The Impact of Coexisting Coeliac Disease on Type 1 Diabetes

By Anna Pham-Short

Thesis including publications

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Supervisors

Professor Maria Craig, Professor Kim C Donaghue, Clinical Professor Geoffrey

Ambler, Associate Professor Sarah Garnett

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STATEMENT OF ORIGINALITY

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree of other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Anna N T L Pham-Short

21st December 2018

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Finally, I am eternally grateful for my family. To my mum Vicky, thank you for instilling in me the value of education and perseverance. To my darling husband, Matthew, without whose love, support, encouragement and patience, this PhD journey would not have been possible. Thank you for supporting me whilst I PhD away in Sydney and London. I love you dearly.

DEDICATION

This thesis is dedicated to my daughter, Charlotte, may you always have an enquiring mind, a kind heart, and a warm smile. May you always know how much we love you.

ABSTRACT

Coeliac disease (CD) coexists with type 1 diabetes (T1D) substantially more than in the general population. This body of work examines the broad and pervasive relationship between CD on T1D, including the epidemiology, screening practices, microvascular complications, quality of life (QoL), nutrition, glycaemic variability, and bone health. In particular, the contribution of gluten free diet (GFD) adherence is explored.

Study 1: The 20-year incidence of CD in 4,379 people with T1D aged ≤18 years was 7.7 per 1000 person years. Incidence was significantly higher in those with T1D onset < age 5 years, but this subgroup developed CD after significantly longer T1D duration than those with T1D onset ≥5 years.

Study 2: We systematically reviewed the epidemiology of CD in 11,157 youth with T1D alone and 587 with coexisting CD; 55% of CD cases were diagnosed within 2 years of T1D and 79% within 5 years. We concluded that CD screening should be performed at T1D diagnosis and repeated within 5 years of T1D.

Study 3: Comparing 129 youth with T1D and CD vs 2,510 with T1D alone, retinopathy, albumin excretion rate (AER) and neuropathy did not differ. HbA1c was lower in those with CD (8.3% vs 8.6%, p=0.04), however elevated AER was more prevalent in those who did not adhere to the GFD (40% vs 23%, p=0.04).

Study 4: In a case control study of 35 youth with T1D and 35 with coexisting CD, and their carers, generic and diabetes-specific QoL did not differ. Youth using insulin pumps had similar generic and diabetes specific QoL to those using multiple daily injections. However, those who did not adhere to the GFD had lower diabetes specific QoL and lower general wellbeing, as did their carers.

Study 5: In a case control study using continuous glucose monitoring, youth with T1D and CD had greater glycaemic variability, with a shorter time to peak blood glucose levels (BGL), higher peak, and higher postprandial BGLs than T1D alone, despite similar pre-meal BGLs. Both groups had inadequate calcium, folate and fibre, with excessive saturated fat and sodium intake.

Study 6: In a case control study utilising dual energy x-ray absorptiometry and peripheral quantitative computational tomography, youth with coexisting T1D and CD had lower bone mineral content, abnormal trabecular and cortical bone development, and a lower bone turnover state with reduced muscle pull vs T1D alone.

These studies further our understanding of the impact of coexisting CD in T1D. The findings inform screening and management of CD, and provide evidence in support of GFD adherence to optimise clinical, dietary, and psychosocial management.

PRESENTATION OF THESIS

This thesis is presented as a compilation of six published papers. The papers describe the background, methods, results and discussion of separate research projects undertaken in this candidature. Chapter 2 provides the introduction to the area of the coexistence of coeliac disease and type 1 diabetes, in particular the epidemiology, screening frequency, microvascular complications, quality of life, glycaemic variability, nutrient intake and bone health. Chapters 3 to 8 contain the following manuscripts. The candidate is the principal author for each of the papers.

Chapter 3: Coeliac disease in type 1 diabetes from 1990 to 2009: higher incidence in young children after longer diabetes duration, *Diabetic Medicine,* 29, e286-e289 (2012)

Chapter 4: Screening for celiac disease in type 1 diabetes: a systematic review, *Pediatrics,* 136 (1), e170-176 (2015)

Chapter 5: Early elevation of albumin excretion rate is associated with poor gluten-free diet adherence in young people with coeliac disease and diabetes, *Diabetic Medicine,* 31, 208-212 (2014)

Chapter 6: Quality of life in type 1 diabetes and celiac disease: role of the gluten free diet, *The Journal of Pediatrics 179:131-8 (2016)*

Chapter 7: Greater postprandial glucose excursions and inadequate dietary intake with youth with type 1 diabetes and celiac disease, *Nature Scientific Reports - http://www.nature.com/articles/srep45286 (2017)*

Chapter 8: Abnormal cortical and trabecular bone in youth with type 1 diabetes and celiac disease, *Diabetes Care; 42, 1-7 (2019)*

AUTHORSHIP ATTRIBUTION STATEMENT

Chapter 3 of this thesis is published as *Coeliac disease in Type 1 diabetes from 1990 to 2009: higher incidence in young children after longer diabetes duration,* Pham-Short A., Donaghue KC., Ambler G., Chan AK., Craig ME., *Diabetic Medicine,* 29, e286-e289 (2012). I co-designed the study with the co-authors, extracted the data, analysed the data and wrote, reviewed and revised the drafts of the manuscript.

Chapter 4 of this thesis is published as *Early elevation of albumin excretion rate is associated with poor gluten-free diet adherence in young people with coeliac disease and diabetes,* Pham-Short A., Donaghue KC., Ambler G., Chan AK., Hing S., Cusumano J., Craig ME., *Diabetic Medicine,* 31, 208-212 (2014). I co-designed the study, extracted the data, analysed the data and wrote, reviewed and revised the drafts of the manuscript.

Chapter 5 of this thesis is published as *Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review,* Pham-Short A., Donaghue KC., Ambler G., Phelan H., Twigg S., Craig ME., *Pediatrics,* 136 (1), e170-176 (2015). I co-designed the study with the co-authors, analysed the data, and wrote, reviewed and revised the drafts of the manuscript.

Chapter 6 of this thesis is published as *Quality of Life in Type 1 Diabetes and Celiac Disease: Role of the Gluten-Free Diet,* Pham-Short A., Donaghue KC., Ambler G., Garnett S., Craig ME., *The Journal of Pediatrics, 179:131-8 (2016).* I co-designed the study with the co-authors,

recruited patients, collected data, analysed the data, and wrote, reviewed and revised the drafts of the manuscript.

Chapter 7 of this thesis is published as *Greater postprandial glucose excursions and inadequate nutrient intake in youth with type 1 diabetes and celiac disease,* Pham-Short A., Donaghue KC., Ambler G., Garnett S., Craig ME, *http://www.nature.com/articles/srep45286 (2017).* I co-designed the study with the co-authors, recruited patients, collected data, analysed the data, and wrote, reviewed and revised the drafts of the manuscript.

Chapter 8 of this thesis is published as *Abnormal cortical and trabecular bone in youth with type 1 diabetes and celiac disease,* Pham-Short A., Donaghue KC., Ambler G., Briody J., Garnett S., Munns CF, Craig ME, *Diabetes Care 2019; 42:1-7).* I co-designed the study with the co-authors, recruited patients, collected data, analysed the data, and wrote, reviewed and revised the drafts of the manuscript.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Anna Pham-Short 19th June 2019

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Maria E Craig 19th June 2019

PRESENTATIONS RELATED TO THIS THESIS

Results from the research in this thesis were presented at both national and international meetings as outlined below (as first author):

1. **International Society of Pediatric and Adolescent Diabetes (ISPAD) Annual Conference, Oct 2016, Valencia, Spain** (Oral presentation): *Greater postprandial glucose excursions and inadequate dietary intake with youth with type 1 diabetes and celiac disease*. **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME

2. **ISPAD Annual Conference, Oct 2016, Valencia, Spain** (Poster presentation): *Quality of life in type 1 diabetes and Celiac Disease: Role of the Gluten Free Diet,* **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME

3. **Postgraduate Research Student Conference, August 2016, Sydney,** (Oral presentation): *Glycaemic excursions and nutrient intake in youth with type 1 diabetes and coeliac disease,* **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME

4. **ISPAD Annual Conference, Sept 2014, Toronto,** (Poster presentation): *Screening intervals for coeliac disease in youth with type 1 diabetes: Systematic Review,* **Pham-Short A**, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME

5. **Postgraduate Research Student Conference, Aug 2014, Sydney,** (Oral presentation): *How often should we screen for coeliac disease in type 1 diabetes: systematic review***, Pham-Short A**, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME

6. **American Diabetes Association 74th Annual Scientific Sessions, June 2014, San Francisco** (Poster presentation): *"Abnormal cortical bone and muscle in celiac disease and type 1*

diabetes" **Pham-Short A,** Donaghue KC, Ambler G, Briody J, Garnett S, Munns C, Craig ME

7. Postgraduate Research Student Conference, Aug 2013, Sydney (Oral presentation): *"The impact of coeliac disease on type 1 diabetes"* **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME

8. American Diabetes Association 73rd Annual Scientific Sessions, June 2013, Chicago (Poster presentation): *"Early elevation of albumin excretion rate is associated with poor gluten free diet adherence in young people with coeliac disease and diabetes"* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME

9. Postgraduate Research Student Conference, 2012, Sydney (Oral presentation): *"Are young people with type 1 diabetes and coeliac disease at greater risk of microvascular complications?* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME

10. Australasian Paediatric Endocrine Group Annual Scientific Meeting (ASM), August 2012, Queenstown - New Zealand (Poster presentation): *"Increased risk of microalbuminuria in young people with diabetes and coeliac disease with poor gluten free diet adherence"* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME,

11. ISPAD Annual Conference, October 2011, Miami, Florida – USA (Poster presentation): *"Young people with coeliac disease are not at increased risk of microvascular complications",* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME

12. **ISPAD Annual Conference, October 2010, Buenos Aires, Argentina** (Oral presentation): *"Younger age at diabetes diagnosis increases risk of coeliac disease",* **Pham, A.,** Donaghue, K.C., Chan, A., Craig M.E

PUBLISHED ABSTRACTS

1. Greater postprandial glucose excursions and inadequate nutrient intake in youth with type 1 diabetes and coeliac disease., **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME, *Pediatric Diabetes,* 17 (Suppl. 24): p33, Oct 2016 DOI 10.111/pedi.12450

2. Quality of life in type 1 diabetes and coeliac disease: role of the gluten-free diet., **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME, *Pediatric Diabetes,* 17 (Suppl 24), p119, Oct 2016., DOI 10.1111/pedi.12451

3. Screening intervals for coeliac disease in youth with type 1 diabetes: Systematic review**.**, **Pham-Short A,** Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME, *Pediatric Diabetes,* 15:p119, Oct 2014

4. Abnormal trabecular and cortical bone and muscle in celiac disease and type 1 diabetes., **Pham-Short A,** Donaghue KC, Ambler G, Briody J, Howman-Giles R, Munns CF, Craig ME., *Diabetes,* 63: pA328 Jun 2014

5. Young people with coeliac disease are not at increased risk of microvascular complications., **Pham-Short A,** Donaghue KC, Ambler G, Chan AK, Cusumano J, Hing S, Craig ME, *Pediatric Diabetes,* 12: 15, p52 Oct 2011

6. Younger age at diagnosis of type 1 diabetes increases risk of coeliac disease, **Pham A,** Donaghue KC, Chan A, Craig ME, *Pediatric Diabetes,* 11: 14 p22 Oct 2010

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- JDRF Early Stage Researcher Travel Grant for the ADA 73rd Annual Scientific Session, Chicago, USA (2013)
- Juvenile Diabetes Research Foundation (JDRF) – Early Stage Researcher Travel Grant for the American Diabetes Association (ADA) 74th Annual Scientific Session, San Francisco, United States of America (USA) (2014)

- ISPAD Travel Grant for the ISPAD 40th Annual Conference Toronto, Canada (2014)
- ISPAD Travel Grant for the ISPAD 42nd Annual Conference, Valencia, Spain (2016)

PRIZES RELATED TO THIS THESIS

The following prizes were awarded arising from research presentations related to this thesis:

- Postgraduate Research Student Support, University of Sydney (2011,2012,2014)
- Prize for first year candidate, University of Sydney School of Paediatrics and Child Health Postgraduate Research Student Conference, Sydney (2012)
- Prize for Excellent Student Presentation, University of Sydney School of Paediatrics and Child Health Postgraduate Research Student Conference, Sydney, (2016)

LIST OF ABBREVIATIONS

Abbreviation	
ADA	American Diabetes Association
AER	Albumin Excretion Rate
ADDN	Australasian Diabetes Data Network
AGEs	Advanced Glycation End Products
APEG	Australasian Paediatric and Endocrinology Group
ASM	Annual Scientific Meeting
BMC	Bone Mineral Content
BMD	Bone Mineral Density
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring Systems
CRP	C-reactive protein
CSII	Continuous Subcutaneous Insulin Infusion
CD	Coeliac disease
CHW	Children's Hospital at Westmead
DCAS	Diabetes Complications Assessment Service
DXA	Dual Energy X-ray Absorptiometry
ESR	Erythrocyte Sedimentation Rate
GF	Gluten Free
GFD	Gluten Free Diet
GFD-	Gluten Free Diet Non-adherent
GI	Glycaemic Index
HbA1c	Glycated haemoglobin
IQR	Inter Quartile Range
ISPAD	International Society for Pediatric and Adolescent Diabetes
JDRF	Juvenile Diabetes Research Foundation
LTM	Lean Tissue Mass

MDI	Multiple Daily Injections
NICE	National Institute for Health and Care Excellence
PPE	Post-prandial Excursions
pQCT	Peripheral Quantitative Computer Tomography
QoL	Quality of Life
SD	Standard Deviation
SDS	Standard Deviation Score
T1D	Type 1 diabetes
vBMD	Volumetric Bone Mineral Density

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CHAPTER 1: THESIS OVERVIEW AND AIMS

THESIS OVERVIEW

The overarching theme of this body of work is to examine the broad impact of coexisting coeliac disease in young people with type 1 diabetes. Research questions explored the epidemiology, screening practices, microvascular complications, quality of life (QoL), nutrition, glycaemic variability, and bone health. In particular, the contribution of gluten free diet (GFD) adherence to clinical outcomes in young people with both conditions is explored.

RESEARCH HYPOTHESES AND AIMS

Primary Hypotheses:

i. Children with co-existing type 1 diabetes and coeliac disease are younger at diabetes onset compared with those with type 1 diabetes alone

ii. Published studies on the recommendations for frequency of screening for coeliac disease in type 1 diabetes are varied and not evidence based

iii. Young people with type 1 diabetes and coeliac disease, who do not adhere to the gluten free diet, have higher complications rates, independent of glycaemic control, compared with those who adhere

iv. Quality of life scores are lower (a) in youth with type 1 diabetes and coeliac disease compared with type 1 diabetes only, and (b) in those who do not adhere to the gluten-free diet compared with those who adhere

v. Youth with type 1 diabetes and coeliac disease demonstrate greater glycaemic excursions and lower nutrient intake compared with those with type 1 diabetes alone

vi. Youth with type 1 diabetes and coeliac disease exhibit abnormal measures of bone health compared with those with type 1 diabetes alone

Aims

i. To determine the incidence and prevalence of coeliac disease in young people with type 1 diabetes and to examine the association with age at diabetes onset

ii. To systematically review the epidemiology of coeliac disease in people with type 1 diabetes to inform screening guidelines

iii. To compare microvascular complications rates in youth with and without coeliac disease and examine the association between gluten-free diet adherence and complications

iv. To evaluate quality of life and glycaemic control in youth with type 1 diabetes and coeliac disease versus type 1 diabetes only

v. To compare glucose variability using continuous glucose monitoring in youth with type 1 diabetes and coeliac disease compared to those with type 1 diabetes alone

vi. To compare macronutrient, micronutrient and fibre intake in youth with type 1 diabetes and coeliac disease compared to those with type 1 diabetes alone

vii. To compare bone mineral density in youth with type 1 diabetes and coeliac disease versus type 1 diabetes alone

CHAPTER 2: LITERATURE REVIEW

2.1 PATHOPHYSIOLOGY OF COELIAC DISEASE

Coeliac disease (CD) is a chronic autoimmune condition characterised by an immune mediated reaction to dietary gluten in genetically susceptible individuals. More than 95% of people with CD have the major histocompatibility complex II class human leukocyte antigen (HLA) DQ2 or DQ8 haplotype, although only 1 in 30 people who have HLA DQ2 or HLA DQ8 will develop coeliac disease. Treatment requires a strict, life-long gluten free diet (GFD), which excludes the ingestion of the grains; wheat, rye, oats and barley. Symptoms at presentation may include diarrhoea, recurrent abdominal pain, bloating, failure to thrive, iron-deficiency anaemia or reduced bone density. However, it is also recognised that patients may have minimal, or no overt symptoms. Undiagnosed, and untreated, CD is one of the most common causes of chronic malabsorption (Rubio-Tapia et al. 2013).

CD is diagnosed by detection of CD-specific serology, and confirmed by an intestinal biopsy (Bai et al. 2013, Mahmud et al. 2018). Screening for CD is based on detection of IgA antibodies (tissue transglutaminase [tTG-A] and/or endomysial [EmA]), and in those with IgA deficiency, IgG-specific antibodies (tTG or EmA IgG). The Marsh classification is widely used in clinical practice to classify histologic damage, with villous atrophy (Marsh type 3, Figure 1) diagnostic of CD (Marsh et al. 1995, Bai et al. 2013).

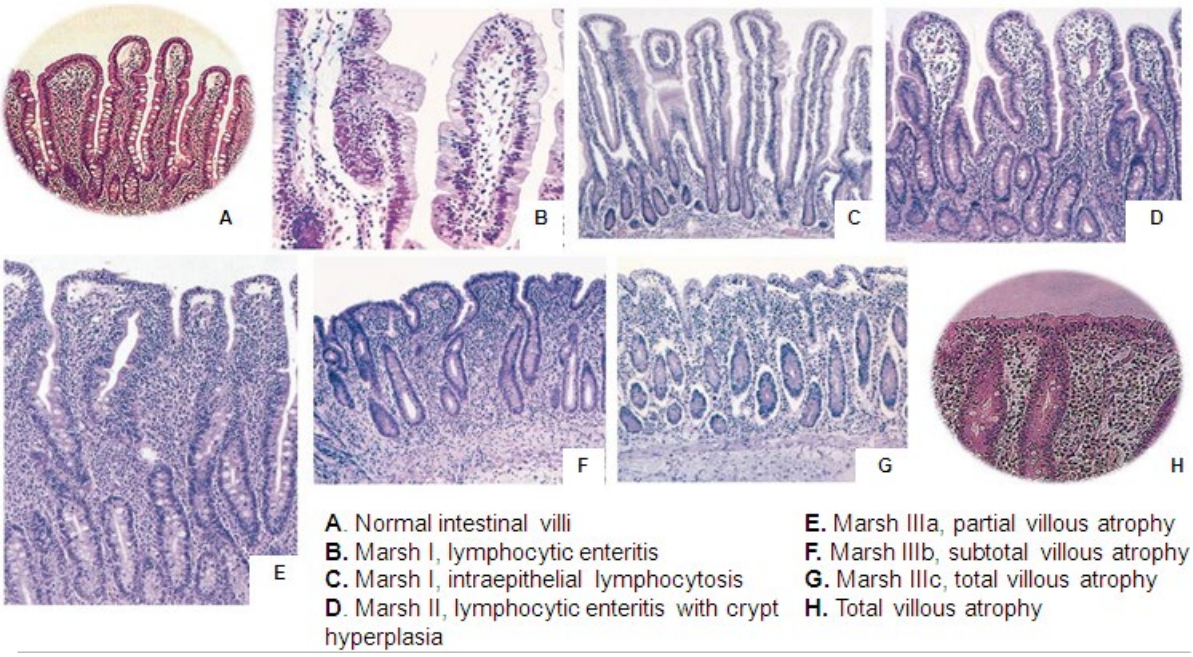

Figure 2.1 Histological stages of villous atrophy according to Marsh Criteria (Marsh et al. 1995).

2.2 EPIDEMIOLOGY OF TYPE 1 DIABETES AND COELIAC DISEASE

Coeliac disease (CD) frequently coexists with type 1 diabetes (T1D), with rates ranging from 1.6% to 16.4% in T1D (Westman et al. 1999, Poulain et al. 2007, Kordonouri et al. 2014). This is substantially higher than the general population prevalence of CD, ranging from 0.3 to 1.0% (Bai et al. 2013). Over a million children and adolescents are estimated to be living with T1D globally (International Diabetes Federation 2017), and therefore thousands are living with both chronic conditions. The global mean annual incidence rates of T1D are presented in Figure 2.2.

The management of T1D requires a life-long regimen of daily insulin injections or continuous subcutaneous insulin infusion (CSII) and blood glucose testing by finger-prick or continuous glucose monitoring (CGM), which must be balanced with carbohydrate intake. However, the treatment is imperfect and creates a burden for the individual, their family/carers and the health care system. Overlayed by the requirement of a gluten-free diet (GFD) for the management of CD, the impact of living with both conditions has possible adverse effects on psychosocial well-being, and health related outcomes such as microvascular complications, adverse bone health, and dietary related inadequacies. To date, most studies examining the coexistence of both conditions have focused on glycaemic control and growth (Mohn et al. 2001, Sud et al. 2010).

CD often presents asymptomatically in children with T1D (Mahmud et al. 2018) and is not necessarily associated with poor growth or deterioration in glycaemic control (Rami et al. 2005, Simmons et al. 2007, Sun et al. 2009). There is some evidence that dietary treatment improves quality of life (QoL) in silent CD, but studies in people with coexisting T1D and CD are limited. Adherence to the GFD for those with T1D and CD improves growth (Sponzilli et al. 2010), weight z-scores, haemoglobin and serum ferritin (Hansen et al. 2006).

