type 1 diabetes. APEG + ISPAD (International Society of Paediatric and Adolescent Diabetes), Brisbane, Australia, 2015.

Paterson MA, Smart C, Lopez P, Morbey C, McElduff P, Goodwin G, King B. The impact of the quantity of protein in a meal on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy. Advanced Technologies and Treatments for Diabetes, Milan, Italy, February 3–6 2016.

Paterson MA, Smart C, Foskett D, Price D, Howley P, Maher A, Fenton B, Rafferty J, King B. A 30% increased insulin dose is necessary to control postprandial hyperglycaemia for high protein meals in individuals with type 1 diabetes using insulin pump therapy. American Diabetes Association 79th Annual Scientific Sessions, San Francisco, CA USA, June 2019.

Paterson MA. The glycaemic impact of dietary protein in type 1 diabetes. Australian Diabetes Educator Association NSW Branch conference (invited speaker), May 2015.

Statements of Contribution by Others

STATEMENT OF CONTRIBUTION: PAPER 1

I attest that Research Higher Degree candidate Megan Paterson contributed substantially in terms of study concept and design, data collection and analysis, and preparation of the manuscript entitled:

'Impact of dietary protein on postprandial glycaemic control and insulin requirements in type 1 diabetes: A systematic review'.

Co-authors:

Dr Prudence Lopez

Date

Dr Carmel Smart

Date

Professor Bruce King

Date

Miss Tenele Smith

Date

Jordan Rafferty

Date

Ms Megan Paterson (candidate)

Date

14/10/19

Lesley MacDonald-Wicks

Date

Assistant Dean Research Training

17/10/19

STATEMENT OF CONTRIBUTION: PAPER 2

I attest that Research Higher Degree candidate Megan Paterson contributed substantially in terms of study concept and design, data collection and analysis, and preparation of the manuscript entitled:

'Influence of dietary protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy'.

Co-authors:

_____ Professor Bruce King	_____ Date
_____ Dr Carmel Smart	_____ Date
_____ Dr Prudence Lopez	_____ Date 29 Sep 2019
_____ Professor Patrick McElduff	_____ Date
_____ Dr Claire Morbey	_____ Date
_____ Professor John Attia	_____ Date
_____ Ms Megan Paterson (candidate)	_____ Date
_____ Lesley MacDonald-Wicks	_____ Date
_____ Assistant Dean Research Training	_____ 17/10/19

STATEMENT OF CONTRIBUTION: PAPER 3

I attest that Research Higher Degree candidate Megan Paterson contributed substantially in terms of study concept and design, data collection and analysis, and preparation of the manuscript entitled:

'Increasing the protein quantity on a meal results in dose-dependent effects on postprandial glucose levels in individuals with type 1 diabetes mellitus'.

Co-authors:

Professor Bruce King

Date

Dr Carmel Smart

Date

Dr Prudence Lopez

Date

29 Sep 2019

Professor Patrick McElduff

Date

Dr Claire Morbey

Date

Professor John Attia

Date

A/Professor Peter Howley

Date

Ms Megan Paterson (candidate)

Date

Dr Lesley MacDonald-Wicks

Date

Assistant Dean Research Training

17/10/19

STATEMENT OF CONTRIBUTION: PAPER 4

I attest that Research Higher Degree candidate Megan Paterson contributed substantially in terms of study concept and design, data collection and analysis, and preparation of the manuscript entitled:

'High protein meals require 30% additional insulin to prevent delayed hyperglycemia'.

Co-authors:

Professor Bruce King	Date
----------------------	------

Dr Carmel Smart	Date
-----------------	------

A/Professor Peter Howley	Date
--------------------------	------

Professor Darrell Price	Date
-------------------------	------

Ms Megan Paterson (candidate)	Date
-------------------------------	------

Ms Deborah Foscett	Date
--------------------	------

Dr Lesley MacDonald-Wilks	Date
---------------------------	------

Assistant Dean Research Training

17/10/19

Table of Contents

Statement of Originality	ii
Thesis by Publication	iii
Acknowledgements	iv
List of Publications.....	v
List of publications included as part of this thesis.....	v
List of additional publications relevant to the thesis	v
List of conference presentations of relevance to the thesis	vi
Statements of Contribution by Others	vii
Table of Contents	xi
List of Figures	xvi
List of Tables	xvi
List of Abbreviations.....	xvii
Abstract	xix
1. Introduction	1
1.1 Background.....	1
1.1.1.1 Type 1 diabetes	1
1.1.1.2 Diagnosis of type 1 diabetes	1
1.1.1.3 Pathogenesis of type 1 diabetes	2
1.1.1.4 Genetic susceptibility	2
1.1.1.5 Immune activation and islet cell autoimmunity.....	3
1.1.1.6 Environmental triggers.....	3
1.2 Incidence and prevalence of type 1 diabetes mellitus	4
1.2.1.1 Internationally	4
1.2.1.2 Australia	4
1.3 Complications of type 1 diabetes mellitus	5
1.3.1.1 Acute complications	6
1.3.1.2 Chronic complications	6
1.4 Postprandial hyperglycaemia and complications of diabetes	8
1.4.1.1 Causes of postprandial hyperglycaemia.....	10
1.1.1.1 Glycaemic impact of carbohydrate.....	10
1.1.1.2 Glycaemic impact of fat	11
1.1.1.3 Glycaemic impact of protein	13
1.5 Glycaemic targets and assessment of glycaemic control	14
1.5.1.1 Glycaemic targets	14
1.5.1.2 Glycated haemoglobin (HbA1c)	15

1.5.1.3	Self-monitoring of blood glucose (SMBG)	16
1.5.1.4	Continuous glucose monitoring (CGM)	16
1.5.1.5	Flash glucose monitoring (FGM)	17
1.6	Insulin therapy in type 1 diabetes	17
1.6.1.1	Multiple daily injections (MDI)	18
1.6.1.2	Insulin pump therapy (IPT)	18
1.6.1.3	Sensor-augmented pumps and closed-loop systems	19
1.7	Nutritional management	19
1.8	Multidisciplinary diabetes education	20
1.9	Conclusions.....	21
1.10	Explanation of thesis.....	22
1.10.1.1	Primary aim of the thesis	22
1.10.1.2	Specific aims of the thesis.....	22
1.10.1.3	Structure of the thesis	22
1.1.1.4	Chapter 2: Influence of dietary protein on postprandial glycaemic control and insulin requirements in individuals with type 1 diabetes: A systematic review.....	22
1.1.1.5	Chapter 3: Influence of dietary protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy.....	23
1.1.1.6	Chapter 4: Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels in individuals with type 1 diabetes mellitus.	23
1.1.1.7	Chapter 5: High-protein meals require 30% additional insulin to prevent delayed hyperglycaemia	24
1.1.1.8	Chapter 6: Conclusion to the thesis.....	24
2.	<i>Impact of dietary protein on postprandial glycaemic control and insulin requirements in type 1 diabetes: A systematic review.....</i>	25
2.1	Introduction.....	25
2.2	Paterson MA, King BR, Smart CEM, Smith T, Rafferty J and Lopez PE. Impact of dietary protein on postprandial glycaemic control and insulin requirements in type 1 diabetes: A systematic review. Diabetic Medicine 2019. DOI: 10.1111/dme.14119.....	26
2.2.1.1	Abstract	26
2.2.1.2	Background.....	26
2.2.1.3	Objective	26
2.2.1.4	Methods	26
2.2.1.5	Results	26
2.2.1.6	Conclusions.....	26
2.2.1.7	Introduction	27
2.2.1.8	Methods	28
2.2.1.9	Search strategy and selection criteria	28
2.2.1.10	Data extraction and quality assessment	28
2.2.1.11	Description of the studies	29
2.2.1.12	Study design.....	29
2.2.1.13	Study demographics.....	29