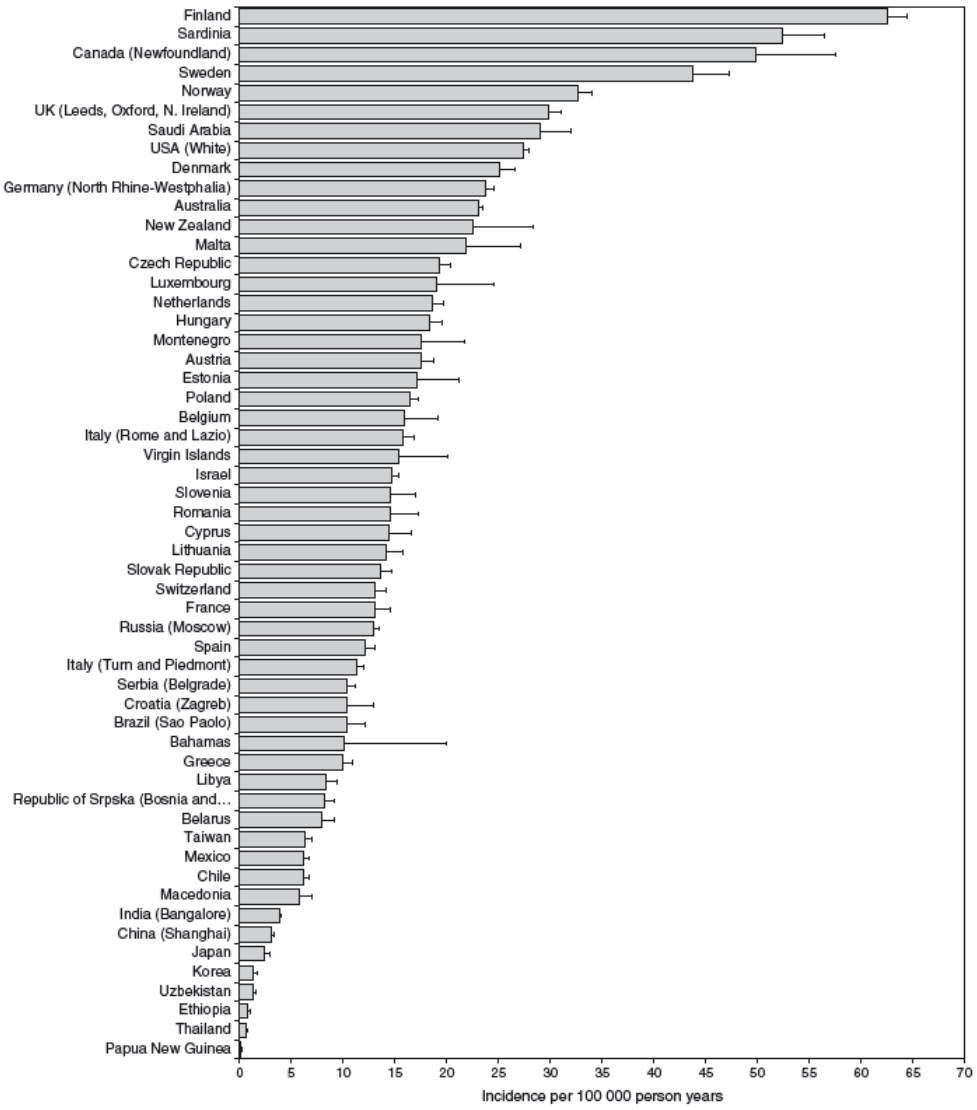

Figure 2.2. Global mean annual incidence rates of type 1 diabetes in children and adolescents aged 0-14 yr (Craig et al. 2014)

2.2.1 PREVALENCE OF COELIAC DISEASE IN TYPE 1 DIABETES

The prevalence of CD is higher in T1D compared to the general population, with rates reported between 1.6% - 16.4%, vs 1% (Poulain et al. 2007, Kordonouri et al. 2014) and 2 to 8% in Australia (Doolan et al. 2005). The higher prevalence of CD in T1D reflects the shared genetic predisposition of both conditions, as well as regular screening at and after diagnosis

of T1D (Mahmud et al. 2018). Those that develop both CD and T1D appear to be younger at T1D diagnosis compared with the typical age distribution of T1D onset (Cerutti et al. 2004, Frohlich-Reiterer et al. 2011) and are generally diagnosed after relatively short diabetes duration (Larsson et al. 2008). However, a clear relationship between age at T1D diagnosis, and time development to CD diagnosis has yet to be established. This may provide guidance for the frequency of CD screening, which could be stratified by age at T1D diagnosis.

Chapter 3 of this thesis presents the results of a clinic-based, 20-year cohort study of 4,379 youth with T1D; to determine the incidence and prevalence of CD and examine the relationship between age at T1D onset and disease duration. Our novel finding of a relationship between younger age at diabetes diagnosis and longer time to CD seroconversion had not been recognized previously, highlighting the importance of regular screening. We reported an incidence rate of 7.7 per 1,000 person years, and a prevalence rate of 7.1%. Since Chapter 3 was published, clinical characteristics associated with the T1D and CD presentation included iron deficiency (Al-Hussaini et al. 2012), female gender (Al-Hussaini et al. 2012, Bianchi et al. 2016) and a higher prevalence in the first 2 years after diabetes diagnosis (Bybrant et al. 2014). Notably, a large multi-national cross-sectional study of 52,571 youth from Germany/Austria, the United States, the United Kingdom and Australia found CD in 3.5% of patients; their findings similarly found a higher prevalence in those younger at diabetes diagnosis compared to T1D alone, with the prevalence rate from the Australasian Diabetes Data Network (ADDN) database of 7.7%. The majority of T1D patients who then develop biopsy-proven CD are asymptomatic of CD, reinforcing the importance of routine screening, which is systematically reviewed in Chapter 5.

2.2.2 SCREENING FOR COELIAC DISEASE IN TYPE 1 DIABETES

Screening for CD in T1D is widely recommended, however recommendations for frequency of screening are variable and not evidence based. The International Society of Pediatric and Adolescent Diabetes (ISPAD) recommends screening at the time of diagnosis and every 1 to 2 years thereafter, with more frequent assessment if clinically indicated or if there is a first-degree relative with CD (Kordonouri et al. 2014) . In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidelines recommend screening for CD at the time of T1D diagnosis, and when symptomatic (National Institute for Health and Care Excellence 2015). Up until, and including 2017, the American Diabetes Association's (ADA) annual Standards of Medical Care in Diabetes recommendations for CD screening were to consider CD screening soon after diabetes diagnosis in those with symptoms suggestive of CD (American Diabetes Association 2017).

Prospective studies have reported seroconversion after T1D diagnosis, with patients testing negative for CD antibody tests at diabetes onset becoming positive during the follow-up period and CD confirmed on small bowel biopsy (Barera et al. 2002, Glastras et al. 2005, Larsson et al. 2008). Seroconversion from negative to positive CD autoantibodies can occur beyond 10 years of diabetes duration, highlighting the necessity for repeated CD screening (Glastras et al. 2005). These studies provide evidence to justify the practice of screening for CD in children with T1D. In T1D, undiagnosed CD may be associated with unstable blood glucose levels, a greater risk of hypoglycaemia (Mohn et al. 2001), and increased risk of retinopathy (Hill et al. 2005). In view of the variable recommendations, risks associated with undiagnosed CD, and to build upon the findings of Chapter 3 that those at greatest risk of

developing diabetes, were likely to develop CD over a longer median period of diabetes duration, the epidemiology of CD in people with T1D was systematically reviewed to inform screening guidelines (Chapter 5).

2.3 ADHERENCE TO THE GLUTEN-FREE DIET

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines state following the diagnosis of CD, dietary counselling for a GFD is paramount, followed by serological normalisation of CD-specific antibody titres (Husby et al. 2012). Dietary assessment of GFD compliance by a dietitian via a thorough interview is considered the best available method (Leffler et al. 2007).

GFD adherence in youth with CD has been reported to vary from 25% to 81% of participants in those with or without coexisting T1D (Saadah et al. 2004, Wagner et al. 2008, van Koppen et al. 2009, Husby et al. 2012). GFD adherence is often assessed by a thorough dietary assessment (Saadah et al. 2004), self-reported (Wagner et al. 2008) or with the normalisation of CD specific serology (van Koppen et al. 2009, Husby et al. 2012). Factors found to increase compliance with the GFD include being female, younger of age, having better school academic performance and higher self-esteem (Greco et al. 1997). Those diagnosed with CD at a younger age are more likely to maintain a GFD, with dietary transgressions most likely to occur in adolescents or those diagnosed via mass screening (Hogberg et al. 2003). A Swedish study (Hogberg et al. 2003) measuring compliance utilising a questionnaire and serological markers found at least 80% of patients who were diagnosed with CD before the age of 4 complied to the GFD, compared to 36% of patients aged more

than 4 at CD diagnosis. This study also highlights the importance of early diagnosis to minimise the risk of CD-related complications and reduced well-being.

Adherence to the GFD is also variable in patients with CD alone. In a follow-up evaluation of adolescents with CD diagnosed following mass screening, adherence to the GFD was 52.2% with dietary transgressions reported as occasional and commonly happening on weekends (Fabiani et al. 1996). This same Italian study group later compared adherence to the GFD in those with screen-detected CD, vs those symptomatic of CD prior to diagnosis, and report a higher proportion of dietary transgressions in those screen-detected (Fabiani et al. 2000). In contrast, a Finnish study found no difference in GFD adherence between screen-detected, or symptom-detected children and adolescents (71% vs 84% strict adherence, P=0.11) (Kinos et al. 2012).

In comparison, patients with coexisting CD and T1D have lower compliance to the GFD than those with CD alone, and this has been demonstrated to be less than 30% of participants (Westman et al. 1999, Saadah et al. 2004), as assessed by a dietitian.A case controlled study from Australia (Westman et al. 1999) assessed the growth, diabetes control, dietary intake and compliance with a GFD in children with T1D and CD. Dietary intake and compliance were assessed by a 3 day food record and a 7 day food frequency questionnaire, diabetes control was measured by HbA1c and was found to be similar in for those with or without CD. Strict compliance to the GFD was observed in only 30% of patients, with no differences in energy or nutrient intake, growth, or diabetes control. Of note, the availability of gluten free foods is greater today than 20 years ago.

Glycaemic control in those with coexisting T1D and CD was shown to be no different compared to those with T1D alone (Rami et al. 2005, Simmons et al. 2007, Sun et al. 2009). A trend towards a lower BMI SDS score, but not height SDS scores denoting negative weight gain has also been observed in patients with T1D and CD who were non-compliant with the GFD (Rami et al. 2005), which may be attributed to CD affecting the absorption of some nutrients.

2.3.1 BARRIERS TO THE ADHERENCE OF THE GFD

Adolescence is often described as a very difficult and tumultuous time during which the young person attempts to find their individuality, fit in amongst friends, and rebel towards adults; these challenges may be further complicated by living with a chronic condition, and more so by two. Hence it can be expected that GFD compliance during adolescence is lower compared to other age groups (Cinquetti et al. 1997, Wagner et al. 2008). In a qualitative Swedish study using focus group sessions in 47 adolescents aged 15-18 years with confirmed CD, who had been on the GFD for at least a year, compliance with the GFD was easiest at home, where family members were well acquainted with the GFD and foods were readily available. This is likely due to home providing an easy environment where adolescents did not have to ask questions or explain the need for a GFD (Olsson et al. 2008). By contrast, situations outside the home were more troublesome for adolescents – contributory factors included limited social support and lack of CD-related knowledge in significant others (such as teachers, school-kitchen staff, friends, extended family members), the unavailability of GF foods, problems with sensory acceptance, the absence of symptoms following the ingestion of gluten, and lack of knowledge of the health-related

harms of gluten ingestion (Olsson et al. 2008). This study highlights the multi-factorial and overlapping nature of factors affecting GFD compliance in adolescents with CD alone. However, there is no research on factors affecting GFD adherence in youth with coexisting T1D and CD.

2.3.2 CLINICAL BENEFIT OF THE GFD IN PATIENTS WITH T1D AND CD

Following introduction of the GFD in those with coexisting T1D and CD, a range of clinical parameters can improve. A Swedish study of patients followed over 2 years while consuming a GFD showed improvements with weight-SDS scores, haemoglobin, and serum ferritin, with no difference in glycaemic control (Hansen et al. 2006). However, as HbA1c measures average blood glucose levels, fluctuations between hypoglycaemia and hyperglycaemia are not detected. Indeed, patients experienced fewer hypoglycaemic episodes after the start of the GFD, which was also demonstrated by another study of youth (Mohn et al. 2001).

Maintaining a GFD in those with screen detected CD shows improved clinical parameters. In a comparative study from Colorado of children with T1D and CD identified by screening, and matched controls, those with positive CD screen at baseline had altered body composition with lower weight Z scores, body mass index, mid-arm circumference, and increased bone turnover (Simmons et al. 2007). In contrast, both groups had similar BMD and glycaemic control. The follow up study of this group is currently the largest prospective study in children with T1D and CD autoimmunity, with 80% retention during the follow-up (Simmons et al. 2011). All children who screened positive for CD received dietary education on the

GFD, but self-selected whether to consume a GFD or a gluten-containing diet: 43/79 (54%) chose a GFD and 36 (46%) chose a regular diet. Those who had persistently high CD antibodies throughout the study period had lower weight and BMI z scores, increased bone turnover, and lower vitamin D 25-OH levels, conferring an increased fracture risk, and lower ferritin levels, indicating generalised malnutrition. Consistent with other studies (Hogberg et al. 2003), a relationship between age and CD compliance was also observed, with school-age children less compliant than younger children and adults.

2.4.1 COMPLICATIONS OF TYPE 1 DIABETES

The landmark Diabetes Control and Complications Trial (DCCT 1993) was a multi-centre, randomised controlled clinical trial involving 1441 patients with T1D, which showed that intensive therapy reduced the risk of diabetes related complications. Participants were assigned to either conventional diabetes therapy of one or two daily injections of insulin or intensive diabetes management, consisting of three or more daily injections of insulin or CSII, with target blood glucose ranges pre and post-prandially. Intensive therapy delayed the onset and slowed the progression of clinically important retinopathy, including vision-threatening lesions, nephropathy, and neuropathy. Risk reductions ranged from 39% for microalbuminuria to more than 76% for retinopathy (DCCT 1993). This widely cited study provided unequivocal evidence that intensive diabetes treatment and improved glycaemic control, often measured by glycated haemoglobin (HbA1c) conferred a significant risk reduction for vascular complications. Glycated haemoglobin (HbA1c) has its metric limitations as it does not consider the degree of fluctuations between high and low blood glucose levels – this is best defined by glycaemic variability. Glycaemic variability is a

potential complication of T1D, as even in those without diabetes, is an independent risk factor for cardiovascular disease (Hirsch 2015).

2.4.2 COMPLICATIONS OF COELIAC DISEASE

There is strong evidence that individuals with untreated CD are at risk of complications such as iron deficiency, anaemia, growth retardation, fertility problems and gastrointestinal malignancy (Gasbarrini et al. 2000, Bai et al. 2013), as well as low BMD and osteoporosis (Matysiak-Budnik et al. 2007, Zanchetta et al. 2016). Even asymptomatic individuals in whom CD is detected by screening are at risk of these co-morbidities (Bjorck et al. 2017), including children with coexisting T1D (Hansen et al. 2006).

BMD is reduced in children and adults with CD (Bianchi et al. 2008, Mora 2008) and low BMD in children improves after the introduction of a GFD (Tuna Kirsaclioglu et al. 2016). There is also an increased risk of osteoporotic fracture (Kamycheva et al. 2017) and severe osteopenia (Zanchetta et al. 2016), which can be corrected by adherence to the GFD (Newnham et al. 2016, Zanchetta et al. 2017). In a Swedish prospective population-based cohort study, screening detected CD 10-year old children had reduced BMD and lower levels of vitamin D compared to controls (Bjorck et al. 2017). In comparison, the same study reported similarly aged children diagnosed with CD via screening at the age of three, and commenced on a GFD were found to have no difference in BMD compared to controls, indicating children with screening-detected CD benefit from early diagnosis and treatment.

2.4.3 VASCULAR COMPLICATIONS IN PEOPLE WITH T1D AND CD

There is strong evidence that individuals with either T1D or CD are at risk of complications, which have a multifactorial aetiology including poor compliance with treatment. Therefore, it can be speculated that the co-existence of both conditions may confer a greater risk of complications, particularly in the setting of suboptimal adherence to therapy. In a case-control study from the UK of adults with T1D, those with undetected CD demonstrated worse glycaemic control (8.2 vs 7.5%, P=0.05), and a higher prevalence of both retinopathy (58.3% vs 25%, p=0.02) and nephropathy (41.6% vs 4.2%, p=0.009) (Leeds et al. 2011). Similarly, a population-based Swedish cohort study of 41,566 patients, of whom 980 (2.3%) had coexisting CD, demonstrated that CD duration >10 years was an independent risk factor for the development of diabetic retinopathy (Mollazadegan et al. 2013). CD was an independent risk factor for retinopathy and nephropathy in patients with T1D (Rohrer et al. 2015), with CD duration > 15 years associated with a 2.8 fold increased risk of death (Mollazadegan et al. 2013). These studies highlight not only the importance of screening and treating CD in T1D, but also monitoring for the development of microvascular complications.

Established risk factors for vascular complications of diabetes include worse glycaemic control and higher blood pressure, but there are limited data on the role of GFD adherence on microvascular complications. In the UK study of adults with coexisting T1D and CD (Leeds et al. 2011), nine individuals who were GFD adherent for one year had clinically significant favourable increases in HDL cholesterol, total cholesterol: HDL ratios, and a lower prevalence of advanced nephropathy; however the authors acknowledged their limitations of small numbers.

In view of the limited data on microvascular complications in those living with coexisting CD and T1D, the PhD candidate sought to compare complications rates in youth with or without CD and examined the association between GFD adherence and complications. Chapter 4 presents the results of a comparative study of 2,510 adolescents with T1D alone and 129 with CD, of whom 60 (47%) did not adhere to the GFD.

2.5 QUALITY OF LIFE (QOL) OF PATIENTS WITH T1D OR CD

The intensive management of T1D, which includes multiple daily insulin injections or CSII, regular blood glucose monitoring and carbohydrate counting, has the potential to negatively affect QoL. There is some evidence that QoL is lower in children and adolescents with diabetes compared with healthy children (Varni et al. 2003, Delamater et al. 2018), particularly when parents rate their children's QoL (Varni et al. 2003, Hesketh et al. 2004, Yi-Frazier et al. 2016). QoL is lower in girls and youths with shorter diabetes duration, those with disease-related family conflict (Delamater 2009), or the fear of hypoglycaemia (Johnson et al. 2013). However in general, when youth with diabetes rate their own QoL, it does not differ from their healthy peers (Laffel et al. 2003, Varni et al. 2003, Hesketh et al. 2004).

The only treatment for CD is strict adherence to a GFD, which is safe and efficient, but is very restrictive. The GFD poses both lifestyle restrictions, with some families avoiding travelling or eating out (Cinquetti et al. 1997, Roma et al. 2010) as well as financial strain due to increased costs of gluten-free foods compared to gluten-containing foods (Lee et al.

2007, Stevens et al. 2008). Gluten-free foods are less readily available and more costly; a study from Canada demonstrated that gluten-free products were 252% more expensive than regular products (Stevens et al. 2008). The restrictive nature, limited availability, and increased costs of the GFD may result in social burden and poor compliance (Matysiak-Budnik et al. 2007, Olsson et al. 2008).

The role of a supportive family for children and adolescents living with either T1D or CD plays a pivotal role in the child's management adherence (Olsson et al. 2008, Delamater et al. 2018). Supportive behaviours such as family cohesion, agreement about management responsibilities, and collaborative problem-solving are associated with better regimen adherence and glycaemic control in T1D (Delamater et al. 2018) and those with a familial better perception of their own health have higher QoL (van Doorn et al. 2008). In contrast, conflict, diffusion of responsibilities and regimen-related conflict have been associated with worse regimen adherence and glycaemic control in T1D (Wysocki et al. 2008, Hilliard et al. 2013, Tsiouli et al. 2013, Delamater et al. 2018), and the perception that GFD adherence is difficult (Barratt et al. 2011).

Nutritional management is a cornerstone of care for both T1D and CD. In T1D, mealtime behaviour problems are commonly reported and range from parents feeling anxious or frustrated when feeding their child, does not readily come to mealtimes, or has a poor appetite in young children (Powers et al. 2002), and are often compounded by the demands of carbohydrate counting, eating to manage blood glucose levels independent of hunger

(Mehta et al. 2009), and normal child developmental behaviours such as fussy eating. QoL is higher in people with T1D treated with CSII (Misso et al. 2010, Craig 2011), which allows flexibility with meal times and food choices (Overby et al. 2008, Mehta et al. 2009). As a GFD requires substitution of commonly available carbohydrate foods such as wheat-based breads, cereal, and pasta (Stevens et al. 2008), CSII could alleviate the restrictive nature of the GFD. However, the impact of CSII on QoL in people with coexisting T1D and CD, and the impact of carbohydrate free meals on total insulin doses has not been studied

To date, there is only one paediatric study examining the impact of coexisting CD and T1D on QoL, which found no difference in generic, or diabetes-specific QoL compared to children with T1D alone (Sud et al. 2012). However, CD specific QoL was not examined, nor was the effect of symptoms on QoL. Surprisingly, QoL did not differ between those GFD adherent, vs GFD non-adherent, although the number GFD non-adherent in this study was small (n=6), which may suggest this subgroup analysis was underpowered. Chapter 6 of this thesis reports a larger comparative study of youth with T1D (n=35) vs T1D and CD (n=35), and their parents (n=70), and further stratified results by GFD adherence, symptoms of CD, and mode of diabetes management - MDI vs CSII.

2.6 DIETARY QUALITY AND GLYCAEMIC VARIABILITY OF THE GLUTEN FREE DIET

CD is managed by a strict GFD, requiring the complete avoidance of the grains wheat, oats, barley and rye, which is often replaced by white rice or corn (Lee et al. 2009). These grains may contribute to a higher glycaemic index (GI) (Atkinson et al. 2008), higher glycaemic load

(Farnetti et al. 2014) and lower fibre diet (Hopman et al. 2006, Shepherd et al. 2013) compared to the gluten containing equivalents. Higher fibre diets in the general population have well-known benefits such as improved cardiovascular and bowel health (Anderson et al. 2009), and in T1D, these benefits extend to improved glycaemic control (Katz et al. 2014).

Restrictive diets such as the GFD may cause nutritional deficiencies, requiring increased vigilance in growing children and adolescents (Collin et al. 1989). The mandatory fortification of wheat flour with micronutrients such as thiamine and folic acid (FSANZ 2016), but not gluten-free grains further places those consuming a GFD at risk of inadequate nutrient intake. Studies investigating the nutritional composition of the GFD in adults have shown inadequacies of specific micronutrients including thiamine, folate, vitamin A and calcium (Thompson et al. 2005, Shepherd et al. 2013). However, there are limited dietary studies in youth with CD (Mariani et al. 1998, Hopman et al. 2006, Ohlund et al. 2010) and only one in children with coexisting T1D (Liu et al. 2018).

Adults and children with CD have lower carbohydrate intake, compared to the general population (Mariani et al. 1998, Shepherd et al. 2013), which has been attributed to poor palatability, and increased costs of the GFD (Stevens et al. 2008). Carbohydrate intake in children with T1D is often at the lower level of dietary guidelines (Delahanty et al. 2009), which may be due to a conscious effort to reduce the risk of postprandial hyperglycaemia (Mehta et al. 2009). In studies of children with CD, fibre and iron intakes are also significantly lower than recommendations (Mariani et al. 1998, Hopman et al. 2006), due to

the naturally low fibre and iron content of GF grains (Thompson et al. 2005). However, whether the coexistence of T1D and CD is associated with a greater reduction in carbohydrate and fibre intake has not been previously examined. It is unknown whether the traditional GFD, with a higher GI and lower fibre content, impacts on glycaemic variability in this population.

Technological advancements in diabetes management include continuous glucose monitoring systems (CGMS) measuring 5-minutely readings of interstitial glucose levels (Bailey et al. 2014), enabling a 24 hour glucose profile, as well as studying the effect of individual meals and snacks on blood glucose levels. Utilising this technology, Chapter 7 of this thesis reports a comparative case-control, observational study of youth with T1D vs T1D and CD. We hypothesised that youth with coexisting T1D and CD would demonstrate greater glycaemic excursions and lower nutrient intake. Participants wore a blinded CGMS for 6 days, maintained weighed 3 day food diaries, and consumed a test GF meal to compare post-prandial excursions (PPE), and macronutrient, micronutrient and fibre intakes.

2.7 BONE HEALTH IN TYPE 1 DIABETES AND COELIAC DISEASE

There is substantial evidence that adults with T1D have abnormal bone mineral density (BMD) and are at increased risk of fractures (Thong et al. 2018). There is also limited evidence that children and adolescents with T1D have lower BMD (Thrailkill et al. 2005) and smaller bone mass (Lettgen et al. 1995, Roggen et al. 2013). Whilst the mechanisms for

adverse bone health are multifactorial; in T1D they include inadequate accrual of peak bone mass due to impaired bone formation and osteoblast function (Hamann et al. 2012), elevated HbA1c (Campos Pastor et al. 2000), and increased production of advanced glycation end products (AGEs) (Botushanov et al. 2009) .

Adults with CD also have an increased fracture risk (Heikkila et al. 2015), while both children and adults with CD have lower BMD compared with the general population. Proposed mechanisms include dietary malabsorption of calcium and vitamin D, which are important for bone growth and development (Forestier-Zhang et al. 2016), or chronic intestinal inflammation, which interferes with bone formation and increases bone resorption (Larussa et al. 2012).

Collectively these data suggest that individuals with coexisting T1D and CD have an additive risk for adverse measures of bone health, but the evidence for this is limited. Low BMD at the lumbar spine, defined as a z-score < -2SD, was more prevalent in a cross-sectional study of children and adolescents with T1D and coeliac autoimmunity (but not biopsy confirmed CD) vs T1D only (12% vs 3%), however actual BMD z-scores were not reported (Simmons et al. 2016). In contrast, coexisting T1D and CD was not associated with an increased fracture risk in a population based Swedish cohort study of individuals aged <30 years, however BMD was not examined (Reilly et al. 2016).

Traditional measures of bone, utilizing dual energy x-ray absorptiometry (DXA) in children and adolescents, include BMD for age, height and weight, bone mineral content (BMC) and BMC for lean tissue mass (LTM). In comparison to DXA, peripheral quantitative computed tomography (pQCT) provides characterization of bone, including measures of volumetric BMD (vBMD), bone geometry (dimension, area, and cortical thickness), and quantifies mineral distribution within the cross-section (Stagi et al. 2016). These parameters allow for calculation of bone strength. pQCT also enables the separate measurement of trabecular and cortical bone compartments, which may allow for earlier detection of changes in bone in response to disease (Stagi et al. 2016). Trabecular bone is metabolically active, and thus any changes in bone structure would usually first be observed here (Lettgen et al. 1995, Roggen et al. 2013). Whilst pQCT has demonstrated that children with T1D have smaller bones compared with non-diabetic controls (Lettgen et al. 1995, Roggen et al. 2013), this tool has not been used to examine bone in youth with coexisting T1D and CD.

Chapter 8 of this thesis presents a case-control study using both DXA and pQCT, of young people with coexisting T1D and CD vs T1D alone to address our hypothesis that coexisting CD confers a greater risk of abnormal BMD, BMC and bone structure.

2.8 SUMMARY

Chapter 2 provided the background upon which this doctoral body of work is based. The increased prevalence of T1D and CD compared to the general population is due to the shared genetic predisposition of both conditions, as well as regular screening (Mahmud

2018). However, a clear relationship between the age at T1D diagnosis, and time development to CD diagnosis has yet to be established. This relationship is explored and reported in Chapter 3, and may provide guidance on the frequency of CD screening, which could be stratified by age at T1D diagnosis.

Screening for CD in T1D is widely recommended, however recommendations for frequency of screening are variable. Seroconversion from negative to positive CD autoantibodies can occur beyond 10 years of diabetes duration (Glastras 2005), highlighting the necessity for repeated CD screening. Chapter 4 presents a systematic review of the epidemiology of CD in people with T1D to inform screening guidelines.

There is strong evidence that individuals with either T1D or CD are at risk of complications, which have a multifactorial aetiology including poor compliance with treatment. Therefore, it can be speculated that the co-existence of both conditions may confer a greater risk of complications, particularly in the setting of suboptimal adherence to therapy. In adults, the coexistence of T1D and CD was associated with worse glycaemic control, higher prevalence of retinopathy and nephropathy (Leeds et al 2011). CD duration > 10 years is an independent risk factor for rentionpathy (Mollazadegan et al 2013), and >15 years associated with a 2.8 fold increase of risk of death. Chapter 2 presents the importance of not only screening and managing CD in T1D, but also monitoring for the development of microvascular complications. Chapter 5 presents a study comparative study of complications

rates in 2,510 adolescents with T1D alone and 129 with CD. The role of GFD adherence in particular, is also examined.

T1D and CD management requires multiple daily injections, or CSII, regular blood glucose monitoring, carbohydrate counting, and the identification of GF foods. The pervasive nature of both conditions is expected to impact of QoL. However, there is only one paediatric study examining the impact of coexisting CD and T1D on QoL, which found no difference in generic, or diabetes-specific QoL compared to children with T1D alone (Sud et al 2012). However, CD specific QoL was not examined, nor was the effect of symptoms on QoL. Chapter 6 of this thesis presents a larger comparative study of youth and their parents, and further stratifies results by GFD adherence.

CD is managed by a strict GFD, requiring the complete avoidance of the grains wheat, oats, barley and rye, which is often replaced by white rice or corn (Lee et al. 2009). These grains may contribute to a higher glycaemic index (GI) (Atkinson et al. 2008), higher glycaemic load (Farnetti et al. 2014) and lower fibre diet (Hopman et al. 2006, Shepherd et al. 2013) compared to the gluten containing equivalents. The restrictive nature of the GFD may cause nutritional deficiencies, requiring increased vigilance in growing children and adolescents (Collin et al. 1989). In adults, the GFD has shown to be inadequate of thiamine, folate, vitamin A and calcium (Thompson et al. 2005, Shepherd et al, 2013). Carbohydrate intake in children with T1D (Delahanty et al. 2009), and CD alone (Mariani et al. 1998) is often at the lower end of dietary guidelines. However, whether the coexistence of T1D and CD is

associated with a greater reduction in carbohydrate and fibre intake has not been previously examined. The impact of the GFD on glycaemic variability has also not been previously examined. Chapter 7 of this thesis reports a case-control, observational study of youth with T1D vs T1D and CD which examines glycaemic excursions and nutrient intake.

There is substantial evidence that adults with T1D have abnormal BMD and are at increased risk of fractures (Thong et al. 2018). There is also limited evidence that youth with T1D have lower BMD (Thrailkill et al. 2005) and smaller bone mass (Lettgen et al. 1995, Roggen et al. 2013). Adults with CD also have an increased fracture risk (Heikkila et al. 2015), while both children and adults with CD have lower BMD compared with the general population. Collectively, these data suggest those with coexisting T1D and CD have an additive risk for adverse measures of bone health. Chapter 8 of this thesis presents a case-control study of youth with coexisting T1D and CD vs T1D alone which examines bone health and bone quality, as measured by DXA and pQCT.

Understanding the impact of the coexistence of T1D and CD in youth may be important in shaping clinical practice guidelines and assist in the practical management of both chronic conditions. Obtaining evidence to support CD diagnosis, and thus GFD adherence may optimise clinical, dietary and psychosocial management in youth and their families. The following chapters present published works relating to the epidemiology of type 1 diabetes and coeliac disease – the importance of screening (Chapter 3), and recommendations for screening frequency (Chapter 4). The clinical impact of the dual diagnosis on the risk of

microvascular complications (Chapter 5), quality of life (Chapter 6), glycaemic variability and nutrient intake (Chapter 7), and bone health (Chapter 8) follows.

CHAPTER 3: COELIAC DISEASE IN TYPE 1 DIABETES FROM 1990 TO 2009: HIGHER INCIDENCE IN YOUNG CHILDREN AFTER LONGER DIABETES DURATION

Pham-Short A, Donaghue KC, Ambler G, Chan AK, Craig ME, *Diabetic Medicine* 2012 Sept; 29(9): e286-e289. Epub 2012 Aug 12

SYNOPSIS

This chapter presents a manuscript that reports the incidence and prevalence of CD in young people with T1D. The primary hypothesis for this study (Hypothesis 1) was that children with co-existing type 1 diabetes and coeliac disease are younger at diabetes onset compared with those with type 1 diabetes alone. Key findings include the observation that children with coexisting T1D and CD were younger at diabetes onset and those in the youngest age group (< 5 years) developed CD after longer diabetes duration compared with older children who developed CD.

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Short Report: Epidemiology

Coeliac disease in Type 1 diabetes from 1990 to 2009: higher incidence in young children after longer diabetes duration

A. Pham-Short[1,2], K. C. Donaghue[1,2], G. Ambler[1,2], A. K. Chan[1,2] and M. E. Craig[1,2,3]

[1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, [2]Discipline of Paediatrics and Child Health, University of Sydney and [3]School of Women's and Children's Health, University of New South Wales, NSW, Australia

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Abstract

Aims To determine the incidence of coeliac disease in young people with Type 1 diabetes and to examine the effect of age at diabetes onset and disease duration.

Methods This was a clinic-based observational cohort study of 4379 people aged ≤ 18 years (49% male) between 1990 and 2009 from Sydney, Australia. Screening for coeliac disease was performed at diagnosis and 1–2 yearly using anti-endomysial and/or anti-tissue transglutaminase immunoglobulin A (IgA) antibodies. Coeliac disease was diagnosed by small bowel biopsy based on Marsh score ≥ III.

Results Coeliac disease was confirmed by biopsy in 185; of these, 61 (33%) were endomysial or tissue transglutaminase IgA antibody-positive at diabetes diagnosis. Mean age at diabetes onset was 6.6 ± 4.0 vs. 8.4 ± 4.1 years in those without coeliac disease ($P < 0.001$). Mean incidence was 7.7 per 1000 person years (95% CI 6.6–8.9) over 20 years. Incidence was higher in children aged < 5 years at diabetes diagnosis (10.4 per 1000 person years) vs. ≥ 5 years (6.4 per 1000), incidence rate ratio 1.6 (95% CI 1.2–2.2, $P = 0.002$). Coeliac disease was diagnosed after 2, 5 and 10 years of diabetes in 45, 78 and 94% of cases, respectively. Median time to coeliac disease diagnosis was longer in children aged < 5 years at diabetes onset (3.3 years) compared with older children (0.7 years, $P < 0.001$).

Conclusions Coeliac disease is common in young people with Type 1 diabetes; the risk is greatest with diabetes onset < 5 years, but after longer diabetes duration. Screening for coeliac disease should be performed at diabetes diagnosis and for at least 10 years in young children.

Diabet. Med. 29, e286–e289 (2012)

Keywords age of onset, diet, paediatrics, screening, Type 1 diabetes

Introduction

The association between Type 1 diabetes and coeliac disease is well documented, but there are few longitudinal studies reporting incidence [1]. Prevalence rates vary from 1 to 10% worldwide [2–6] and from 2 to 8% in Australia [7–9]. There is some evidence for an association with younger age at Type 1 diabetes diagnosis [3] and shorter diabetes duration [4]; however, none of the published studies have been sufficiently large enough to determine the influence of both age and duration on incidence of coeliac disease in the population with diabetes. Incidence provides a more robust measure of disease risk and has implications for screening.

Left untreated, long-term effects of coeliac disease include iron deficiency, anaemia, growth retardation [10] and osteoporosis [11]. In Type 1 diabetes, untreated coeliac disease may be associated with unstable blood glucose levels and a greater risk of hypoglycaemia [12]. The rationale for coeliac disease screening includes prevention of these complications and maximizing growth [13].

The present study was designed to determine the incidence and prevalence of biopsy-confirmed coeliac disease in a diabetes clinic cohort over 20 years and to examine the association between age at diabetes diagnosis and diabetes duration on risk

Correspondence to: Maria Craig, Institute of Endocrinology and Diabetes, Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. E-mail: m.craig@unsw.edu.au

of coeliac disease. We also sought to examine whether screening guidelines should vary with age at diagnosis of Type 1 diabetes.

Patients and methods

This was an observational cohort study of 4379 young people (2147 male, 49%) with Type 1 diabetes, aged < 18 years, attending the Children's Hospital at Westmead, a tertiary paediatric diabetes centre in New South Wales, Australia, between January 1990 and December 2009. Type 1 diabetes was diagnosed by clinical criteria and the presence of islet antibodies (IAA, GAD and IA-2), as previously described [14]. Serological screening for coeliac disease was performed by endomysial immunoglobulin A (IgA) autoantibodies, measured by indirect immunofluorescence until June 2004 and subsequently by anti-tissue transglutaminase IgA antibodies measured by enzyme-linked immunosorbent assay. Screening was performed at diagnosis and 1–2 yearly thereafter [1]. Coeliac disease was diagnosed by small bowel biopsy findings of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocyte count (Marsh score ≥ III) [15].

Children were classified into three groups by age at diabetes diagnosis (< 5, ≥ 5 and ≥ 10 years). Continuous variables were compared between groups using analysis of variance and categorical variables using χ^2-tests. Incidence of coeliac disease was estimated for the entire population, and by age group, as the number of new coeliac disease cases during the study period divided by total person years of follow-up [16]. Incidence was also estimated by age at diabetes diagnosis (< or ≥ 5 years). Poisson regression was used to examine the effect of age group, gender and time period on incidence; estimates are reported as incidence rate ratio and 95% confidence interval. The prevalence of coeliac disease in 2009 was estimated as the number of young people with coeliac disease divided by the total Type 1 diabetes clinic population at that time [16]. Statistical analyses were performed using Stata version 11.0 (Stata Corp., College Station, TX, USA).

Results

Of the 4379 young people, 185 were diagnosed with coeliac disease; of these 61 (33%) were endomysial or tissue transglutaminase IgA antibody-positive at diabetes diagnosis. Mean age at diabetes diagnosis was 6.6 ± 4.0 vs. 8.4 ± 4.1 years in those without coeliac disease ($P < 0.001$). Characteristics of children stratified by age group at diabetes diagnosis are shown in Table 1. Children aged < 5 years at diagnosis had a significantly longer median time to coeliac disease diagnosis (3.3 years) compared with older children (0.7 years, $P < 0.001$). One female aged 13 years was diagnosed with coeliac disease prior to Type 1 diabetes. After excluding this case, 45, 78 and 94% of children were diagnosed with coeliac disease within 2, 5 and 10 years of diabetes diagnosis, respectively. A greater proportion of children aged < 5 years at diabetes diagnosis were diagnosed after longer diabetes duration compared with older children ($P < 0.001$) (Fig. 1). An additional 12 children who were endomysial or tissue transglutaminase IgA antibody-positive subsequently became antibody negative and/or had a negative small bowel biopsy, yielding an assay sensitivity of 94%. Frequency of screening did not vary significantly over time ($P = 0.25$) or by age ($P = 0.1$). More children were of Caucasian ethnicity among those with coeliac disease (93%) vs. without coeliac disease (83%, $P = 0.004$).

The incidence of coeliac disease over the 20-year period was 7.7 per 1000 person years (95% CI 6.6–8.9). Comparing the two decades, incidence was 7.5 per 1000 (95% CI 5.8–9.5) in 1990–1999 vs 7.7 (95% CI 6.4–9.3) per 1000 in 2000–2009 ($P = 0.85$). Incidence of coeliac disease was higher in children aged < 5 years at diabetes diagnosis (10.4 per 1000 person years) vs. ≥ 5 years (6.4 per 1000), incidence rate ratio 1.6 (95% CI 1.2–2.2, $P = 0.002$). Incidence did not differ by gender ($P = 0.25$) or across the two different antibody assays ($P = 0.26$). Prevalence of coeliac disease was 7.1% (95% CI 5.6–8.8) in 2009 (75 biopsy-proven coeliac disease/1051 clinic population).

Discussion

In this 20-year study of 4379 young people with Type 1 diabetes, coeliac disease incidence was 7.7 per 1000 person years. Incidence was 60% higher in children aged < 5 years at diabetes onset, but they were more likely to be diagnosed after longer diabetes duration. Our data support the importance of screening for coeliac disease throughout childhood [4], particularly in children diagnosed with diabetes in early childhood. The consistent screening frequency over time across all age groups and steady incidence despite changes in assay methodology suggest these findings are not attributable to methodological bias. In contrast to a higher rate of coeliac disease in females in the general population, we found no gender bias, reflecting a population at high risk of coeliac disease [3,17].

There are few longitudinal studies reporting coeliac disease incidence in children with Type 1 diabetes [1] and none of these have examined the effect of age at diabetes diagnosis, although two studies demonstrated an association between younger age at diabetes diagnosis and coeliac disease prevalence [3,18]. Incidence is a robust measure of assessing disease risk within a population that has varying times of follow-up [16] and is particularly useful for determining appropriate screening frequency. In contrast, prevalence represents the number of diagnosed cases at a single time point and is therefore not the best measure to examine the effect of age or diabetes duration on disease risk.

The relationship between younger age at diagnosis of Type 1 diabetes and longer time to coeliac disease seroconversion has not been recognized previously. The median time between diagnosis of diabetes and coeliac disease was 3 years in children aged < 5 years at diabetes onset, vs. 0.7 years in those aged

Table 1 Characteristics of young people at diagnosis of coeliac disease, stratified by age group (n = 185)

	Age at diabetes diagnosis			
	< 5 years (n = 80)	5–10 years (n = 61)	≥ 10 years (n = 44)	P-value
Mean age at coeliac disease diagnosis (SD)	7.1 (3.4)	10.5 (2.6)	13.3 (1.6)	
Male gender (%)	50	46	51	NS
Median time in years to diagnosis of coeliac disease after diabetes diagnosis (range)	3.0 (0.1–14.3)	2.1 (0.1–10)	0.7 (0.2–3.8)	< 0.001
Diagnosed with coeliac disease within 2 years of diabetes (%)	33	48	75	< 0.01
Incidence of coeliac disease per 1000 person years (95% CI)	10.4 (8.2–13.0)	6.5 (4.7–8.8)	6.4 (4.9–8.2)	< 0.01*

*< 5 years vs. ≥ 5 years.
NS, not significant.

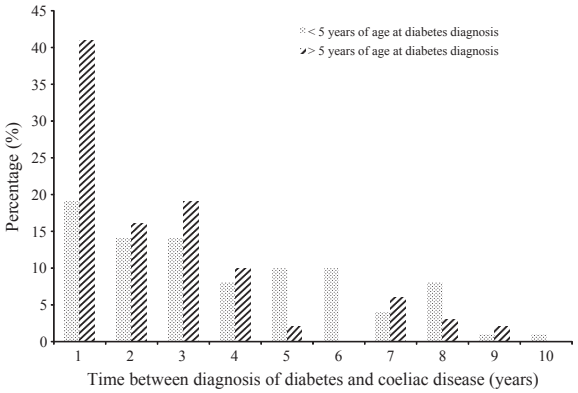

FIGURE 1 Proportion of young people diagnosed with coeliac disease within each year following diabetes diagnosis, stratified by age at diabetes diagnosis; χ^2 = 41.4 (d.f. 9), P < 0.001.

≥ 10 years (Table 1). In a Finnish birth cohort study of children at genetic risk of Type 1 diabetes, 3/51 (6%) of young children who developed Type 1 diabetes also developed coeliac disease [19]. While the sample size is small, the contemporaneous diagnosis of both conditions may reflect the high background risk of the population studied, although it is likely that additional cases of coeliac disease will be diagnosed over time. In contrast, the temporal association between onset of Type 1 diabetes and coeliac disease in children aged ≥ 10 years in our population may reflect the more gradual preclinical onset of both diseases in older children.

The 7.1% prevalence of coeliac disease indicates a substantial burden of disease in our diabetes population. In a multi-centre study from Germany and Austria, there was an increasing prevalence of coeliac disease over time, which coincided with a marked increase in screening. However, the prevalence was relatively low (1.2%), suggesting under-ascertainment of cases. In contrast, we found no difference in coeliac disease incidence over the two decades, in parallel with an unchanged rate of coeliac disease screening.

The rationale for early detection and treatment of coeliac disease in asymptomatic children with Type 1 diabetes is improved health outcomes following introduction of a gluten-free diet, as demonstrated in two recent longitudinal studies [20,21]. Clinical improvements in weight z-scores, haemoglobin and serum ferritin were observed in those compliant with a gluten-free diet [21]. In contrast, non-compliance was associated with lower total bone mineral density, lower volumetric lumbar spine z-score, higher bone turnover, lower vitamin D and lower ferritin [20]. These findings support routine coeliac disease screening in young people with Type 1 diabetes and highlight the importance of adherence to a gluten-free diet to prevent complications of untreated coeliac disease. The higher risk of coeliac disease at the time of diagnosis of Type 1 diabetes in the older children in our cohort emphasizes the importance of timely diagnosis, education and initiation of the gluten-free diet to maximize the adolescent's growth and bone mineral density, particularly as preclinical coeliac disease may have been present prior to diabetes diagnosis.

Potential limitations of our study include its observational design; however, data were collected prospectively in our hospital database. While cases are from one centre, the sample is population-based for Western Sydney. Furthermore, because the majority of children with diabetes are managed through tertiary referral diabetes centres, the study population represents more than half of young people with diabetes in New South Wales. The change in screening assay from endomysial to tissue transglutaminase IgA antibodies may have influenced case ascertainment; however, the consistent frequency of screening and unchanged incidence both over time and across screening assays argue against increased detection in recent years. Finally, those diagnosed with diabetes in recent years have shorter duration of follow-up, but the majority were followed for longer than 2 years.

Coeliac disease was diagnosed within the first 5 years of diabetes for most children (78%); but the proportion was lower among those aged < 5 years at diabetes diagnosis (64%). The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines [5] advocate screening at diagnosis in all children with Type 1 diabetes; our findings support this recommendation. The guidelines further recommend repeat annual screening for the first 5 years after diagnosis and second yearly thereafter; our data demonstrate ongoing screening of

younger children is required for at least 10 years, as they are more likely to seroconvert. Our findings also indicate that the yield from annual screening is low beyond 5 years of diabetes duration in older children. However, children with symptoms suggestive of coeliac disease should be screened irrespective of diabetes duration [5].

Competing interests

Nothing to declare.