2.2.1.14	Glucose measurement	30
2.2.1.15	Insulin dosing strategy.....	30
2.2.1.16	Protein load	30
2.2.1.17	Blinding.....	31
2.2.1.18	Risk of bias.....	31
2.2.1.19	Results.....	31
2.2.1.20	Glycaemic impact of protein when consumed alone	31
2.2.1.21	Glycaemic impact of protein when consumed as part of a mixed meal	32
2.2.1.22	Insulin requirements and dosing for protein	34
2.2.1.23	Hypoglycaemia	35
2.2.1.24	Discussion	36
2.2.1.25	Conclusion.....	38
3.	<i>Influence of dietary protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy</i>	47
3.1	Introduction.....	47
3.2	Paterson MA, Smart CEM, Lopez P, McElduff P, Attia J, Morbey C and King BR. Influence of dietary protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy. Diabetic Medicine 2015. DOI: 10.1111/dme.13011	49
3.2.1.1	Abstract	49
3.2.1.2	Aim	49
3.2.1.3	Methods	49
3.2.1.4	Results	49
3.2.1.5	Conclusions.....	49
3.2.1.6	Introduction	50
3.2.1.7	Patients and methods	50
3.2.1.8	Study procedure.....	51
3.2.1.9	Test drinks	51
3.2.1.10	Glucose measurement	52
3.2.1.11	Statistical analysis.....	52
3.2.1.12	Results.....	53
3.2.1.13	Postprandial glucose excursions	54
3.2.1.14	Mean time to peak glucose rise	56
3.2.1.15	Discussion.....	56
4.	<i>Increasing the protein content in a meal results in dose dependent effects on postprandial glucose levels in individuals with type 1 diabetes mellitus</i>	59
4.1	Introduction.....	59
4.2	Paterson MA, Smart CE, Lopez PE, Howley P, McElduff P, Attia J, Morbey C, King BR. Increasing the protein content in a meal results in dose dependent effects on postprandial glucose levels in individuals with type 1 diabetes mellitus. 2017, February; DOI: 10.1111/dme.13347	61
4.2.1.1	Abstract	61

4.2.1.2	Aim	61
4.2.1.3	Methods	61
4.2.1.4	Results	61
4.2.1.5	Conclusions.....	61
4.2.1.6	Introduction	62
4.2.1.7	Research design and methods	62
4.2.1.8	Statistical analysis	63
4.2.1.9	Results	64
4.2.1.10	Postprandial glucose excursions	64
4.2.1.11	Dose response	65
4.2.1.12	Discussion	65
5.	<i>High-protein meals require 30% additional insulin to prevent delayed hyperglycaemia.</i>	67
5.1	Introduction.....	67
5.2	Paterson MA, Smart CM, Foskett D, Price D, Howley P, King BR. High-protein meals require 30% additional insulin to prevent delayed hyperglycaemia.....	69
5.2.1.1	Abstract	69
5.2.1.2	Objective	69
5.2.1.3	Research design and methods	69
5.2.1.4	Results	69
5.2.1.5	Conclusions.....	69
5.2.1.6	Introduction	70
5.2.1.7	Research design and methods	70
5.2.1.8	Test drinks	72
5.2.1.9	Data analysis.....	72
5.2.1.10	Sample size calculation.....	73
5.2.1.11	Results.....	73
5.2.1.12	Mean glucose excursions	74
5.2.1.13	Hypoglycaemic events.....	76
5.2.1.14	Conclusions	76
6.	<i>Conclusion and identification of areas for future research</i>	79
6.1	Introduction.....	79
6.2	Summary of major thesis findings.....	79
6.2.1.1	The role of dietary protein in postprandial hyperglycaemia.....	79
6.2.1.2	Influence of dietary protein on postprandial blood glucose levels when consumed alone	80
6.2.1.3	Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels	81
6.2.1.4	High-protein meals require a 30% increased insulin dose to prevent delayed hyperglycaemia .	82
6.3	Limitations of the research	82
6.3.1	General limitations of the thesis:	82
6.3.2	Specific limitations of the studies	83
6.3.2.1	Influence of dietary protein on postprandial blood glucose levels when consumed alone	83

6.3.2.2	High-protein meals require a 30% increased insulin dose to prevent delayed hyperglycaemia .	84
6.4	Implications for clinical practice.....	84
6.4.1.1	Influence of dietary protein on postprandial blood glucose levels when consumed alone	84
6.4.1.2	Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels	85
6.4.1.3	High-protein meals require a 30% increased insulin dose to prevent delayed hyperglycaemia .	86
6.5	Implications for future research.....	88
6.5.1.1	The role of dietary protein in postprandial hyperglycaemia.....	88
6.5.1.2	Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels	88
6.5.1.3	High-protein meals require a 30% increased insulin dose to prevent delayed hyperglycaemia .	89
6.6	Summary	90
7.	References	91

List of Figures

Figure 1.1 Summary of mechanisms underlying cardiovascular disease and type 1 diabetes	9
Figure 2.1 PRISMA flow diagram	29
Figure 2.2 Cochrane Risk of Bias summary	31
Figure 3.1 Recruitment and analysis attrition	54
Figure 3.2 Mean postprandial glycaemic excursions for 27 participants following consumption of 8 test drinks containing 0, 12.5, 25, 50, 75 and 100g of protein, with two glucose (CHO) test drinks given for comparison in amounts of 10 and 20g without insulin.	56
Figure 4.2 Mean postprandial glucose excursion by meal type	65
Figure 5.1 Recruitment and analysis attrition	74
Figure 5.2 Mean postprandial glucose excursions (95% CI) by insulin dose at each time-point (30-min intervals 0–240 min).....	75