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CHAPTER 4: SCREENING FOR CELIAC DISEASE IN TYPE 1 DIABETES: A SYSTEMATIC REVIEW

Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME, *Pediatrics,* 136:1, e170-176 (2015)

SYNOPSIS

This chapter presents a manuscript that builds on the findings of Chapter 3, which highlighted the importance of regular screening. Chapter 4 answers the research question associated with hypothesis 2 that published guidelines on the frequency of screening for coeliac disease in type 1 diabetes are varied and not evidence based. Key findings of this study were that the highest yield of CD cases was within 1, 2 and 5 years of diabetes duration, at 40%, 55% and 79% respectively, and thus screening should be considered at diagnosis, and within 2 and 5 years thereafter. Another key finding of this paper was that 85% of CD cases were asymptomatic at the time of CD diagnosis. Although the merits of early diagnosis may be argued, we demonstrate in Chapter 5 the benefits of GFD adherence on reducing the risk of complications, and further examine the impact of the coexistence of both conditions on QoL in chapter 6, glycaemic variability in chapter 7 and bone health in chapter 8.

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Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review

Anna Pham-Short, Kim C. Donaghue, Geoffrey Ambler, Helen Phelan, Stephen Twigg and Maria E. Craig

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Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review

Anna Pham-Short, BSc(Nutr)(Hons-I), GCDEM[a,b], Kim C. Donaghue, MBBS, PhD, FRACP[a,b], Geoffrey Ambler, MBBS, MD, FRACP[a,b], Helen Phelan, RN, BA, MPH[c], Stephen Twigg, MBBS Hons-I, PhD, FRACP[b,d], Maria E. Craig, MBBS, PhD, FRACP, MMed(ClinEpi)[a,b,e]

abstract

BACKGROUND AND OBJECTIVES: Prevalence rates of type 1 diabetes (T1D) and celiac disease (CD) vary from 1.6% to 16.4% worldwide. Screening guidelines are variable and not evidence based. Our aim was to conduct a systematic review of CD in T1D.

METHODS: Medline, Embase, and the Cochrane Library were searched. Studies were limited to those in English and in humans. We selected longitudinal cohort studies screening for CD in T1D with at least 5 years of follow-up. Screening rates, characteristics, and prevalence of biopsy-proven CD in people with T1D were extracted.

RESULTS: We identified 457 nonduplicate citations; 48 were selected for full-text review. Nine longitudinal cohort studies in 11 157 children and adolescents with 587 cases of biopsy-proven CD met the inclusion criteria. Median follow-up was 10 years (range: 5–18 years). The weighted pooled prevalence of CD was 5.1% (95% confidence interval: 3.1–7.4%). After excluding 41 cases with CD onset before T1D, CD was diagnosed in 218 of 546 (40%) subjects within 1 year, in 55% within 2 years, and in 79% within 5 years of diabetes duration. Two studies (478 cases) reported higher rates of CD in children aged <5 years at T1D diagnosis. The duration of follow-up varied across the included studies. CD screening frequency progressively decreased with increased T1D duration.

CONCLUSIONS: Because most cases of CD are diagnosed within 5 years of T1D diagnosis, screening should be considered at T1D diagnosis and within 2 and 5 years thereafter. CD screening should be considered at other times in patients with symptoms suggestive of CD. More research is required to determine the screening frequency beyond 5 years of diabetes duration.

[a]*Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia;* [b]*Discipline of Pediatrics and Child Health, University of Sydney, Sydney, Australia;* [c]*John Hunter Hospital, Newcastle, Australia;* [d]*Royal Prince Alfred Hospital and Charles Perkins Centre, Sydney Medical School, University of Sydney, Sydney, Australia; and* [e]*School of Women's and Child's Health, University of New South Wales, Sydney, Australia*

Ms Pham-Short designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Donaghue, Ambler, Twigg, and Craig designed the study and reviewed and revised the manuscript; Ms Phelan designed the study, carried out the initial analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Maria E. Craig, MBBS, PhD, FRACP, MMed(ClinEpi), Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. E-mail: m.craig@unsw.edu.au or maria.craig@health.nsw.gov.au

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The association between type 1 diabetes (T1D) and celiac disease (CD) is well documented in young people, although reported rates vary. Prevalence rates from both cross-sectional and longitudinal studies range from 1.6% to 16.4% worldwide,[1–5] with the majority of studies only including children and adolescents. In contrast, CD prevalence is 0.3% to 1.0% in the general population of all ages.[6] A greater risk is conferred by female gender,[1,7] younger age, and, in type 1 diabetes, younger age at diabetes diagnosis.[7,8]

Recognized adverse effects of untreated CD include iron deficiency, anemia, growth retardation, and osteoporosis.[9] In T1D, undiagnosed CD may be associated with unstable blood glucose levels, a greater risk of hypoglycemia,[10] and increased risk of retinopathy.[11] In those with confirmed CD and T1D, nonadherence to a gluten-free diet (GFD) is associated with early elevation of albumin excretion rate,[12] whereas CD duration >10 years, irrespective of GFD adherence, is a risk factor for the development of diabetic retinopathy.[13] Other clinical improvements associated with GFD compliance, including weight *z* scores, hemoglobin, and serum ferritin, have been reported,[14] as well as height *z* scores and the reversal of iron-deficiency anemia.[15] In contrast, noncompliance with a GFD was associated with lower total bone mineral density, lower volumetric lumbar spine *z* score, higher bone turnover, lower vitamin D, and lower ferritin.[16] The rationale for CD screening is to prevent these adverse effects and complications, and to maximize growth. Because seroconversion from negative to positive CD autoantibodies can occur beyond 10 years of diabetes duration,[17] repeated screening for CD is necessary.

Despite the well-recognized increased risk of CD in T1D and the potential for increased morbidity, there are no systematic reviews examining the incidence of CD or optimal screening frequency for CD in T1D. Contemporary guidelines for T1D recommend screening by measurement of tissue transglutaminase (TTG) or anti-endomysial antibodies (EMAs).[18–20] Recommendations for screening frequency are variable and not evidence based. The International Society for Pediatric and Adolescent Diabetes recommends screening at the time of diagnosis and every 1 to 2 years thereafter, with more frequent assessment if clinically indicated or if there is a first-degree relative with CD,[18] whereas the American Diabetes Association recommends considering CD screening soon after diabetes diagnosis and in those with clinical symptoms suggestive of CD.[20] In view of these variable recommendations, we systematically reviewed the epidemiology of CD in people with T1D to inform screening guidelines.

METHODS

Study Aims

There are 2 specific aims of this review. First, we systematically reviewed the epidemiology of biopsy-proven CD in people with T1D, with subgroup analysis by age, gender, and duration of diabetes. Our second specific aim was to examine the risk of CD in people with T1D, at diagnosis and at specific time intervals after diagnosis, to determine the optimal frequency of screening.

Study Selection

Inclusion criteria were longitudinal cohort studies that screened for CD by using either EMAs and/or TTG in children, adolescents, or adults with T1D at least twice. Only studies in humans and reported in the English language were included. Exclusion criteria were studies other than longitudinal cohort studies, not in individuals with T1D, and no reports of screening frequency. The diagnosis of T1D was based American Diabetes Association criteria,[21] and CD was confirmed by small bowel biopsy.

Data Sources and Searches

Two reviewers (A.P.-S. and H.P.) independently searched Medline, Embase, and the Cochrane Library from 1946 to November 30, 2014, for studies of celiac autoimmunity and biopsy-proven CD in people with T1D. Search terms were as follows: "Diabetes Mellitus, type 1/or diabetes mellitus, type 1.mp," "celiac disease or celiac disease.mp," "celiac sprue or celiac sprue.mp," "celiacs or coeliacs.mp," "silent celiac or silent celiac.mp," "asymptomatic celiac or asymptomatic celiac.mp," "subclinical celiac or subclinical celiac.mp," "gluten sensitive enteropathy.mp or exp celiac disease," "reticulin.mp or exp Reticulin," "gliadin.mp or exp Gliadin," "endomysial or endomysium.mp," "tissue transglutaminase.mp," "antireticulin.mp," "antigliadin.mp," "antiendomysial.mp," and "antiendomysium.mp." We also performed manual searches through article reference lists.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from the included studies. For each individual study, data were collected regarding study design, country, population and size, duration of follow-up, age at CD diagnosis, age at diabetes diagnosis, gender, diagnostic test(s) performed, frequency of screening, small bowel biopsy results, and prevalence rates. Reports of CD-related symptoms around the time of CD diagnosis were also collated. Study quality was assessed by using the Newcastle-Ottawa quality assessment scale for cohort studies.[22] This scale evaluates 3 areas, selection, comparability (confounding factors), and outcome (assessor blinding and follow-up), giving a possible total score of 9, with

a score of >7 indicating good methodologic quality. Corresponding authors of included studies were contacted to request additional data when applicable.

Data Synthesis and Analysis

Meta-analysis of prevalence rates for CD was conducted by using a quality-effects model, which takes into account differences in study quality in the estimation of weighted pooled prevalence.[23] Incidence density, which provides an estimate of incident cases of CD during a specified time period, was calculated as the total number of diagnosed cases divided by the number of patients screened during follow up (n = 4839, 8789, and 20 299 at 1, 2, and 5 years, respectively). Incidence is reported per 1000 patient-years, with 95% confidence intervals estimated assuming a Poisson distribution. Statistical analyses were performed by using Stata, version 13 (StataCorp, College Station, TS), and meta-analysis of prevalence was conducted by using MetaXL (Epigear, Brisbane Australia).[23]

RESULTS

The initial search returned a total of 605 citations. After review of abstracts and full texts, 596 studies were excluded (Fig 1), leaving 9 cohort studies that met the inclusion criteria.[1,7,8,17,24–28] The studies were from Europe (n = 7) and Australia (n = 2). Study characteristics are summarized in Table 1. They included a total of 11 157 young people diagnosed with T1D ≤21 years of age (range: 0.6–21.0 years). The overall methodologic quality of the studies was fair, with 4 of 9 studies (44%) scoring ≥7 on the Newcastle-Ottawa Scale.[8,24,26,27] No adult studies were identified. There were a total of 587 cases of coexisting biopsy-proven CD and T1D, and of these, 41 were diagnosed before T1D. Median follow-up after diabetes diagnosis was 10 years (range: 5–18 years).

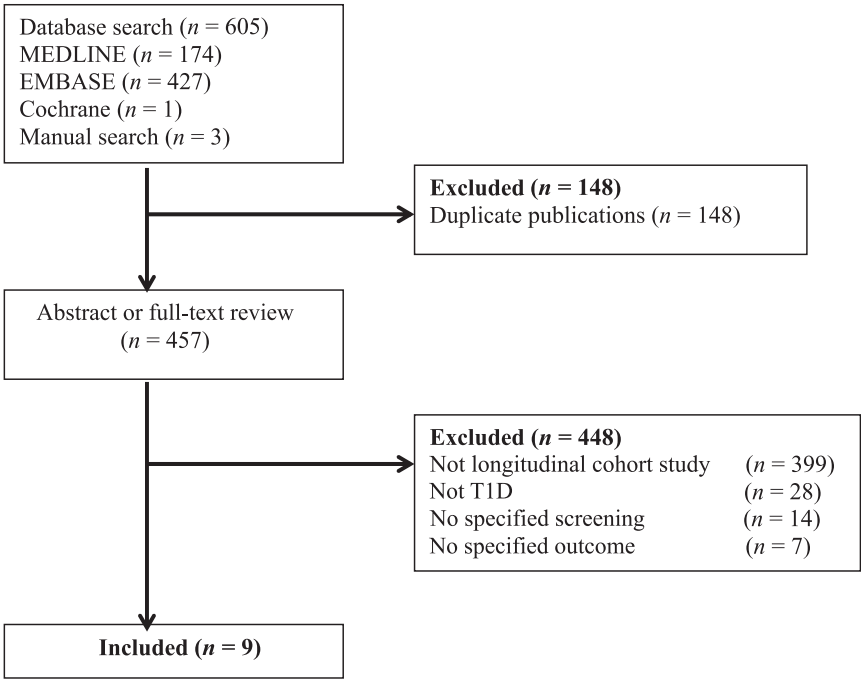

FIGURE 1
Flowchart showing the number of citations retrieved by individual searches and number of studies included in the review.

Definition of T1D

Three studies provided a definition of T1D[8,17,28] or reported the presence of islet autoantibodies.[8,17]

Prevalence of Biopsy-Proven CD

Prevalence was reported by all studies and varied from 1.6% to 9.7% (Fig 2). CD was reported in 587 of 11 157 children and adolescents with T1D; a meta-analysis of prevalence using the quality-effects model was 5.1% (95% confidence interval: 3.1–7.4%). CD was diagnosed in 41 cases before diabetes diagnosis (7% of all CD cases), and these cases were excluded from further analysis.

Incidence and Incidence Density

Two Australian studies[8,17] reported the incidence of biopsy-proven CD per 1000 person-years, with similar rates: 7.2 (1990–1996)[17] and 7.7 (1990–2009).[8] For 6 studies,[7,8,24–27] the number of patients screened per year of diabetes duration was available, enabling incidence density to be calculated (Table 2). Incidence density was 43.4 per 1000 patient-years at 1 year, 32.8 at 2 years, and 20.1 at 5 years (Table 3). This finding indicates that the rate of CD was highest within the first year after diagnosis of T1D. The incidence density rates decreased significantly between the 3 time points: year 2 compared with year 1 (P = .002) and year 5 compared with year 2 (P < .001).

Seroconversion

Five studies reported seroconversion to positive EMAs and/or TTG after diabetes diagnosis[1,17,24,25,27]; time to seroconversion ranged from 2 years[1] to 10.2 years.[17] The other 4 studies reported time between CD and T1D diagnosis, without providing information on seroconversion.

Association Between CD, Gender, and Age

Seven studies reported CD prevalence by gender,[1,7,8,17,25,26,28] and of these, the prevalence was higher in girls in 2 studies (67% and 61%),[1,7] higher in boys in 3 studies (range: 64–69%),[25,26,28] and not different in

TABLE 1 Characteristics of Included Studies Screening for CD in T1D

First Author, Year	Country	Study Design	Number Screened	CD Prevalence, %	Follow-up, y	Age at CD Diagnosis,[a] y	Age at Diabetes Diagnosis, y	Screening Test	Screening Frequency	Newcastle-Ottowa Scale
Barera, 2002[24]	Italy	Prospective	274	6.2	6	NR	8.3 ± 4.6	EMA IgA; if IgA deficient, IgG EMAs and AGAs	At diagnosis and annually	7
Cerutti, 2004[7]	Italy	Retrospective	4322	6.8	10	7.2 ± 4.3	5.5 ± 3.7	IgA/IgG AGAs and/or EMAs	Annually	6
Crone, 2003[25]	Austria	Longitudinal	157	5.1	8	NR	NR	EMAs	2–3 times yearly	5
Glastras, 2005[17]	Australia	Prospective	173	4.6	13	NR	NR	EMAs and/or AGAs	At diagnosis, 1–3 times yearly thereafter	6
Larsson, 2008[26]	Sweden	Prospective	300	9.7	5	11.1	6.5	IgA EMAs	At diagnosis, then annually	8
Pham-Short, 2012[8]	Australia	Prospective	4379	4.2	≥10	9.6 ± 3.7	6.6 ± 4.0	IgA EMAs and/or IgA TTG	At diagnosis 1–2 times yearly thereafter	8
Poulain, 2007[1]	France	Retrospective	950	1.6	>10	9.4 ± 4.8	6.0 ± 4.2	EMA and or TTG	NR	6
Salardi, 2008[27]	Italy	Prospective	331	6.6	18	NR	NR	EMA	At diagnosis and then every 6–12 mo	8
Uibo, 2010[28]	Estonia	Prospective	271	4.1	6	9.9 (range: 3.1–16.2)	NR	IgA EMA and IgA TTG	NR	6

AGA, anti-gliadin antibody; NR. not reported.
[a]Data are presented as means ± SDs or medians (range)NR not reported

2 studies[8,17] Six studies reported CD prevalence by age at diabetes diagnosis,[7,8,17,24,26,28] 2 studies reported an association between younger age (<5 years) at T1D diagnosis and development of CD,[7,8] with 1 study noting a tendency toward younger age at diabetes diagnosis, although the relationship was not statistically significant.[26]

Three studies reported no relationship with age at diabetes diagnosis.[17,24,28]

Association Between CD and Diabetes Duration

Of the 546 CD cases diagnosed after diabetes, 40% were within 1 year of diabetes, 55% within 2 years, and 79% within 5 years of diabetes diagnosis. The proportion of patients screened decreased from 50% at the end of year 1, to 35% ($P < .001$) at the end of year 5, and 12% at the end of year 10.

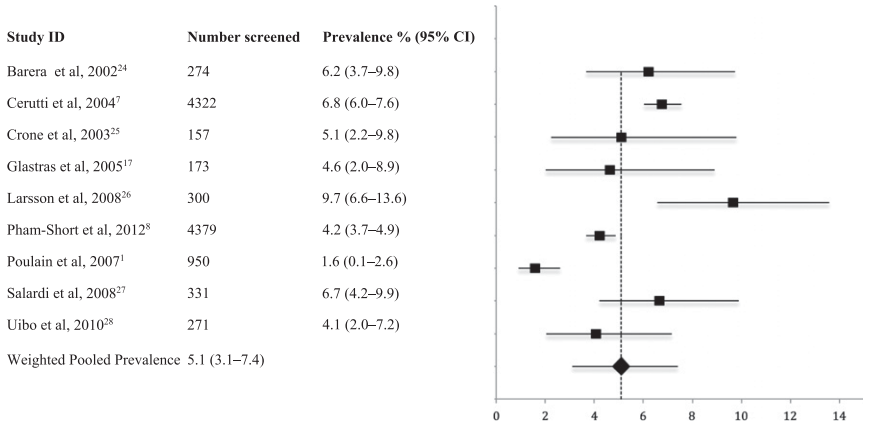

FIGURE 2
Prevalence of CD in T1D. The forest plot shows unadjusted prevalence estimates (boxes) and pooled prevalence (diamond) with 95% confidence intervals (bars).

Symptomatology

Five studies reported data on CD-related symptoms and signs (gastrointestinal, short stature, anemia, or asymptomatic; n = 308),[1,7,25,28,29] with 85% of cases asymptomatic at the time of CD diagnosis.

Recommendations for Screening

The majority of studies (7 of 9) recommended screening for CD at least once in people with T1D.[1,7,8,17,24–26] Four studies recommended screening at diabetes onset,[1,8,24,26] whereas follow-up screening recommendations were variable in frequency and duration, ranging from annually for at least 2 years[26] up to an unspecified duration of diabetes (described as several years).[1,17,24]

TABLE 2 Number of New CD Cases Diagnosed in Relation to T1D Duration

	Number	Proportion, %
Total CD cases in study	587	
Before diabetes diagnosis	41	7
Within 1 year of diabetes diagnosis	220	37
Within 1–2 years of diabetes diagnosis	78	13
2 to <5 years after diabetes diagnosis	135	24
5–10 years after diabetes diagnosis	89	15
More than 10 years after diabetes diagnosis	25	4

DISCUSSION

In this systematic review of 9 longitudinal cohort studies involving 11 157 children and adolescents with T1D, of whom 587 had biopsy-proven CD, the prevalence of CD varied from 1.6% to 9.7%, with a weighted pooled prevalence of 5.1%. Incidence density at 1, 2, and 5 years of diabetes duration was 43.4, 32.8, and 20.1 per 1000 patients-years, respectively, indicating that the risk of CD is highest within the first year of diabetes duration. Because 55% of cases were diagnosed within 2 years and 79% within 5 years of diabetes duration, screening should be considered at diabetes diagnosis and within 2 and 5 years after diagnosis. Because of limited evidence from long-term studies, it is not possible to recommend the screening frequency beyond 5 years of diabetes duration. However, among the studies with longer follow-up, 16% of CD cases were diagnosed between 5 and 10 years of diabetes duration and 5% were diagnosed after >10 years. CD should be considered at any time in patients with symptoms suggestive of CD.

Prevalence of CD in T1D

There was considerable variation in the prevalence of CD across the 9 included studies. Possible explanations for this heterogeneity include ethnic differences across the study populations, which is likely to reflect the greater risk of CD among individuals with high-risk HLA antigen genotypes,[30] as well as the varying impact of environmental influences across different countries.[31] Our finding of the highest prevalence rate in Sweden (9.7%) is in keeping with the The Environmental Determinants of Diabetes in the Young (TEDDY) study, which recently reported a higher risk of CD in Swedish children compared with those in the United States, Finland, and Germany.[31] The variation in prevalence rates may also be related to differences in study design, including retrospective versus prospective, the frequency of screening, and duration of follow-up. To address this issue, we chose to use a quality-effects model in the meta-analysis of prevalence,[23] which accounts for study quality in the estimation of pooled prevalence.

Clinical Importance of CD Screening in T1D

It is notable that 85% of cases presented asymptomatically in this review. Although the merits of early diagnosis may be argued,[32] especially in those with a milder disease phenotype,[33] compliance to a GFD in those with biopsy-proven CD may improve clinical variables such as weight and serum ferritin.[14] Improvements in quality of life and depression scores have been reported 1 year after CD diagnosis.[34] In contrast, nonadherence to a GFD has been associated with elevated albumin excretion rate,[12] lower bone mineral density, lower vitamin D, and lower ferritin[14] in youth with coexisting CD and T1D. These clinical and psychological improvements support routine CD screening in T1D and highlight the importance of adherence to a GFD to prevent complications of untreated CD.

TABLE 3 Pooled Incidence Density of CD in Young People With T1D

	Population Screened	Biopsy-Proven CD Cases	Incidence per 1000 Patient-Years (95% CI)
Year 1	4839	210	43.4 (37.8–49.5)
Year 2	8789	288	32.8 (29.2–36.7)
Year 5	20 299	407	20.1 (18.2–22.1)

Incidence was calculated from available data in 6 publications.[7,8,24–27] Year 2 versus year 1, $P = .002$; year 5 versus year 2, $P < .001$. CI, confidence interval.

Strengths and Weaknesses

This is the first systematic review, to our knowledge, to examine screening for CD in T1D to determine the optimal screening frequency. The strengths of this review are the large sample size and long observation period, providing representative data on the epidemiology in T1D across different countries. Our analysis is limited by the variable follow-up periods across the studies, as well as missing data on the number of patients screened throughout each year of diabetes duration. The frequency of antibody screening for CD progressively decreased with increased duration of diabetes, which is likely to have led to an underestimate of incidence and prevalence.

There are various factors associated with the systematic review process that may influence our findings. Although predetermined selection criteria were implemented to ensure an unbiased selection, we sought to minimize this bias by placing no limitations on the basis of age; however, the lack of adult studies identified may influence the generalizability of our results beyond the pediatric age range. Another potential weakness is that the populations of the included studies were predominantly of European descent, whereas no studies from other regions such as North America and the Middle East met the eligibility

criteria. The reduced screening frequency between years 2 and 5 coincided with reduced prevalence and incidence rates; however, we estimate that this would not have significantly influenced case detection rates had the screening rate been maintained at 50% between 2 and 5 years. Furthermore, some studies did not provide sufficient information to be able to calculate incidence density,[1,17,28] and thus our reported values are conservative.

Screening in Adults

No longitudinal adult studies examining the screening frequency of CD in T1D were identified. However, a retrospective study in 118 adults with T1D and CD[35] found that 48% of those diagnosed with T1D after age 18 years reported CD symptoms for >5 years before CD diagnosis, in contrast to the group whose diabetes was diagnosed in childhood, with a majority (59%) reporting CD-related symptoms for <6 months before CD diagnosis. Prospective studies are required in adults to determine the optimal frequency of screening.

Implications for Clinical Practice

On the basis of our systematic review of data from cohort studies, more than half of CD cases were diagnosed within 2 years of diabetes duration, with most cases diagnosed within the first 5 years after diabetes diagnosis. The contemporaneous diagnosis of both conditions most likely describes the diagnosis of preexisting CD not previously recognized and may reflect the high background risk of the population studied.[30] Although CD can be diagnosed beyond 10 years after diabetes diagnosis, more research is required to establish the optimal screening frequency beyond 5 years of diabetes duration as well as the optimal screening frequency in adults with T1D. The impact of gender, age at diabetes diagnosis, and diabetes duration on CD development is unclear. In patients with clinical symptoms such as growth failure, weight loss, and frequent unexplained hypoglycemia, or those with a first-degree relative with CD, screening for CD should be considered irrespective of diabetes duration.[18,36] Although not examined in this review, it should be noted that screening for immunoglobulin (Ig) A deficiency (prevalence: 1:500) is recommended in recent guidelines[18] due to the risk of a false-negative TTG result, and if present, then IgG-specific antibody tests (TTG or EMA IgG or both) should be performed.[18,19]

Future Directions

This systematic review shows an elevated risk of CD in people with T1D, particularly in the early course of disease. We were unable to examine the effect of gender and age at diabetes diagnosis on CD development, highlighting the need for prospective cohort studies beyond 5 years of diabetes duration as well as those that report on the impact of annual CD screening and with the inclusion of adults to further quantify the frequency of CD screening in T1D.

ABBREVIATIONS

CD: celiac disease
EMA: anti-endomysial antibody
GFD: gluten-free diet
Ig: immunoglobulin
T1D: type 1 diabetes
TTG: tissue transglutaminase

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Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review

Anna Pham-Short, Kim C. Donaghue, Geoffrey Ambler, Helen Phelan, Stephen Twigg and Maria E. Craig

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CHAPTER 5 EARLY ELEVATION OF ALBUMIN EXCRETION RATE IS ASSOCIATED WITH POOR GLUTEN FREE DIET ADHERENCE IN YOUNG PEOPLE WITH COELIAC DISEASE AND DIABETES

Pham-Short A, Donaghue KC, Ambler G, Chan AK, Hing S, Cusumano J, Craig ME, *Diabetic Medicine* 2014 Feb; 31(2):208-212. Epub Oct 2013

SYNOPSIS

The following chapters (5,6,7 and 8) present manuscripts which examined the clinical impact of coexisting T1D and CD. This chapter presents a manuscript that reports the diabetes related microvascular complications rates in youth with or without CD and examines the association between GFD and complications. The primary hypothesis for this study (Hypothesis 3) was young people with type 1 diabetes and coeliac disease, who do not adhere to the gluten free diet, have higher complications rates, independent of glycaemic control, compared with those who adhere. Key findings include non-adherence to the GFD, as measured by serological markers and confirmed by dietary assessement and is associated with early elevation of albumin excretion rates, a sign of early kidney disease. The dual diagnosis of T1D and CD and its effects on other aspects of health such as psychological wellbeing, glycaemic variability, nutrient intake and bone health are further examined in chapters 6, 7 and 8.

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Short Report: Complications

Early elevation of albumin excretion rate is associated with poor gluten-free diet adherence in young people with coeliac disease and diabetes

A. Pham-Short[1,2], K. C. Donaghue[1,2], G. Ambler[1,2], A. K. Chan[1], S. Hing[3], J. Cusumano[1] and M. E. Craig[1,2,4]

[1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Westmead, [2]Discipline of Paediatrics and Child Health, University of Sydney, Sydney, [3]Ophthalmology Department, The Children's Hospital at Westmead, Westmead and [4]School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia

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Abstract

Aims There are conflicting data on microvascular complications in coexisting Type 1 diabetes and coeliac disease. We compared complications rates in youth with or without coeliac disease and examined the association between gluten-free diet adherence and complications.

Methods This was a comparative study of adolescents (2510 without coeliac disease, 129 with coeliac disease); 60 (47%) did not adhere to a gluten-free diet—defined as elevated anti-tissue transglutaminase or endomysial immunoglobulin A titres. Retinopathy was detected using 7-field fundal photography and albumin excretion rate by timed overnight urine collections, with early elevation defined as albumin excretion rate ≥ 7.5 μg/min. Logistic regression was used to examine the association between complications and explanatory variables, including coeliac disease vs. no coeliac disease, gluten-free diet adherence vs. non-adherence, diabetes duration and HbA_{1c}.

Results Median age at last assessment was 16.5 years. Those with coeliac disease vs. those without were younger at diabetes diagnosis (7.1 vs. 8.6 years, $P < 0.001$) and had longer diabetes duration (9.3 vs. 7.2 years, $P < 0.001$). HbA_{1c} was lower in those with coeliac disease vs. those without (67 vs. 70 mmol/mol, 8.3 vs. 8.6%, $P = 0.04$) and adherence to a gluten-free diet vs. non-adherence (66 vs. 72 mmol/mol, 8.2 vs. 8.7%, $P = 0.003$). There were no differences in complication rates between those with coeliac disease vs. those without (retinopathy 22 vs. 23%, elevated albumin excretion rate 31 vs. 28%). Non-adherence to a gluten-free diet was associated with elevated albumin excretion rate (40 vs. 23%, $P = 0.04$). In multivariable logistic regression, elevated albumin excretion rate was associated with non-adherence to a gluten-free diet (odds ratio 2.37, 95% CI 1.04–5.40, $P = 0.04$) and diabetes duration (odds ratio 1.13, 95% CI 1.02–1.25, $P = 0.03$), but not HbA_{1c}.

Conclusions While glycaemic control is better in patients with coeliac disease, non-adherence to a gluten-free diet is associated with elevated albumin excretion rate. The possible protection of a gluten-free diet on complications warrants further investigation.

Diabet. Med. 31, 208–212 (2014)

Introduction

There are conflicting data on the risk of microvascular complications among individuals with both Type 1 diabetes and coeliac disease [1–3]. While coexisting coeliac disease is associated with an increased risk of retinopathy in undetected coeliac disease [3] and vascular disease [3,4], several studies have shown a reduced risk of nephropathy and retinopathy following diagnosis of coeliac disease and gluten-free diet commencement [1–3]. The risk factors are likely to be multifactorial, although glycaemic control has not consistently been associated with complications risk in coeliac disease. Furthermore, the effect of long-term gluten-free diet adherence on complications risk has not been examined. We hypothesized that young people with Type 1 diabetes, coeliac disease and poor adherence to a gluten-free diet would have higher complications rates, independent of glycaemic control.

Correspondence to: Maria Craig.
E-mail: m.craig@unsw.edu.au; maria.craig@health.nsw.gov.au

What's new?

- There are no studies investigating the effect of gluten-free diet non-adherence in young people with Type 1 diabetes and coeliac disease.
- This is the first study in young people with Type 1 diabetes with or without coeliac disease, examining the influence of gluten-free diet adherence on complications rates.
- We report data on 2639 young people with Type 1 diabetes, of whom 129 had coeliac disease. While glycaemic control was better in those with coeliac disease, non-adherence to a gluten-free diet was associated with early elevation of albumin excretion rate, a recognized risk factor for diabetic nephropathy.
- Our findings support the need for coeliac disease screening and adherence to a gluten-free diet in those with coeliac disease.

Patients and methods

This was a comparative study of 2510 young people with Type 1 diabetes without coeliac disease and 129 with coeliac disease aged < 20 years at their most recent visit to the Diabetes Complications Assessment Service from 1990 to 2010. Type 1 diabetes was diagnosed by clinical criteria and the presence of islet antibodies [insulin, glutamic acid decarboxylase (GAD) and islet antigen 2 (IA-2)], as previously described [5]. Coeliac disease was diagnosed by positive coeliac serology, either endomysial immunoglobulin A (IgA) or anti-tissue transglutaminase IgA antibodies, and confirmed by small bowel biopsy [6]. For those with coeliac disease, a gluten-free diet was defined as endomysial or tissue transglutaminase autoantibodies within the normal range at the complications assessment and non-adherence to a gluten-free diet defined as elevated endomysial or tissue transglutaminase autoantibodies. The study was approved by the Sydney Children's Hospital Network Ethics Committee.

Complications assessment

At their most recent visit, participants were assessed using our established complications screening methods [7–10], including clinical examination, anthropometry, 7-field stereoscopic fundal photography for retinopathy, timed overnight urine collections for measurement of albumin excretion rate, quantitative sensory methods (thermal threshold and vibration perception at the foot) for peripheral neuropathy and pupillometry for autonomic neuropathy. Early elevation of albumin excretion rate was defined as ≥ 7.5 μg/min, which we have shown predicts subsequent development of persistent microalbuminuria [7]. HbA_{1c} was assessed by high-performance liquid chromatography (Diamat BioRad, Hercules, CA, USA; non-diabetic range 4–6%). Endomysial or tissue transglutaminase were performed at all study visits.

Statistical analysis

Cases of coeliac disease were stratified as adherence or non-adherence to a gluten-free diet for analysis. Continuous variables were compared between groups using analysis of variance and categorical variables using χ^2-tests (Table 1). Binary logistic regression was used to examine the association between complication outcomes (presence or absence of early retinopathy, early elevation of albumin excretion rate or peripheral nerve abnormalities) and explanatory variables, including adherence to a gluten-free diet vs. non-adherence, age, most recent HbA_{1c} measurement, gender, BMI standard deviation score (SDS), insulin per kg per day and use of continuous subcutaneous insulin infusion therapy. Clinically relevant interaction terms, such as HbA_{1c} × non-adherence to a gluten-free diet, were examined in multivariable models. Analyses were performed using SPSS, version 20 (SPSS Inc., Chicago, IL, USA).

Results

Overall, 129/2639 (4.9%) had coeliac disease, with a median coeliac disease duration of 5.6 years. Comparing patients with coeliac disease and those without, there was no difference in current age, but those with coeliac disease were significantly younger at diabetes diagnosis and therefore had longer diabetes duration (Table 1). HbA_{1c} was lower in those with coeliac disease and more patients with coeliac disease used continuous subcutaneous insulin infusion (Table 1). There was some evidence for a higher total daily insulin dose per kg body weight in those with coeliac disease, but this did not reach statistical significance. There were no differences in anthropometry, total cholesterol or complications rates in those individuals without coeliac disease vs. those with coeliac disease. When patients with coeliac disease were matched for age, diabetes duration and HbA_{1c} with those without coeliac disease (2:1), complications rates did not differ between the two groups (data not shown).

Adolescents adhering to a gluten-free diet had significantly better glycaemic control vs. non-adherence at the most recent visit and over the preceding 12 months (Table 1). Despite this, reported total daily insulin dose was higher in those without a gluten-free diet. There were no differences in current age, gender, diabetes duration or coeliac disease duration between adherence to a gluten-free diet and non-adherence (Table 1). There was a high correlation between gluten-free diet adherence status (adherence or non-adherence) at the last visit and at previous complications assessments (data not shown).

The frequency of early elevation of albumin excretion rate was significantly higher in non-adherence vs. adherence to a gluten-free diet. In multivariable logistic regression, elevated

Table 1 Characteristics and complication rates in young people with Type 1 diabetes, stratified by (1) coexisting coeliac disease and (2) gluten-free diet adherence

n	Type 1 diabetes 2510	Type 1 diabetes + coeliac disease 129	*P*	Gluten-free diet, adherent 69	Gluten-free diet, non-adherent 60	*P*
Age at diabetes diagnosis (years)	8.6 (5.3–11.4)	7.1 (2.9–10.0)	< 0.001	6.7 (2.9–9.6)	7.3 (2.8–1.0)	0.48
Current age (years)	16.5 (14.8–17.9)	16.1 (14.3–17.8)	0.13	15.8 (14.4–17.8)	16.4 (14.3–17.9)	0.43
Diabetes duration (years)	7.2 (4.9–10.4)	9.3 (6.3–12.2)	< 0.001	9.2 (6.60–12.22)	9.4 (6.3–12.3)	0.81
Coeliac disease duration (years)	—	6.6 (3.0–10.3)		6.2 (3.1–9.6)	6.7 (2.8–11.5)	0.54
Male gender (%)	1206/2510 (48%)	55/129 (43%)	0.24	26/69 (38%)	29/60 (48%)	0.22
HbA_{1c} (mmol/mol)	70 (61–81)	67 (60–78)	0.04	66 (60–75)	72 (62–86)	0.003
HbA_{1c} (%)	8.6 (7.7–9.6)	8.3 (7.6–9.3)	0.04	8.2 (7.6–9.0)	8.7 (7.8-10.0)	0.003
Mean HbA_{1c} over last 12 months (%)	70 (62–81)	67 (62–79)	0.08	66 (62–73)	73 (62–8.6)	0.009
Mean HbA_{1c} over last 12 months (mmol/mol)	8.6 (7.8–9.6)	8.3 (7.8–9.4)	0.08	8.2 (7.8–8.8)	8.8 (7.8–10.0)	0.009
HbA_{1c} > 75 mmol/mol (9.0%)	927/2447 (38%)	33/127 (26%)	0.025	10/69 (14%)	23/58 (40%)	0.002
Insulin pump therapy	322/2468 (13%)	25/126 (20%)	0.04	15/68 (22%)	10/58 (17%)	0.50
Height SDS	0.23 (–0.45 to 0.90)	0.20 (–0.58 to 0.85)	0.28	0.75 (–0.60 to 0.72)	0.29 (–0.58 to 1.00)	0.51
Weight SDS	0.78 (0.17–1.26)	0.75 (0.15–1.22)	0.86	0.59 (0.13–1.13)	0.95 (0.22–1.33)	0.39
BMI SDS	0.70 (0.15–1.20)	0.81 (0.16–1.26)	0.59	0.61 (0.06–1.10)	1.00 (0.28–1.30)	0.61
Cholesterol (mmol/l)	4.3 (3.8–5.0)	4.4 (3.8–5.0)	0.54	4.20 (3.70–5.00)	4.45 (3.93–5.1)	0.08
Insulin dose (unit kg^{-1} day^{-1})	1.05 (0.87–1.28)	1.08 (0.91–1.34)	0.08	1.03 (0.88–1.27)	1.15 (0.99–1.46)	0.002
Albumin excretion rate ≥ 7.5 μg/min	600/2118 (28%)	36/117 (31%)	0.60	15/65 (23%)	21/52 (40%)	0.04
Peripheral nerve abnormality	627/2425 (26%)	36/128 (28%)	0.61	17/68 (25%)	19/60 (32%)	0.40
Retinopathy	556/2381 (23%)	27/125 (22%)	0.75	12/67 (18%)	15/58 (26%)	0.38
Pupillary abnormality	1020/1771 (58%)	63/105 (60%)	0.69	32/55 (58%)	31/50 (62%)	0.69

Data are number (%) or median (interquartile range).
SDS, standard deviation score.

albumin excretion rate was associated with non-adherence to a gluten-free diet (odds ratio 2.37, 95% CI 1.04–5.40, $P = 0.039$) and diabetes duration (odds ratio 1.13, 95% CI 1.02–1.25, $P = 0.026$). HbA_{1c} was not significant in univariate analysis (odds ratio 1.24, 95% CI 0.96–1.61, $P = 0.1$) or in the multivariable model. The interaction between HbA_{1c} and non-adherence to a gluten-free diet was also not significant ($P = 0.13$). Non-adherence to a gluten-free diet was not associated with higher rates of other microvascular complications. When the subgroup of gluten-free diet adherence were compared with those without coeliac disease, there was no difference in the rate of early elevation of albumin excretion rate ($P = 0.36$).

Discussion

The burden of coexisting Type 1 diabetes and coeliac disease may be expected to result in worse glycaemic control, conferring a greater risk of complications. However, in our study of 2639 young people with Type 1 diabetes, glycaemic control was actually better in the 129 individuals with coeliac disease, despite younger age at diabetes onset and longer diabetes duration. Reassuringly, coeliac disease was not associated with higher rates of any microvascular complications, lower height SDS [11–13] or adverse lipid profiles. There was a higher rate of continuous subcutaneous insulin infusion use in those with coeliac disease, which may have contributed to better glycaemic control and may assist in management of both diseases, although this was not explored in the present study.

This is the first study in young people with coexisting Type 1 diabetes and coeliac disease to compare complication rates stratified by gluten-free diet adherence. We found early evidence of renal disease associated with non-adherence vs. adherence to a gluten-free diet. Conversely, a case–control study (matched for age, sex, duration and

HbA_{1c}) found albumin:creatinine ratio was lower in those with coeliac disease vs. those without coeliac disease [1], those with coeliac disease had negative tissue transglutaminase antibodies, indicating a gluten-free diet. However, there was no comparison group of those non-adherent to the gluten free diet. The authors speculated that this lower albumin:creatinine ratio was attributable to consumption of less high-temperature processed foods in the gluten-free diet, demonstrated by lower plasma advanced glycation end-product fluorescence in coeliac disease vs. no coeliac disease-. Whilst we did not assess dietary intake, we speculate our patients not adhering to a gluten-free diet (as demonstrated by the patients' elevated antibodies) may have consumed more highly processed gluten-containing foods, along with higher salt and high-fat intake. Whilst we did not measure inflammatory markers, non-adherence to a gluten-free diet may be associated with chronic low-grade inflammation, which may also play a role in early elevation of albumin excretion rate. Collectively, these data support further investigation of dietary factors, including advanced glycation end-products on complications risk, particularly in coeliac disease.

In adults, only a few studies have examined the impact of coeliac disease on microvascular complications [2–4] and none investigated the role of gluten-free diet non-adherence beyond 1 year of coeliac disease duration. Whilst undetected coeliac disease was associated with higher nephropathy prevalence [3], 1 year of gluten-free diet adherence resulted in a reduction in estimated glomerular filtration rate (eGFR). A large Swedish study found coeliac disease duration > 10 years was a risk factor for retinopathy [4]; however, neither gluten-free diet adherence nor glycaemic control were examined. An Italian study showed the combination of Type 1 diabetes and coeliac disease was associated with severe subclinical atherosclerosis than either condition alone [14], independent of glycaemic control, disease duration, lipid and anthropometric parameters. Similarly, glycaemic control was not associated with early elevation of albumin excretion rate in our patients with coeliac disease, suggesting the risk of albumin excretion rate in coeliac disease is multifactorial, including diet, inflammation, blood pressure and genetic predisposition [17].

Potential limitations of our study include the use of cross-sectional analysis, which cannot determine causality, however, we elected to analyse data at the last study visit to enable the longest diabetes and coeliac disease duration to be included in the analysis. The singular tissue transglutaminase measurement as a marker of gluten free diet adherence may not reflect the general adherence to the gluten-free diet over time; however, gluten free diet adherence status was consistent with previous visits in the majority of cases.

In summary, we have demonstrated that gluten free diet non-adherence is associated with early elevation of albumin excretion rate, which is a recognized risk factor for future development of microalbuminuria in Type 1 diabetes [7,15–17]. While the role of poor glycaemic control on microvascular complications development is well established, non-adherence to a gluten-free diet was associated with albumin excretion rate, independent of HbA_{1c}. Our findings support the need for adherence to the gluten-free diet in people with coeliac disease and regular dietetic review to ensure adequate dietary education. They also provide further rationale for coeliac disease screening in Type 1 diabetes [8,18,19].

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Competing interests

None declared.

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CHAPTER 6 QUALITY OF LIFE IN TYPE 1 DIABETES AND CELIAC DISEASE: ROLE OF THE GLUTEN-FREE DIET

Pham-Short A, Donaghue KC, Ambler G, Garnett S, Craig ME, *The Journal of Pediatrics,* 179: 131-8 (2016)

SYNOPSIS

Chapter 5 demonstrated that GFD non-adherence was associated with early signs of renal disease, which suggests that those who struggle with the coexistence of two chronic conditions are at higher risk of complications. However, there is a paucity of data on the impact of living with both conditions on QoL and general well-being. This chapter presents a manuscript that helps fill this knowledge gap. Chapter 6 answers the research question associated with hypothesis 4 that quality of life scores are lower (a) in youth with type 1 diabetes and coeliac disease compared with type 1 diabetes only, and (b) in those who do not adhere to the gluten-free diet compared with those who adhere. Key findings are there was no difference in QoL in those with diabetes alone, vs those with T1D and CD, however once stratified by GFD adherence, found those non-adherent had lower QoL, and worse glycaemic control. This highlights the role of GFD adherence and the importance of finding strategies to understand and improve adherence in those with both conditions.

Quality of Life in Type 1 Diabetes and Celiac Disease: Role of the Gluten-Free Diet

Anna Pham-Short, BSc(Nutr)(Hons-I)[1,2], Kim C. Donaghue, MBBS, PhD, FRACP[1,2], Geoffrey Ambler, MBBS, MD, FRACP[1,2], Sarah Garnett, BSc, MNutrDiet, PhD[1,2], and Maria E. Craig, MBBS, PhD, FRACP[1,2,3]

Objective To evaluate quality of life (QoL) and glycemic control in youth with type 1 diabetes (T1D) and celiac disease vs T1D only. We hypothesized that QoL scores would be lower in youth with T1D and celiac disease and those nonadherent to the gluten-free diet (GFD).

Study design This case control study included 35 youth with T1D and 35 with T1D and celiac disease matched for age, sex, diabetes duration, and hemoglobin A1c level. QoL was assessed in participants and parents using the Pediatric Quality of Life Inventory Generic Core Scale, Pediatric Quality of Life Inventory Diabetes Module. and the General Well-Being Scale; youth with T1D and celiac disease also completed the celiac disease-specific DUX questionnaire and parents completed the Pediatric Quality of Life Inventory Family Impact Scale. Questionnaires were scored from 0 to 100; higher scores indicate better QoL or well-being. Scores were compared between T1D vs T1D with celiac disease, with subgroup analysis by GFD adherence vs nonadherence and therapy (continuous subcutaneous insulin infusion vs multiple daily injections).

Results Youth with T1D and celiac disease reported similar generic and diabetes-specific QoL to T1D only. GFD nonadherent vs adherent youth reported lower diabetes-specific QoL (mean score 58 vs 75, $P = .003$) and lower general well-being (57 vs 76, $P = .02$), as did their parents (50 vs 72, $P = .006$), and hemoglobin A1c was higher (9.6% vs 8.0%, $P = .02$). Youth with T1D and celiac disease using continuous subcutaneous insulin infusion vs multiple daily injections had similar generic and diabetes-specific QoL and A1C (8.6 vs 8.2%, $P = .44$), but were less happy having to follow a lifelong diet (59 vs 29, $P = .007$).