List of Tables

Table 1.1 Criteria for diagnosis of diabetes mellitus.....	2
Table 1.2 Summary of complications of T1DM	5
Table 1.3 Glucogenic and ketogenic amino acids.....	14
Table 2.1 Characteristics of included studies	40
Table 3.1 Summary of clinical characteristics of participants	54
Table 3.2 Mean postprandial glucose excursions (mmol/L) compared with control	55
Table 4.1 Summary of clinical characteristics of participants	64
Table 5.1 Summary of clinical characteristics of participants	73
Table 5.2 Mean (standard deviation) of postprandial blood glucose (mmol/L) by dosing amount at 30 minute intervals.....	75

List of Abbreviations

AUC	area under the curve
BG	blood glucose
BGL	blood glucose level
BMI	body mass index
CHO	carbohydrate
CI	confidence interval
CVD	cardiovascular disease
CMIT	carotid intima-media thickness
CGM	continuous glucose monitoring
CSII	continuous subcutaneous insulin infusion
DKA	diabetic ketoacidosis
FPU	fat protein unit
FGM	flash glucose monitoring
FII	food insulin index
FFAs	free fatty acids
GAD	glutamic acid decarboxylase
GIP	gastric inhibitor polypeptide
GLP-1	glucagon-like peptide-1
GI	glycaemic index
GL	glycaemic load
HbA1c	glycated haemoglobin
HCL	hybrid closed loop
HDL	high-density lipids
HLA	human leukocyte antigen

HP/HF	high-protein/high-fat
HP/LF	high-protein/low-fat
IA-2	insulinoma-associated 2 molecule
IAA	insulin autoantibodies
ICR	insulin to carbohydrate ratio
IGF-1	insulin-like growth factor
IIT	intensive insulin therapy
IPT	insulin pump therapy
IV	intravenous
LDL	low-density lipids
LF/LP	low-fat/low-protein
MDI	multiple daily injections
NICE	National Institute for Health and Care Excellence
OR	odds ratio
SMBG	self blood glucose monitoring
SD	standard deviation
TIR	time in range
TAGs	triacylglycerols
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
ZnT8	zinc transporter 8

Abstract

Type 1 diabetes is a serious, life-long, autoimmune condition that occurs predominantly during childhood and adolescence. It is well recognised that intensive insulin therapy is the optimal method of managing type 1 diabetes. This approach has been demonstrated to reduce the risk of long-term complications of diabetes by reducing glycaemic variability and HbA1c. Despite the increased use of intensive insulin therapy, postprandial glycaemic excursions remain a significant challenge for many people living with type 1 diabetes. This is important as postprandial hyperglycaemia has been identified as an independent risk factor for the development of long-term complications of type 1 diabetes, often despite careful pre-meal insulin dosing and in-target HbA1c.

A key component of intensive insulin therapy is matching meal-time insulin doses to the carbohydrate content of a meal, together with the pre-prandial blood glucose level. This is based on the assumption that carbohydrates are the main macronutrient to influence postprandial glycaemia. However, there is increasing evidence that other macronutrients – protein and fat – can also have a significant impact on postprandial glycaemia. The primary purpose of this thesis is to investigate the postprandial glycaemic effects and subsequent insulin requirements of dietary protein.

A systematic review of the literature revealed that dietary protein can cause significant delayed and sustained postprandial hyperglycaemia and increased insulin requirements in individuals with type 1 diabetes. This review has highlighted that gaps in the literature exist regarding how dietary protein impacts postprandial glycaemia in type 1 diabetes and that strategies to reduce glycaemic excursions following high-protein meals are needed.

Overall, the sequence of studies presented in this thesis have sought to gain an improved understanding of the glycaemic effects of dietary protein, in order to improve the effectiveness of meal-time insulin dosing strategies and reduce the risk of postprandial hyperglycaemia. The clinical implications of the findings of the studies conducted are presented, with practical recommendations described for the management of high-protein meals with the aim of improving long-term outcomes for people living with type 1 diabetes.