Conclusions Youth with T1D and celiac disease who do not adhere to the GFD have lower QoL and worse glycemic control. Novel strategies are required to understand and improve adherence in those with both conditions. *(J Pediatr 2016;179:131-8).*

Emerging evidence indicates long-term negative outcomes for individuals living with type 1 diabetes (T1D) and celiac disease, including an increased risk of retinopathy, nephropathy, and subclinical atherosclerosis. We recently demonstrated an association between lack of adherence to the gluten-free diet (gluten-free diet nonadherence [GFD–]) and early evidence of renal disease, independent of glycemic control.[1] This suggests that those who struggle with the coexistence of 2 chronic conditions are at higher risk of complications; however, there is a paucity of data on the impact of living with both conditions on quality of life (QoL) and general well-being.

It is well-established that T1D negatively affects QoL, particularly among girls and prepubertal children.[2] Mealtime behavior problems are common,[3,4] which may be compounded by the demands of carbohydrate counting, eating to manage blood glucose levels independent of hunger,[5] and normal child developmental behaviors such as fussy eating. QoL is higher in people with T1D treated with continuous subcutaneous insulin infusion (CSII),[6,7] which allows flexibility with meal times and food choices.[5,8] Because a GFD requires substitution of commonly available carbohydrate foods such as wheat-based breads, cereal, and pasta,[9] CSII could alleviate the restrictive nature of the GFD by allowing for carbohydrate-free meals. However, the impact of CSII on QoL in people with coexisting T1D and celiac disease has not been studied.

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CDDUX	Celiac disease–specific DUX
CSII	Continuous subcutaneous insulin infusion
GFD	Gluten-free diet
GFD+	Gluten-free diet adherence
GFD–	Gluten-free diet nonadherence
GWBS	General Well-Being Scale
HbA1c	Hemoglobin A1c
MDI	Multiple daily injections
T1D	Type 1 diabetes
QoL	Quality of life

From the [1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Australia; [2]Discipline of Child and Adolescent Health, University of Sydney, Sydney, New South Wales, Australia; and [3]School of Women's and Child's Health, University of New South Wales, Sydney, New South Wales, Australia

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In the general population, celiac disease is diagnosed either by clinical suspicion or screening of at-risk individuals, who are frequently asymptomatic.[10] In those who are symptomatic, the uptake of a GFD may be expected to have a greater impact on QoL than for asymptomatic individuals. Indeed, QoL was higher in symptomatic youth with biopsy proven celiac disease who were GFD adherent (gluten-free diet adherence [GFD+]).[11] In a Swedish study of asymptomatic school children screened for celiac disease, QoL did not differ between those with biopsy-confirmed celiac disease and their peers after 1 year.[12] In contrast, asymptomatic adults with celiac disease randomized to a GFD experienced alleviation of anxiety and improved perception of health after 1 year compared with those randomized to a gluten-containing diet.[13]

The only pediatric study to examine the impact of coexisting celiac disease and T1D on QoL found no difference in generic and diabetes-specific QoL compared with children who had T1D alone.[14] However, celiac disease–specific QoL was not examined, nor was the effect of symptoms on QoL. Surprisingly, QoL did not differ between youth who were GFD+ vs GFD–, although the number of youth who were GFD– was small (n = 6), suggesting that this subgroup analysis may have been underpowered.[14] In contrast, the coexistence of T1D and celiac disease in adults was associated with lower generic and diabetes-specific QoL.[15] Given these conflicting findings, we examined the effect of the "double diagnosis" on QoL, well-being and eating behaviors in youth and their parents. We hypothesized that QoL scores would be lower in children with celiac disease, and those GFD–, compared with their peers with T1D only. We also examined the relationship between QoL and presence or absence of celiac disease symptoms and therapy (CSII vs multiple daily injections [MDI]).

Methods

This cross-sectional case control study was conducted at the Sydney Children's Hospital Network (Westmead), Australia, from May 2013 to December 2014. Inclusion criteria were age 8-18 years, T1D for ≥1 year, and biopsy-proven celiac disease for ≥6 months. Patients with T1D and celiac disease were recruited at routine clinic appointments. Celiac disease was diagnosed based on our screening protocol: all patients with diabetes undergo serologic testing for celiac disease at the time of diabetes diagnosis and 1-2 yearly thereafter.[16] Screening was performed by measurement of serum IgA and anti-tissue transglutaminase IgA antibodies by enzyme-linked immunosorbent assay. Deamidated IgG antibodies were also measured to account for false-negative results in patients who were IgA-deficient. Those with a positive screen were referred to a pediatric gastroenterologist and, where indicated, underwent small bowel biopsy. The control population was drawn from the same clinic population within the study time period and were matched by age (±1 year), diabetes duration (±1 year), most recent hemoglobin A1c (HbA1c) (±0.5%), and mode of diabetes management (MDI or CSII). The control population had a negative screening test for celiac disease at least once within the previous 12 months. Exclusion criteria were unknown celiac disease status, treatment other than MDI or CSII, and the inability of a child/parent to speak or read English fluently. The study was approved by the Sydney Children's Hospital Network research ethics committee. Written consent was obtained from parents and verbal assent from children aged 12-16 years before participation.

Demographic and clinical characteristics documented were sex, age at diabetes diagnosis, T1D duration, mode of diabetes management (CSII or MDI), insulin dose (U/kg/d), age at celiac disease diagnosis, celiac disease duration, celiac disease–related symptoms (documented at the time of celiac disease diagnosis), anthropometric measurements (height, weight, and body mass index [BMI]), with z-scores computed using Centers for Disease Control and Prevention (CDC) 2000 reference data. The use of the US-CDC growth charts is standard practice in Australia, both in a clinical and research setting, and aligns with the Australian National Health and Medical Research Council's recommendations.[17] Most recent HbA1c was documented and lifetime mean HbA1c was computed from all available data.

Questionnaires

All participants and their parents/guardians complete age-specific questionnaires and proxy questionnaires at the study visit. Generic, diabetes-specific, eating behaviors–specific, and celiac disease–specific questionnaires were used to enable measurement of a wide spectrum of QoL domains. Specifically, all patients and parents completed the PedsQL Generic Core Scale (version 4.0), PedsQL Diabetes Module (Version 3.2), General Well-Being Scale (GWBS, Standard Version), and an eating behaviors questionnaire.[18] Parents/guardians also completed the PedsQL Family Impact Scale. Patients with celiac disease completed the validated celiac disease-specific DUX (CDDUX) questionnaire.[19]

The PedsQL Generic Core Scale is a 23-item questionnaire that evaluates QoL in the subdomains of physical, emotional, social, and school functioning, with 2 age-specific scales (8-12 and 13-18 years). It has been validated for use in the pediatric population with T1D.[20] The GWBS is a 7-item questionnaire measuring generic well-being and health. The Diabetes Module is a 32-item questionnaire that examines diabetes-specific QoL in the subdomains of diabetes symptoms, treatment barriers, treatment adherence, worry, and communication. The Family Impact Scale, completed by parents is a 36-item questionnaire that evaluates the impact of pediatric chronic health conditions on parents and the family in the subdomains of physical, emotional, social, cognitive functioning, communication, worry, daily activities, and family relationships.

Respondents were asked to rate how frequently each item was problematic over the past 1 month. Each questionnaire was assigned a total and subdomain score ranging from 0 to 100, with higher scores reflecting higher QoL/general well-being or healthier eating behaviors.

The eating behaviors questionnaire was modified from a locally developed questionnaire used in the Researching Effective Strategies to Improve Insulin Sensitivity in Children and Teenagers (RESIST) study,[18] which contains 23 items in the

subdomains of individual child, family and social environment, and diabetes-related eating behaviors (**Table I**; available at www.jpeds.com). The questionnaire aimed to understand how T1D, with or without celiac disease, affected the child and their family's meal patterns. The test items had a 5-option response format: never, almost never, sometimes, often, and almost always, corresponding to scores from 0 to 100.

The CDDUX questionnaire[19] consisted of 16 items related specifically to celiac disease across the subscales of communication, diet, and having celiac disease. Respondents used a visual scale to indicate how they felt about various aspects of celiac disease, with corresponding scores ranging from 0 to 100.

GFD Adherence

GFD adherence was assessed both clinically and serologically. An accredited practicing dietitian documented families' usual dietary intake, precautions taken when eating out, and their perceived GFD adherence. Tissue transglutaminase IgA and deamidated IgG serology were measured to document adherence. Patients with tissue transglutaminase titers in the normal range (or declining titers if recently diagnosed) and GFD+ as assessed by the dietitian were classified as GFD+. Patients with elevated titers and GFD– as assessed by the dietitian were classified as GFD–. Assessment of GFD adherence by a dietitian is recognized as the best available measure.[21]

Sample size calculations performed before recruitment indicated that 33 patients were required with celiac disease and T1D and 33 controls with T1D only, matched 1:1. Because no data on QoL in T1D among children were available at the time of study design, this was based on an estimated between group difference in parent proxy QoL scores of young people with T1D compared with parents of healthy peers of 11.05 (SD 12.33), using the PedsQL Pediatric Quality of Life Inventory Generic Core Scales,[20] with an alpha of 0.05 and 95% power.

Data Analyses

Youth were classified as having T1D, with or without celiac disease. Those with celiac disease were further stratified by GFD adherence (GFD+ vs GFD–) and mode of diabetes management (MDI or CSII). Categorical variables were compared between groups using χ^2 tests. Continuous variables, including questionnaire subdomain and total scores for youth and their parents, were compared between groups using the Student *t* test for normally distributed data and the Mann-Whitney *U* test for skewed data. Internal consistency was determined by Cronbach α coefficient, which was calculated for each questionnaire subdomain and total score, with values of >0.70 considered satisfactory.[22] Statistical analyses were performed using SPSS version 22.0 (IBM, SPSS Inc, Chicago, Illinois) and Stata version 13.0 (Stata Corp, College Station, Texas).

Results

Of the 42 youth with T1D and celiac disease who met the inclusion criteria, the first 35 to attend routine clinic appointments were approached and all agreed to participate. We also recruited 35 controls with T1D matched for age, diabetes duration, HbA1c, and mode of treatment. The total study population had a mean ± SD age of 13.6 ± 3.0 years, age at diabetes diagnosis of 6.1 ± 3.8 years, BMI z-score of 0.3 ± 0.8, and HbA1c of 8.4% ± 1.5% (68 ± 10.5 mmol/mol). Characteristics of participants stratified by presence or absence of celiac disease are shown in **Table II**. Patients with coexisting celiac disease had a significantly higher BMI z-score than their matched controls, but all other characteristics were comparable.

Presentation and Symptoms of Celiac Disease

Celiac disease was diagnosed after diabetes in all cases at median diabetes duration of 2.4 years. Classical celiac disease–related

Table II. Clinical characteristics of patient groups stratified by presence or absence of celiac disease and GFD adherence in those with celiac disease

	T1D only (n = 35)	T1D and celiac disease (n = 35)	*P*	GFD+ (n = 24)	GFD– (n = 11)	*P*
Female n (%)	19 (54)	20 (57)	.81	12/24 (50%)	8/11 (73%)	.21
Age at study visit (y)	13.6 ± 3.0	13.7 ± 3.1	.93	13.5 ± 3.1	14.2 ± 3.1	.52
Age at diabetes diagnosis (y)	6.1 ± 3.8	6.1 ± 3.9	.9	6.3 ± 4.1	5.7 ± 3.6	.68
Diabetes duration (y)	7.5 ± 3.0	7.6 ± 3.3	.57	7.2 ± 3.4	8.5 ± 3.0	.26
HbA1c at visit (%)	8.4 ± 1.6	8.5 ± 1.6	.99	**8.0 ± 1.2**	**9.6 ± 1.9**	**.02**
HbA1c at visit (mmol/mol)	68 ± 6	69 ± 6	.99	**64 ± 5**	**81 ± 9**	**.02**
Lifetime HbA1c (%)	7.8 ± 0.8	8.0 ± 0.7	.21	**7.8 ± 0.7**	**8.5 ± 0.6**	**.007**
Lifetime HbA1c (mmol/mol)	62 ± 3	64 ± 3	.21	**62 ± 3**	**69 ± 3**	**.007**
Mean HbA1c year before visit (%)	8.1 ± 1.1	8.3 ± 1.1	.55	8.0 ± 1.1	8.8 ± 1.0	.08
Mean HbA1c year before visit (mmol/mol)	65 ± 4	67 ± 4	.55	64 ± 4	73 ± 3	.08
CSII, n (%)	26 (74)	23 (66)	.43	16 (67)	7 (64)	.86
Insulin, U/kg/d	0.9 ± 0.3	0.9 ± 0.2	.50	0.9 ± 0.2	0.9 ± 0.3	.9
Age at celiac disease diagnosis (y)	-	9.1 ± 3.5		9.1 ± 3.6	9.1 ± 3.6	.98
Duration of celiac disease (y)		4.6 ± 2.7		4.4 ± 2.7	5.2 ± 2.7	.42
Symptomatic before celiac disease diagnosis		21/35 (60%)		**18/24 (75%)**	**3/11 (27%)**	**.007**
GFD adopted within first year		25/35 (71%)		24/24 (100%)	1/11 (9%)	<.001
Height z-score	0.4 ± 1.1	0.4 ± 1.0	.79	0.4 ± 1.0	0.2 ± 0.8	.52
Weight z-score	0.3 ± 0.8	0.6 ± 0.8	.19	0.6 ± 0.7	0.5 ± 0.9	.72
BMI z-score	**0.1 ± 0.9**	**0.6 ± 0.7**	**.03**	0.5 ± 0.8	0.7 ± 0.7	.54

Data are n (%) or mean ± SD.
Bold signifies results of significance, $P < .05$.

symptoms such as abdominal pain, bloating, diarrhea, steatorrhea, poor growth, or iron deficiency were reported before celiac disease diagnosis in 14 of the 35 cases (40%) and a further 7 of those 35 (20%) who reported improvement on the GFD (with symptoms noted in retrospect) were classified as symptomatic for data analysis. Patients and their families received standardized GFD education from a dietitian.

GFD Adherence

On the basis of dietitian review and celiac titers, 24 of the 35 patients with celiac disease (69%) were classified as GFD+, and 11 of the 35 (31%) as GFD−. There was complete concordance between dietetic assessment of GFD+ or GFD− and celiac titers. Characteristics of GFD+ vs GFD− are shown in **Table II**; the GFD+ group had significantly better glycemic control at the study visit, were more likely to be symptomatic before diagnosis, and were more likely to adopt the GFD within the first year of celiac disease; all other clinical variables were similar.

QoL Assessments

Four questionnaires (the PedsQL Generic Core Scale Version 4.0, the PedsQL Diabetes Module Version 3, the PedsQL GWBS Standard version, and the Eating Behaviors questionnaire) were completed by all 35 youth with T1D and 5 questionnaires (the PedsQL Generic Core Scale Version 4.0, the PedsQL Diabetes Module Version 3.2, the PedsQL GWBS Standard version, the Eating Behaviors questionnaire, and the PedsQL Family Impact Scale) were completed by 33 parents/guardians (2 parents did not attend clinic). Five questionnaires (the PedsQL Generic Core Scale Version 4.0, the PedsQL Diabetes Module Version 3.2, the PedsQL GWBS Standard version, the Eating Behaviors questionnaire, and the CDDUX) were completed by all 35 youth with T1D and celiac disease and 5 questionnaires (the PedsQL Generic Core Scale Version 4.0, the PedsQL Diabetes Module Version 3.2, the PedsQL GWBS Standard version, the Eating Behaviors questionnaire, and the PedsQL Family Impact Scale) were completed by their parents/guardians. Internal consistency (α coefficients) for the questionnaires' total scores were >0.7 (considered satisfactory), with the exception of the Eating Behavior Questionnaire (**Tables III** and **IV**).

T1D and Celiac Disease Compared with T1D

QoL scores in children did not differ in those with and without celiac disease, for generic, diabetes-specific, GWBS, family impact, and eating behavior scales (**Table III**). However, for the eating behaviors questionnaire, in the Family and Social Eating Behaviors subdomain, youth with coexisting celiac disease scored lower on, "I eat the same meals as the rest of the family" ($P = .03$) and lower for "Choosing foods is easy when eating out with family/friends" ($P = .04$), with parents scoring higher for "shopping for food is expensive" ($P < .001$) and "it is difficult to find foods my child likes to eat" ($P < .001$) (**Table I**).

Children Compared with Their Parents

Youth with T1D and celiac disease and their parents reported similar generic ($P = .07$) and diabetes-specific QoL ($P = .21$). No differences in any subdomains were found between youth with T1D and celiac disease and their parents. Youth with T1D and their parents also reported similar generic QoL ($P = .06$) and diabetes-specific QoL ($P = .46$). However, parents of youth with T1D only reported lower scores in the school subdomain ($P = .02$), indicating that parents perceived more problems at school than their children did.

Youth Who Were GFD+ vs GFD−

Youth who were GFD− reported lower general well-being ($P = .02$) and diabetes-specific QoL ($P = .003$) than youth who were GFD+ (**Table IV**). Although total celiac disease-specific QoL was similar between youth who were GFD+ and GFD− ($P = .78$), those who were GFD+ were more likely to indicate sadness for "having celiac disease" ($P = .04$) and in response to "being given gluten-containing food at school" ($P = .05$). Although there was no difference between how those GFD+ and GFD− reported finding the uptake of the GFD, both groups scored very low, indicated sadness at "having to follow a diet for my celiac disease" (33 vs 28; $P = .36$) and "not being able to eat anything I want" (25 vs 16; $P = .19$). Both youth who were GFD− and their parents were less likely to find the diet beneficial than their GFD+ peers ($P = .04$ and $P = .03$, respectively).

Symptomatic vs Asymptomatic of Celiac Disease

Patients who were symptomatic and had T1D and celiac disease were more likely to think what they ate was important compared with asymptomatic youth (87 vs 64; $P = .048$). In the family impact scale, parents of those with symptoms reported more problems with emotional (57 vs 77; $P = .006$) and social functioning (69 vs 81; $P = .03$) as well as family relationships (64 vs 81; $P = .02$) than parents of asymptomatic youth, despite there being no difference in overall scores (62 vs 72; $P = .26$).

CSII vs MDI Therapy in T1D and Patients with Celiac Disease

Most youth were treated with CSII (70%); the proportions were similar in those with or without celiac disease, and GFD+ vs GFD− (**Table II**). Glycemic control was similar between those using CSII vs MDI (8.6% vs 8.2%; $P = .44$). Mode of diabetes management was not associated with differences in child or parent generic and diabetes-specific QoL (data not shown). However, in the CDDUX, those treated with CSII indicated they were unhappier about "having to pay attention to what I eat" ($P = .007$) and "having to follow a life-long diet" ($P = .01$). Parents of youth treated with CSII reported greater diabetes treatment barriers on the diabetes- specific PedsQL ($P = .02$) and treatment adherence ($P = .009$), despite an overall similar diabetes specific QoL score to their children ($P = .35$). In the MDI group, youth and their parents had similar scores in all variables.

Duration of Celiac Disease and T1D

Duration of celiac disease, either as a continuous variable or as a categorical variable (<5 years vs ≥5 years) was not associated with any of the QoL measures, for either youth or their parents. Similarly, duration of T1D, as a continuous variable

Table III. QoL scores for youth with T1D vs youth with T1D and celiac disease youth

		T1D		T1D and celiac disease		
	Items	Mean ± SD	α	Mean ± SD	α	P
GWBS						
Child self-report		n = 35		n = 35		
Total score	7	64 ± 26	0.90	70 ± 24	0.90	.44
Parent proxy report		n = 33		n = 33		
Total score	7	72 ± 25	0.84	65 ± 22	0.84	.29
PedsQL Generic Inventory						
Child self-report		n = 35		n = 35		
Total score	23	83 ± 12	0.87	81 ± 12	0.88	.34
Physical functioning	8	88 ± 11	0.61	86 ± 14	0.71	.7
Emotional functioning	5	77 ± 18	0.76	75 ± 18	0.72	.57
Social functioning	5	91 ± 18	0.91	91 ± 14	0.79	.41
School functioning	5	77 ± 14	0.54	81 ± 12	0.84	.34
Parent proxy report		n = 33		n = 33		
Total score	23	76 ± 16	0.94	76 ± 13	0.89	.98
Physical functioning	8	85 ± 23	0.86	77 ± 24	0.91	.10
Emotional functioning	5	69 ± 19	0.83	68 ± 18	0.85	.78
Social functioning	5	85 ± 21	0.91	88 ± 14	0.69	.43
School functioning	5	64 ± 24	0.87	71 ± 21	0.85	.15
PedsQL Diabetes Module 3.2						
Child self-report		n = 35		n = 35		
Total score	33	73 ± 14	0.84	70 ± 16	0.95	.36
Diabetes symptoms	15	64 ± 11	0.73	60 ± 12	0.82	.13
Treatment barriers	5	78 ± 18	0.66	75 ± 18	0.63	.38
Treatment adherence	6	81 ± 14	0.69	84 ± 17	0.84	.21
Worry	3	63 ± 27	0.76	63 ± 28	0.89	.86
Communication	4	79 ± 20	0.70	68 ± 25	0.82	.09
Parent proxy report		n = 33		n = 33		
Total score	33	70 ± 17	0.94	66 ± 15	0.91	.29
Diabetes symptoms	15	62 ± 14	0.89	60 ± 12	0.84	.46
Treatment barriers	5	69 ± 22	0.83	64 ± 18	0.72	.24
Treatment adherence	6	78 ± 15	0.74	74 ± 18	0.78	.34
Worry	3	65 ± 28	0.86	67 ± 24	0.90	.72
Communication	4	68 ± 23	0.89	64 ± 25	0.88	.53
Eating behavior specific						
Child report		**n = 35**		**n = 35**		
Total score	24	64 ± 9	0.60	62 ± 13	0.82	.34
Individual child behaviors	7	71 ± 11	0.33	73 ± 14	0.61	.16
Family and social eating behaviors	12	64 ± 10	0.43	61 ± 12	0.48	.54
Diabetes related behaviors	5	59 ± 18	0.46	49 ± 26	0.64	.34
Parent report		**n = 33**		**n = 33**		
Total score	24	**68 ± 10**	**0.73**	**62 ± 13**	**0.78**	**.045**
Individual child behaviors	7	72 ± 12	0.53	69 ± 16	0.68	.43
Family and social eating behaviors	12	**69 ± 14**	**0.66**	**61 ± 12**	**0.65**	**.005**
Diabetes related behaviors	5	64 ± 18	0.65	56 ± 23	0.71	.14
Family Impact Scale						
Parent Report		**n = 33**		**n = 33**		
Total score	36	70 ± 17	0.97	68 ± 18	0.96	.93
Physical functioning	6	67 ± 21	0.88	67 ± 22	0.90	.77
Emotional functioning	5	65 ± 23	0.91	65 ± 21	0.89	.63
Social functioning	4	76 ± 22	0.89	74 ± 22	0.79	.72
Cognitive functioning	5	75 ± 20	0.95	72 ± 21	0.95	.89
Communication	3	74 ± 25	0.80	68 ± 23	0.76	.31
Worry	5	59 ± 24	0.84	58 ± 24	0.84	.99
Daily activities	3	73 ± 22	0.90	66 ± 29	0.89	.48
Family relationships	5	75 ± 17	0.91	72 ± 21	0.95	.72

Higher scores indicate higher QoL/less difficulty, with lower scores indicating more difficulty.
Bold signifies results of significance, $P < .05$.

or as a categorical variable (<5 years vs ≥5 years), was not associated with any QoL measures (data not shown).

Discussion

The GFD, which is pervasive and life long, coupled with the demands of managing T1D, may be expected to result in lower QoL in youth living with both conditions, as shown in adults.[15] It is, therefore, reassuring that the additional diagnosis of celiac disease does not seem to impair QoL in youth and their parents, although differences emerge when stratifying by GFD adherence. This is the first study to demonstrate that youth who are GFD– have lower well-being and diabetes-specific QoL, accompanied by worse glycemic control. Youth who were symptomatic at the time of diagnosis of celiac

Table IV. QoL in youth who were GFD+ with T1D and celiac disease compared with youth who were GFD–

	Items	GFD+ Mean ± SD	GFD+ α	GFD– Mean ± SD	GFD– α	P
GWBS						
Child self-report						
Total score	7	**76 ± 23**	**0.91**	**57 ± 20**	**0.86**	**.02**
Parent proxy report						
Total score	7	**73 ± 22**	**0.83**	**50 ± 12**	**0.89**	**.001**
PedsQL Generic Inventory						
Child self-report		n = 24		n = 11		
Total score	23	84 ± 10	0.86	75 ± 14	0.88	.11
Physical functioning	8	88 ± 11	0.67	80 ± 17	0.73	.21
Emotional functioning	5	76 ± 16	0.69	71 ± 22	0.8	.66
Social functioning	5	92 ± 13	0.77	89 ± 16	0.84	.64
School functioning	5	**78 ± 14**	**0.62**	**60 ± 22**	**0.81**	**.02**
Parent proxy report		n = 23		n = 10		
Total score	23	77 ± 10	0.88	73 ± 17	0.9	.39
Physical functioning	8	81 ± 22	0.93	69 ± 26	0.84	.22
Emotional functioning	5	68 ± 15	0.73	69 ± 23	0.91	.88
Social functioning	5	88 ± 14	0.76	88 ± 13	0.68	.88
School functioning	5	73 ± 17	0.8	66 ± 29	0.92	.46
PedsQL Diabetes Module 3.2						
Child self-report		n = 24		n = 11		
Total score	33	**75 ± 13**	**0.95**	**58 ± 16**	**0.87**	**.003**
Diabetes symptoms	15	**63 ± 11**	**0.79**	**52 ± 10**	**0.8**	**.05**
Treatment barriers	5	**80 ± 17**	**0.67**	**63 ± 15**	**0.5**	**.007**
Treatment adherence	6	**89 ± 11**	**0.7**	**73 ± 23**	**0.86**	**.02**
Worry	3	**70 ± 24**	**0.86**	**47 ± 30**	**0.86**	**.03**
Communication	4	73 ± 25	0.86	57 ± 22	0.65	.08
Parent-proxy report		n = 23		n = 10		
Total score	33	68 ± 13	0.9	61 ± 17	0.92	.25
Diabetes symptoms	15	62 ± 11	0.81	54 ± 12	0.83	.07
Treatment barriers	5	66 ± 16	0.7	57 ± 22	0.71	.24
Treatment adherence	6	77 ± 16	0.81	66 ± 21	0.72	.16
Worry	3	66 ± 21	0.86	69 ± 30	0.94	.78
Communication	4	68 ± 57	0.85	57 ± 29	0.91	.32
Celiac disease specific						
Child self-report						
Total score	12	41 ± 20	0.91	42 ± 22	0.88	.78
Communication	3	59 ± 25	0.82	43 ± 30	0.86	.11
Having celiac disease	3	**32 ± 23**	**0.78**	**54 ± 27**	**0.58**	**.04**
Diet	6	34 ± 23	0.92	28 ± 28	0.92	.36
Eating behavior specific						
Child Report						
Total score	24	64 ± 14	0.85	57 ± 9	0.66	.08
Individual child behaviors	7	74 ± 15	0.67	71 ± 11	0.33	.49
Family and social eating behaviors	12	62 ± 13	0.62	57 ± 11	0.20	.17
Diabetes related behaviors	5	55 ± 26	0.64	38 ± 25	0.65	.05
Parent report		n = 23		n = 10		
Total score	24	64 ± 13	0.84	57 ± 11	0.79	.11
Individual child behaviors	7	70 ± 18	0.76	71 ± 13	0.58	.79
Family and social eating behaviors	12	62 ± 12	0.72	55 ± 11	0.47	.21
Diabetes related behaviors	5	61 ± 22	0.77	42 ± 24	0.44	.07
Family Impact Scale						
Parent report		**n = 23**		**n = 10**		
Total score	36	69 ± 17	0.96	65 ± 21	0.97	.67
Physical functioning	6	68 ± 22	0.9	67 ± 23	0.92	.96
Emotional functioning	5	69 ± 21	0.91	61 ± 23	0.91	.26
Social functioning	4	75 ± 22	0.85	74 ± 24	0.68	.93
Cognitive functioning	5	72 ± 20	0.94	74 ± 25	0.98	.85
Communication	3	70 ± 23	0.83	63 ± 26	0.7	.42
Worry	5	61 ± 22	0.81	49 ± 25	0.88	.21
Daily activities	3	68 ± 28	0.87	63 ± 32	0.97	.64
Family relationships	5	72 ± 20	0.95	72 ± 24	0.95	.99

Higher scores indicate higher QoL/less problems with the subdomain.
Bold signifies results of significance, $P < .05$.

disease were more likely to adhere to the GFD and reported better QoL. There was no difference in diabetes-specific QoL in youth with celiac disease treated with CSII vs MDI; however, the celiac disease–specific scale suggested a greater burden of having to follow a lifelong diet in those treated with CSII.

Our findings show some parallels with the Canadian study of youth with coexisting T1D and celiac disease,[14] which also

found no overall difference in QoL. Our study population had similar age and duration of T1D and celiac disease. In contrast, a Dutch study demonstrated significantly worse QoL in adults with both conditions compared with T1D only.[15] Notably, their study population had longer duration of diabetes (25 years) and celiac disease (9 years). Although we did not find a relationship between longer celiac disease duration and lower QoL, we speculate that celiac disease is more likely to impact QoL in the longer term. In our study, those who adopted the GFD within the first year of celiac disease diagnosis were more likely to maintain GFD adherence. This identifies a crucial time for follow-up of the GFD and to discuss barriers the family may face.

We have demonstrated a subgroup of youth with celiac disease identified through screening who have difficulty implementing the GFD. This highlights the impact of screening for celiac disease in T1D,[23] particularly given celiac disease often presents asymptomatically.[24] However, symptoms may be identified retrospectively; more than one-half of asymptomatic children diagnosed with celiac disease indicated (on a Likert scale) feeling "much better" or "somewhat better" after starting the GFD compared with beforehand. The majority of patients in this study were GFD+, with adherence influenced by parental support, celiac disease awareness, and availability of gluten-free products.[25] As screening is now recognized as a standard of care in T1D,[26,27] strategies are needed to intervene in those who resist the GFD.

Adherence to a GFD was higher in those displaying celiac disease-related symptoms before being diagnosed with celiac disease. Interestingly, however, parents of symptomatic youth reported greater strain on their family relationships, and emotional and social well-being . This may be owing to parents actively supporting the GFD for their children by educating others and preplanning for meals eaten outside of the home. Although burdensome, this extra support has proven beneficial for the well-being and GFD adherence of adolescents.[28] Youth who are GFD+ and their parents were more likely to consider the diet beneficial, a finding that mirrors studies of youth with celiac disease only.[19] Youth who were GFD+ and their family were more likely to eat together, which is a recognized indicator of greater nutritional quality in the general population,[29] as well as in T1D.[30] This greater level of parental involvement may also extend to T1D management, which is reflected in the better glycemic control in the patients who were GFD+, as we and others have previously reported.[1,31] The lower general well-being reported by youth who were GFD– and their parents may be owing to perceived greater difficulty with the GFD, because youth who were GFD– expressed extreme sadness at having to follow a diet for celiac disease, which has also been reported in celiac disease alone.[32,33]

We found QoL, eating behavior scores, and glycemic control were not different in youth with both conditions when stratified by modality of treatment (CSII vs MDI). In contrast, other investigators[4,8] have shown CSII improves mealtime eating behaviors and increases food flexibility in T1D alone. We were surprised that youth using CSII expressed more sadness about having to pay attention to what they eat; we speculate that the added responsibility of carbohydrate counting and limited choices available on a GFD may have outweighed the flexibility CSII offers. Alternatively, patients who find the GFD more difficult may be more likely to adopt CSII.

Young people with coexisting celiac disease had significantly higher BMI z-scores than control subjects. Although the mean BMI z-score for the total study population confirms our previous observation that young people with T1D are more overweight than their nondiabetic peers,[34] the higher BMI in those with coexisting celiac disease is supported by existing data in celiac disease alone.[35] Weight gain after initiation of a GFD has been attributed to increased caloric intake owing to resolution of gastrointestinal symptoms, which can affect appetite, and increased caloric absorption after intestinal healing.[35] A Harvard study assessing BMI changes after celiac disease diagnosis reported that 139 of 679 participants (20.5%) were classified as overweight (BMI of 25-29.9 kg/m^2) at the time of celiac disease diagnosis, which increased to 164 of the 679 (24.2%) after GFD adoption (mean follow-up, 39.5 months).[35]

Limitations of our study include the cross-sectional nature of the study, which prevents understanding the longitudinal relationship between QoL and variables measured in this study, in particular coexisting celiac disease and GFD–. Even though the study was powered to detect differences in T1D vs T1D and celiac disease, the ability to adjust for potential confounding variables or to detect differences in the subgroup analyses are limited by the sample size. The proportion of patients who were GFD– was relatively low (31%); however, this falls within the reported rates of 19% to 48%[36] and was greater than in the Canadian study, which did not find an effect of adherence on QoL. Other potential limitations include the use of a locally designed eating behaviors questionnaire[18]; however, to our knowledge, there are no validated eating behavior questionnaires for school-aged children. Strengths include the comprehensive assessment of QoL in youth and their parents, more so than the only other study in youth.

We have shown that living with T1D and celiac disease does not seem to impact QoL negatively. However, we identified that youth who do not adhere to the GFD have lower well-being and diabetes-specific QoL, along with worse glycemic control than youth who were GFD+. This places them at risk of vascular complications.[37-39] Regular monitoring of adherence in youth with coexisting T1D and celiac disease will enable identification of the GFD–adherent subgroup, who may benefit from more intensive clinical and psychosocial support. ■

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Reprint requests: Maria E. Craig, MBBS, PhD, FRACP, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. E-mails: m.craig@unsw.edu.au; maria.craig@health.nsw.gov.au

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Table I. Locally modified eating behaviors questionnaire for child/parent

Individual child eating behaviors
1. I like eating meals / meal times are enjoyable
2. I / my child eats the same meals as the rest of the family
3. I / my child gets to choose what to eat
4. I think my parents don't give me enough food / I give my child less food than they want
5. I think my parents give me too much food / I give my child more food than they want
6. I / my child likes trying new goods
7. My parents tell me when and how much to eat
8. I / my child decides how much and when to eat

Family and social environment eating behaviors
1. I help prepare meals / Preparation of family meals is difficult
2. Our family eats dinner together
3. I help shop for food / Shopping for food is difficult
4. Friends are interested in what I / my child eats
5. Friends tease me about what I eat / my friends are not supportive of my child's eating patterns
6. Choosing foods is easy when eating out with family/friends
7. The TV is on during meals
8. I find it hard to eat at school / Meal times are difficult at school
9. My family argues about what I / my child should eat
10. I think what I eat is important / The diet is beneficial for my child
11. Outside of home, we ask how people make food
12. Parent: Shopping for food is expensive
13. Parent: It is difficult to find foods my child likes to eat

Diabetes related eating behaviors
1. My parents count carbohydrates / I count carbohydrates for my child
2. I / my child counts carbohydrates
3. Eating what the hospital has told me to is easy to follow
4. Before I / my child eats, my parents use things to figure out how much I can eat

We use:
- Measuring cups
- Kitchen scales
- Traffic Light Guide To Food Carbohydrate Counter
- Calorie King
- Other

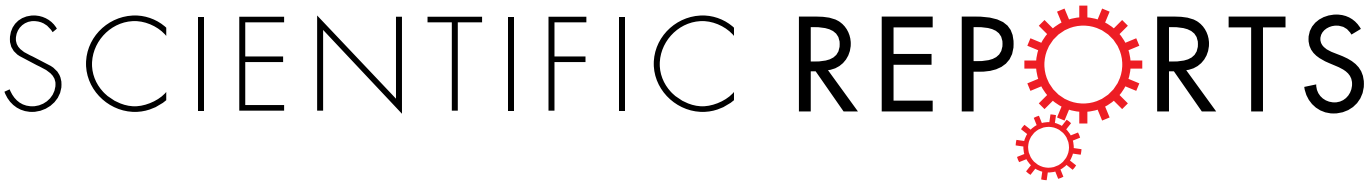
Questions had a 5-option response formal: never, almost never, sometimes, often, and almost always.

CHAPTER 7 GREATER POSTPRANDIAL GLUCOSE EXCURSIONS AND INADEQUATE NUTRIENT INTAKE IN YOUTH WITH TYPE 1 DIABETES AND CELIAC DISEASE

Pham-Short A, Donaghue KC, Ambler G, Garnett S, Craig ME, *Nature Scientific Reports,* DOI: 10.1038/srep45286 (2017)

SYNOPSIS

Chapter 7 answers the research question associated with hypothesis 5, that youth with T1D and CD demonstrate greater glycaemic excursions and lower nutrient intake compared with those with type 1 diabetes alone. Utilising CGM, chapter 7 presents a manuscript that reports glycaemic variability in those with T1D and CD vs T1D alone. A key finding from this study was that youth with coexisting T1D and CD had greater postprandial glucose excursions than those with diabetes alone. Interestingly, there were no differences in the proportional macronutrient intake between the two groups, as those with T1D and CD had more fruit and dairy intake, which negated the expected lower carbohydrate intake often seen in dietary intake studies in those with CD alone.



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Greater postprandial glucose excursions and inadequate nutrient intake in youth with type 1 diabetes and celiac disease

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Anna Pham-Short[1,2], Kim C Donaghue[1,2], Geoffrey Ambler[1,2], Sarah Garnett[1,2] & Maria E. Craig[1,2,3]

The gluten free diet (GFD) has a high glycemic index and low-fiber content, which potentially influences glycemic excursions in type 1 diabetes (T1D) and celiac disease (CD). Participants in this case-control study of youth with T1D+CD (n = 10) and T1D only (n = 7) wore blinded continuous glucose monitoring systems for six days. Blood glucose levels (BGLs) were compared between groups for each meal, including pre-meal, peak, 2-hour postprandial and time-to-peak. Participants consumed a test-breakfast of GF cereal and milk for three days and kept weighed food diaries; nutrient intake was analyzed and compared to national recommendations. Youth with T1D+CD had shorter time-to-peak BGL (77 vs 89 mins, $P = 0.03$), higher peak (9.3 vs 7.3 mmol/L, $P = 0.001$) and higher postprandial BGLs than T1D (8.4 vs 7.0 mmol/L, $P = 0.01$), despite similar pre-meal BGLs (9.2 vs 8.6 mmol/L, $P = 0.28$). Regarding test breakfast, greater pre and post-meal BGL difference correlated with longer CD duration ($R = 0.53$, $P = 0.01$). Total energy and macronutrient intake didn't differ between groups; however the majority of participants collectively had inadequate intake of calcium (76%), folate (71%) and fiber (53%), with excessive saturated fat (12%) and sodium (>2,000 mg/day). The GFD is associated with greater glycemic excursions and inadequate nutritional intake in youth with T1D+CD. Clinical management should address both glycemic variability and dietary quality.

The gluten free diet (GFD) recommended for management of celiac disease (CD) requires the complete avoidance of wheat, rye and barley, which is often replaced by white rice or corn[1]. Such foods may contribute to a higher glycemic index[2], higher glycemic load[3] and lower fiber diet[4,5] compared to gluten containing equivalents. The well-known benefits of a higher fiber diet in the general population include cardiovascular, and bowel health[6] and in type 1 diabetes (T1D), these benefits extend to improved glycemic control[7].

Restrictive diets such as the GFD are at risk of nutritional deficiencies, requiring increased vigilance in growing children and adolescents[8]. The mandatory fortification of wheat flour with micronutrients such as thiamin and folic acid[9], but not gluten-free grains further places those consuming a GFD at risk of inadequate nutrient intake. Studies investigating the nutritional composition of the GFD in adults have shown inadequacies of specific micronutrients including thiamin, folate, vitamin A and calcium[5,10]. However there are limited dietary studies in youth with CD[4,11,12] and none in children with co-existing T1D.

Adults and youth with CD have a lower carbohydrate intake compared with the general population[5,12], which has been attributed to poor palatability and increased costs of the GFD[13]. Carbohydrate intake in children with T1D is often at the lower level of dietary guidelines[14], which may be due to a conscious effort to reduce the risk of postprandial hyperglycemia[15]. In studies of children with CD, fiber and iron intakes are also significantly lower than recommendations[12,16], due to the naturally low fiber and iron content of GF grains[10]. However, whether the coexistence of T1D+CD is associated with a greater reduction in carbohydrate and fiber intake has not been previously examined. It is also unknown whether the traditional GFD, with a higher glycemic index and lower fiber content, impacts on glycemic variability in this population. Therefore the aims of this study were to compare, (i)

[1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia. [2]Discipline of Child and Adolescent Health, University of Sydney, Sydney, Australia. [3]School of Women's and Child's Health, University of New South Wales, Sydney, Australia. Correspondence and requests for materials should be addressed to M.E.C. (email: m.craig@unsw.edu.au)

post-prandial excursions (PPE) and (ii) macronutrient, micronutrient and fiber intake in youth with T1D+CD compared to those T1D alone. We hypothesized that youth with T1D+CD would demonstrate greater glycemic excursions and lower nutrient intake.

Research Design and Methods

Subjects. This was a case-control, observational study of youth with T1D and biopsy-proven CD, individually matched to controls with T1D only by age, diabetes duration and HbA1c ($\pm$0.5%, 3 mmol/mol). Inclusion criteria were T1D+CD, age <18 years, treatment with either multiple daily injections or insulin pump therapy, willingness to test at least four blood glucose levels (BGLs) per day, and the ability to read and record food diaries in the English language. Participants were recruited from the Diabetes Clinic at The Children's Hospital at Westmead, a tertiary pediatric hospital in Sydney, Australia. We aimed to recruit 10 youth with T1D+CD and 10 with T1D. The sample size was based on a minimum mean post-prandial BGL difference of 3 mmol/L (standard deviation 3 mmol/L) between groups over three days (30 meals per group), with $\alpha = 0.5$ and power 80%, assuming a drop out or missed BGL rate of 20%. The study protocol included youth wearing a blinded continuous glucose monitoring system (CGMS), consumption of the same test breakfast for three days, completion of a weighed food diary and documentation of diabetes care (injections or pumps, daily insulin doses and all BGLs measured using a glucometer). All participants attended their diabetes review appointment with their pediatric endocrinologist in the six weeks prior to the study visit for adjustment of insulin doses, or insulin pump settings. Participants used their pre-exiting insulin to carbohydrate ratios and insulin sensitivity factors, which had been set and adjusted according to standard clinical criteria[17].

The study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (study number: 12/SCHN/21, registration date 7th November 2012). The methods were carried out in accordance with the relevant guidelines and regulations. Informed consent was obtained from parents and assent from children aged 12–16 years prior to participation.

Study visit. All participants were assessed by an Accredited Practising Dietitian (A.P-S.). Patients underwent a structured interview, which involved documentation of their typical daily food intake, including weekend variations for meals both inside and outside the home. Carbohydrate counting skills were reviewed using food replicas (Mentone Educational, Australia), food packaging and real food (such as breakfast cereal). Measuring scales and cups were used as educational tools to assist with quantifying carbohydrate intake. Anthropometric measures were taken with the participant in light clothing and without shoes. Height was measured to the nearest 0.1 cm (Harpenden stadiometer) and weight was measured to the nearest 0.1 kg; BMI was calculated with z-scores computed using Centers for Disease Control and Prevention (CDC) 2000 reference data.

Continuous Glucose Monitoring System. CGMS (Medtronic Enlite Sensor with a blinded iPro2 transmitter) was inserted by the diabetes educator and worn uninterrupted for six days. Details of the sensor properties are described in detail elsewhere[18]. Patients were asked to perform at least four BGLs per day; prior to main meals and before bed with their own glucometers. Glycemic targets were set as 4.0–7.8 mmol/l, with hypoglycemia defined as a blood glucose level (BGL) $\leq$ 3.9 mmol/mol, euglycemia between 4.0–7.8 mmol/mol, and hyperglycemia as $\geq$7.9 mmol/mol.

CGMS Data Analysis. Participants were stratified by the presence or absence of CD co-existence for data analysis. For each main meal consumed and accompanied by a pre-prandial insulin bolus, time to reach peak BGL, peak BGL, and 2 hour postprandial BGL were examined. The following variability parameters were measured:

- Total variability (SD_T) was calculated as the standard deviation (SD) for all of the measurements for all of the study days[19].
- Within day glucose variability (SD_w) was calculated as the SD of all measurements in a 24 hour period, averaged over the sensor reading days[19].
- Between day variability was measured by Mean of daily differences (MODD), and calculated as the average of the absolute difference in glucose values at the exact time of day (midnight), and averaged over five days[19].
- Meal effect was measured by Area Under the Curve (AUC) and calculated as the sum of the absolute value of excursions from sensor value at the start of the meal and was calculated for 2 hours[20] following the start of the meal.

Dietary intake. Participants maintained a standardized weighed food diary for three days in which they were asked to document meal and snack times, weigh and/or measure the quantity of all foods and drinks, the brand name and serving size consumed, and all BGL measurements. Participants were provided with electronic kitchen scales and measuring cups. Food diaries were analyzed using Foodworks 7 (Xyris, Australia), which uses the Food Standards Australia New Zealand (FSANZ) published AusNut and NUTTAB 2010 databases[21].

Dietary intake was compared to the Australian National Health and Medical Research Council (NHMRC) age and gender specific nutrient reference values[22]. Dietary intake was compared to the Estimated Average Requirement (EAR), which is a daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage. Inadequate intake in our study is defined as those not meeting EAR recommendations[22]. Energy requirements were calculated by Schofields' Equation using current weight for the basal metabolic rate multiplied by a physical activity level of 1.2[23]. Sodium and fiber recommendations were adopted from the International Society of Pediatric and Adolescent Diabetes (ISPAD), with adequate fiber calculated as age in years

	T1D+CD	T1D	*P*-value
Number	10	7	
Age at visit (years)	14.3 ± 3.6	14.7 ± 2.8	0.76
Diabetes duration (years)	6.7 ± 4.0	5.9 ± 2.2	0.63
Celiac Disease duration (years)	3.6 ± 2.7	—	
Anti-deamidated gliadin IgG (ref 0–30)	14 ± 6	7 ± 7	0.25
Anti-tissue transglutaminase IgA (ref 0–30)	22 ± 14	6 ± 3	0.005
HbA1c at visit (%)	7.5 ± 0.7	8.0 ± 1.2	0.34
HbA1c at visit (mmol/mol)	58 ± 3	64 ± 8	0.34
Insulin pump therapy	7 (70%)	7 (100%)	0.11
Total daily dose	44.5 ± 20.0	50.3 ± 17.1	0.57
Insulin units/kg/day	0.81 ± 0.17	0.77 ± 0.12	0.60
% basal insulin	54 ± 4.3	54 ± 9.0	0.88
Insulin to carbohydrate ratio (ICR) (breakfast)	11.1 ± 6.3	10.4 ± 7.0	0.84
Insulin sensitivity factor (ISF) (breakfast)	3.3 ± 2.2	2.7 ± 1.7	0.54
Height SDS	−0.01 ± 1.6	0.8 ± 1.5	0.33
Weight SDS	0.6 ± 0.8	0.9 ± 1.0	0.52
BMI SDS	0.7 ± 0.7	0.9 ± 1.1	0.68
Serum 25 (OH) D (nmol/L) (ref: 51–250)	86 ± 30	72 ± 19	0.24

Table 1. Clinical characteristics of patients with T1D+CD compared with T1D.

+5 for grams/day[24]. Due to age and gender specific recommendations, proportions meeting the guidelines are reported as opposed to raw values of nutrient intake. Carbohydrate intake documented in the food diary was cross-checked with CGMS reports and insulin pump downloads. Carbohydrates used to treat mild hypoglycemic events (BGL < 4.0 mmol/l) were not included.

Test meal. All participants were given the same low glycemic index breakfast (Ancient Grains Gluten Free Cereal, Freedom Foods, Australia) for consumption on the first three study days together with portion-controlled ultra-high temperature (UHT) milk (Devondale, Our Lightest One). At the study visit, participants indicated their usual portion of cereal; using this information the dietitian weighed out the same quantity and labeled the carbohydrate amount for each individual breakfast. Participants were asked to refrain from consuming other foods for breakfast.

CD Status and Gluten Free Diet Adherence. Tissue Transglutaminase (TTG) IgA and deamidated IgG were measured in all participants at least once within the previous 12 months and negative CD serology was confirmed for the T1D only controls. For T1D+CD patients, GFD adherence was assessed both clinically and serologically as previously described[25]. This included documentation of families' usual dietary intake, including brands of products, family cooking and meal preparation practices, and precautions taken when eating out. GFD adherence was classified by TTG titers in the normal range (or declining titers if recently diagnosed) and assessed as GFD adherent (GFD+) by the dietitian.

Statistical analysis. Descriptive statistics are reported as mean + standard deviation (SD) for normally distributed data or median (range) for skewed data. Continuous variables, including clinical characteristics and glucose variability parameters, were compared between groups using student's t-test for normally distributed data and Mann-Whitney *U* tests for skewed data. Categorical data were compared using chi-squared tests. Statistical analyses were performed using SPSS (IBM, SPSS Inc., Chicago, IL, USA) and Stata 14 (Stata Corp., College Station, TX, USA). *P*-values < 0.05 were considered significant.

Results

Twenty youth (10 with T1D, 10 with T1D+CD) were recruited into the study. Three patients had CGMS equipment failure (two had no data recorded and one had the sensor fall out on the first day of the study). Comparing patients with CD (n = 10) and those without (n = 7), there were no statistically significant differences in demographic or clinical features other than TTG titers (Table 1). Insulin to carbohydrate ratios and insulin sensitivity factors were not different between the two groups, nor percentage of basal insulin. All but one of the T1D+CD patients was GFD adherent, and as results were not significantly different when this patient was excluded, their data were included in the analyses.

Dietary Intake. Dietary intake per participant was calculated as the average of the three recorded days. Total energy and proportional macronutrient intake were not statistically different between those on the gluten-containing or GFD diet (Table 2). For the micronutrients, more T1D+CD participants met the average daily recommended vitamin C intake from fruit (100 vs 43%, p = 0.006). All together, the majority had inadequate

	T1D+CD	T1D	*P*-value
Energy (kJ)	8065 ± 2738	7977 ± 2756	0.92
Estimated Energy requirements	7806 ± 1412	8540 ± 1563	0.10
Carbohydrate (g)	229 ± 80	234 ± 66	0.81
Carbohydrate (% total kJ intake)	49 ± 10	51 ± 9	0.35
Protein (g)	84 ± 38	85 ± 39	0.91
Protein (% kJ total intake)	18 ± 6	18 ± 6	0.77
Total fat (g)	72 ± 37	67 ± 40	0.64
Total fat (% kJ total intake)	32 ± 8	29 ± 9	0.24
Saturated fat (g)	26 ± 14	27 ± 20	0.87
Saturated fat (% kJ total intake)	12 ± 4	13 ± 7	0.64
Sodium (mg)	2287 ± 1229	2287 ± 722	0.99
Patients meeting daily age/gender specific estimated average nutrient requirements (%)			
Dietary fiber	60%	27%	0.20
Thiamin	50%	86%	0.13
Riboflavin	70%	57%	0.59
Niacin equivalents	100%	100%	0.99
Vitamin C	**100%**	**43%**	**0.006**
Total folate	20%	43%	0.31
Sodium	20%	14%	0.76
Iron	30%	57%	0.26
Zinc	60%	57%	0.91
Calcium	30%	14%	0.45

Table 2. Daily dietary analysis for patients with T1D+CD compared with T1D.

dietary calcium (76%), folate (71%), and fiber (53%) with excessive saturated fat (12% total energy intake) and sodium (>2,000 mg/day) intakes.

CGMS Data analysis. A total of 2,245 hours of data were recorded by CGMS, with a mean of 132 ± 26 hours and 1,585 ± 314 sensor readings per patient. Blood glucose profiles did not significantly differ between youth with T1D vs T1D+CD (Table 3), including daily mean BGL and times within the hyperglycemic, euglycemic and hypoglycemic ranges. Overall, total, within day and between day variability was not different between groups.

Meal analysis with CGMS. A total of 222 main meals were identified from CGMS traces and pre-meal BGL records throughout the study period (median 16, range 8–18 meals per patient) and of these 179 (81%) were accompanied by an insulin bolus, with no difference in the proportion of delivered boluses in those with or without coexisting CD (81% vs 80%, p = 0.70). Glycemic profiles for meals where an insulin bolus was delivered are reported in Table 3. Youth with T1D+CD experienced faster time to peak BGL (77 ± 32 mins vs 89 ± 34 mins, $P = 0.03$), higher peak BGL values post prandial (9.3 ± 3.6 vs 7.3 ± 3.4, $P = 0.001$), and 2 hour post prandial BGLs (8.4 ± 3.4 vs 7.0 ± 2.6, $P = 0.02$) (Fig. 1). For the test breakfast, youth with T1D+CD had higher peak (11.3 ± 2.5 vs 6.8 ± 4.2, $P = 0.02$) and 2 hour post prandial BGLS (9.2 ± 2.7 vs 5.9 ± 3.1, $P = 0.02$). The difference between post-meal BGL and peak BGL post-meal was significantly correlated with longer CD duration (R = 0.53, $P = 0.01$). In the diabetes alone group, diabetes duration was not associated with change in pre- to peak BGL values ($P = 0.50$).

Conclusions

This is the first study to examine the impact of the GFD in youth with coexisting CD and T1D on glycemic variability and nutrient intake. The GFD was associated with greater glycemic excursions, characterized by a faster time to peak BGL, higher peak and higher two-hour post prandial BGLs, despite similar exogenous insulin requirements. The GFD and the gluten-containing diet had similar macronutrient distributions that met national nutritional guidelines, however the intake of saturated fat and sodium were above national and international recommendations, while the intake of dietary fiber and calcium was inadequate.

The test meal of GF cereal consumed by all study participants was associated with greater glycemic excursions in youth with T1D+CD compared with their T1D only peers. The observation of faster glucose absorption in those with CD expands on a physiological study in which solutions of increasing glucose concentrations were infused into the small intestine and glucose absorption measured by the production of electrical activity (Apparent Km)[26]. Interestingly, higher apparent Km was correlated with longer duration of GFD consumption in patients with CD and was higher than in controls. Similarly, we found a positive relationship between longer CD duration and higher 2 hour postprandial BGL. This suggests that chronic exposure to the GFD, which has a higher glycemic index, modifies glucose transport and results in more rapid glucose absorption. In support of this hypothesis, three molecules that transport glucose (SGLT1, PEPT1 and NHE3) were higher in patients with treated vs untreated CD[27], implying that carbohydrates specific to the GFD may alter intra-intestinal gene transcription.

	T1D+CD	T1D	*P*-value
All meals			
Number of meals	110	69	
Average pre-meal BGL	9.2 ± 4.1	8.6 ± 4.1	0.28
Peak BG value	**9.3 ± 3.6**	**7.3 ± 3.4**	**0.001**
2 hour post prandial BGL	**8.4 ± 3.4**	**7.0 ± 2.6**	**0.02**
Area Under Curve	47.4 ± 30.1	47.9 ± 38.3	0.92
Time to peak (mins)	**77 ± 32**	**89 ± 34**	**0.03**
Average daily BGL	9.2 ± 1.8	8.9 ± 2.4	0.83
% time BGL >7.8 mmol/l	55 ± 19	56 ± 27	0.78
% time BGL < 7.8 and >3.8 mmol/l	40 ± 16	37 ± 21	0.77
% time BGL <3.8 mmol/l	5 ± 5	7 ± 8	0.47
SD_w Within day variability	4.5 ± 0.6	3.7 ± 0.9	0.09
MODD 5 days Interday variability	3.2 ± 1.2	3.8 ± 0.9	0.38
Test meal			
Test meal starting BGL	7.4 ± 3.0	6.6 ± 2.3	0.49
2 hour post prandial BGL	**9.2 ± 2.7**	**5.9 ± 3.1**	**0.02**
Peak BG value	**11.3 ± 2.5**	**6.8 ± 4.2**	**0.02**
Difference between start and peak BGL	**3.9 ± 1.4**	**0.2 ± 4.8**	**0.05**

Table 3. Results of meal time CGMS in youth with T1D+CD compared with T1D accompanied with an insulin bolus.

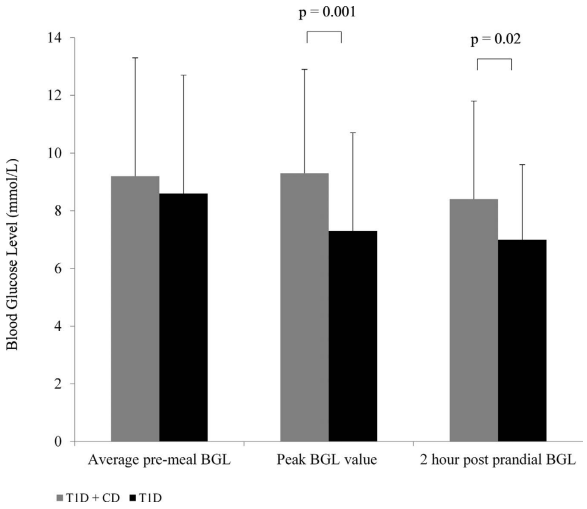

Figure 1. Average pre-meal, peak and post prandial blood glucose levels for meals accompanied with an insulin bolus for youth with T1D+CD compared to T1D alone.

The dietary intake of youth with T1D or T1D+CD was at the lower end of both national and international guideline recommendations for carbohydrates, inadequate for fiber and calcium and high for saturated fats[22,24]. The latter finding is consistent with dietary data in youth with T1D from the US and Europe[28–31], while the inadequate fiber intake is consistent with data in T1D or CD populations[4,10], but not coexisting T1D and CD. Whilst fiber intake was inadequate for those on the GFD, they consumed more fruit, which is a naturally GF carbohydrate food, and may have offset the expected reduction in carbohydrate grain-based products that is often seen in CD alone studies[10], but not observed in our study group. The detailed dietary history obtained from all patients in this study, irrespective of coexisting CD, indicate there is scope for improvement in dietary quality and reinforces the importance of dietary education in their management.

The micronutrient intake in our two study groups was comparable, however more than half of youth reported below average daily recommended intakes for calcium, iron and folate. The low intake of folate is surprising, since fortification of wheat flour with thiamin and folic acid is mandatory in many countries across the world including Australia[32]. Further voluntary fortification is strictly regulated, but nonetheless allows limited quantities of other vitamins and minerals such as niacin, riboflavin, calcium and iron to be added to wheat-based breads and cereals[33,34]. However there is no mandated fortification of GF foods, which may explain the inadequate intake of folic acid, and iron observed in the GFD in other studies[5,33]. Similarly, there was a trend towards more patients

with T1D+CD vs T1D not meeting adequate intake of folate (20% vs 43%) and iron (30% vs 57%), but this did not reach statistical significance, which may be due to the small sample size.

Limitations of our study include the small patient numbers, however most CGMS studies have included similar patient numbers and are adequately powered to investigate glucose variability data[20,35]. Previous studies of the impact of mixed meals on glucose variability were performed under controlled conditions with supervised meals and boluses, only administering insulin for the carbohydrate content of the meals with no additional correction doses for elevated BGLs administered. In contrast, our free-living study enables a more accurate depiction of life with type 1 diabetes, with correction doses of insulin administered pre-meal, thereby providing an unbiased assessment of post-meal glucose excursions. Whilst 3-day food records are commonly used in practice for assessing nutrient intake[36], their duration may not be of sufficient length to measure adequate intake for some vitamins and minerals[37]. All but one of our patients adhered to the GFD and therefore our results may not be applicable to those not adherent; this is a population that warrants further study given we and others have demonstrated they have worse glycemic control and are at greater risk of microvascular complications[25,38].

In conclusion, we have demonstrated that youth with T1D+CD have greater post-prandial glucose excursions, suggesting that either the GFD or intestinal characteristics influence glucose absorption. Youth with co-existing T1D and CD have similar macronutrient intake to their peers with T1D alone. Dietary advice for youth with T1D should emphasize increasing fiber, folate and calcium intake, and reducing saturated fat and sodium intake, with further attention to increase thiamin intake for those on the GFD.

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Author Contributions

A.P.-S. contributed to study design, patient recruitment, data collection, statistical analysis, data interpretation and wrote the manuscript. K.C.D. contributed to study design, data interpretation and revised the manuscript. G.A. contributed to study design, data interpretation and revised the manuscript, S.G. contributed to study design, data interpretation and revised the manuscript. M.E.C. contributed to study design, statistical analysis, data interpretation and revised the manuscript and is the guarantor of this article. All authors reviewed the manuscript.

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CHAPTER 8 ABNORMAL CORTICAL AND TRABECULAR BONE IN YOUTH WITH TYPE 1 DIABETES AND CELIAC DISEASE

Pham-Short A, Donaghue KC, Ambler G, Briody J, Garnett S, Munns CF, Craig ME, *Diabetes Care, 2019; 42:1-7*

SYNOPSIS

This chapter presents the final published study of this thesis, which examines bone health in youth with T1D and CD compared to T1D alone. Chapter 8 answers the research question associated with hypothesis 6, that youth with type 1 diabetes and coeliac disease exhibit abnormal measures of bone health compared with those with type 1 diabetes alone. Utilising both DXA and pQCT, we examined bone structure in those with coexisting T1D and CD, vs those with T1D alone. Chapter 8 demonstrated those with coexisting T1D and CD have abnormal cortical and trabecular bone compared to those with T1D alone. The coexistence of T1D and CD confers a lower bone turnover response to muscle pull. This continues the theme that the duality of disease appears to have an additive effect as shown in Chapter 7.

Abnormal Cortical and Trabecular Bone in Youth With Type 1 Diabetes and Celiac Disease

Anna Pham-Short,[1,2] Kim C. Donaghue,[1,2] Geoffrey Ambler,[1,2] Julie Briody,[2,3] Sarah Garnett,[1,2] Craig F. Munns,[1,2] and Maria E. Craig[1,2,4]

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OBJECTIVE

This study compared bone health in youth with type 1 diabetes and celiac disease (CD) versus type 1 diabetes alone.

RESEARCH DESIGN AND METHODS

This was a case-control study of 42 youth with coexisting type 1 diabetes and CD, and 40 with type 1 diabetes matched for age, sex, diabetes duration, and HbA_{1c}. Bone mineral density (BMD), bone mineral content (BMC), and BMC-to-lean tissue mass (LTM) ratio were measured using DXA and reported as *z*-scores for height. Total, trabecular, and cortical bone and muscle parameters were measured using peripheral quantitative computed tomography (pQCT) and reported as *z*-scores for age.

RESULTS

Mean age at assessment was 14.3 ± 3.1 years, diabetes duration, 8.0 ± 3.5 years; HbA_{1c}, 8.2 ± 1.5% (66 ± 5 mmol/mol); and 25-hydroxy vitamin D, 71 ± 21 nmol/L. Comparing youth with coexisting CD versus type 1 diabetes, DXA showed lower BMC-to-LTM ratio (0.37 ± 1.12 vs. 0.73 ± 2.23, $P = 0.007$) but no difference in total BMD. Youth with coexisting CD also had lower BMC-to-LTM ratio versus the general population ($P = 0.04$). Radial pQCT showed lower total BMC (−0.92 ± 1.40 vs. −0.26 ± 1.23, $P = 0.03$) despite similar bone and muscle cross-sectional area. In multivariable linear regression, lower BMC was associated with higher insulin dose ($P = 0.03$) but not HbA_{1c}.

CONCLUSIONS

Youth with both type 1 diabetes and CD have lower BMC relative to LTM and lower BMC, indicating abnormal trabecular and cortical bone development despite similar bone and muscle size. These findings suggest that the two conditions confer a lower bone turnover state. We recommend further examination of bone health in this population; future research should examine early interventions to improve bone health.

There is substantial evidence that adults with type 1 diabetes have abnormal bone mineral density (BMD) and are at increased risk of fractures (1). There is also limited evidence that children and adolescents with type 1 diabetes have lower bone density (2) and smaller bone mass (3,4). Although the mechanisms for adverse bone health are multifactorial, in type 1 diabetes they include inadequate accrual of peak bone mass due to impaired bone formation and osteoblast function (5), elevated HbA_{1c} (6), and increased production of advanced glycation end products (7).

[1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Westmead, New South Wales, Australia
[2]Children's Hospital Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
[3]Department of Nuclear Medicine, The Children's Hospital at Westmead, Westmead, New South Wales, Australia
[4]School of Women's and Child's Health, University of New South Wales, Sydney, New South Wales, Australia

Corresponding author: Maria E. Craig, m.craig@unsw.edu.au; maria.craig@health.nsw.gov.au

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Adults with celiac disease (CD) also have an increased fracture risk (8), whereas children and adults with CD both have lower BMD compared with the general population. Proposed mechanisms include dietary malabsorption of calcium and vitamin D, which are important for bone growth and development (9), or chronic intestinal inflammation, which interferes with bone formation and increases bone resorption (10).

Collectively, these data suggest that individuals with coexisting type 1 diabetes and CD have an additive risk for adverse measures of bone health, but the evidence for this is limited. Low BMD at the lumbar spine, defined as a *z*-score of <-2 SD, was more prevalent in a cross-sectional study of children and adolescents with type 1 diabetes and celiac autoimmunity (but not biopsy specimen-confirmed CD) versus type 1 diabetes alone (12% vs. 3%); however, actual BMD *z*-scores were not reported (11). In contrast, coexisting type 1 diabetes and CD was not associated with an increased fracture risk in a population-based Swedish cohort study of individuals aged <30 years; however, BMD was not examined (12).

Observed rates of hip fractures in adults with type 1 diabetes exceed calculated theoretical increases, suggesting factors beyond BMD, such as bone quality, contribute to increase fracture risk (6). Traditional measures of bone, using DXA in children and adolescents, include BMD for age, height, and weight, bone mineral content (BMC), and the ratio of BMC to lean tissue mass (LTM), which takes into account the influence of muscle on BMC (13). In contrast, peripheral quantitative computed tomography (pQCT) characterizes bone architecture, including volumetric BMD (vBMD), bone geometry (dimension, area, and cortical thickness), and mineral distribution within the bone cross-section (14). These parameters allow for calculation of bone strength. pQCT also enables the separate measurement of trabecular and cortical bone compartments, which may allow for earlier detection of changes in bone in response to disease (14). Trabecular bone is metabolically active; thus, any changes in bone structure would usually be first observed here (3,4). Although pQCT has demonstrated that children with type 1 diabetes have smaller bones compared with control subjects without diabetes (3,4), this tool has not been used to examine bone in youth with coexisting type 1 diabetes and CD.

Using both DXA and pQCT, we performed a case-control study of young people with coexisting type 1 diabetes and CD versus type 1 diabetes alone to address our hypothesis that coexisting CD confers a greater risk of abnormal BMD, BMC, and bone structure.

RESEARCH DESIGN AND METHODS

Study Design and Population

This was a matched cross-sectional case-control study conducted at The Children's Hospital at Westmead, Australia. Inclusion criteria were age 8–18 years, type 1 diabetes duration $\geq$1 year, and biopsy specimen-proven CD for at least 6 months. Patients with type 1 diabetes and CD were recruited at routine clinic appointments, and the first 42 who consented to participate were included in the study. For each individual case patient, a control patient with type 1 diabetes alone, matched for age ($\pm$1 year), sex, diabetes duration ($\pm$1 year), and HbA_{1c} ($\pm$0.5%) was invited to participate (15).

CD screening was performed based on international guidelines (16). All patients with diabetes had serological testing for CD at the time of diabetes diagnosis and at 1–2 yearly assessments thereafter (17). Screening was performed by measurement of serum IgA and anti-tissue transglutaminase IgA antibodies by ELISA. Deamidated IgG antibodies were also measured to account for false-negative results in IgA-deficient patients. Those with a positive screen were referred to a pediatric gastroenterologist and underwent small bowel biopsy. Only patients with specimen-proven CD were included in this study.

The control population was drawn from patients with type 1 diabetes who were matched by age, diabetes duration ($\pm$1 year), most recent HbA_{1c} ($\pm$0.5%), and mode of diabetes management–either multiple daily injections (MDI) or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]). The control population had a negative screening test result for CD at least once within the previous 12 months. The first 40 to consent to participate were included in the study. Exclusion criteria were unknown CD status or treatment regimens other than MDI or CSII.

The Sydney Children's Hospital Network Research Ethics Committee approved the study. Consent was obtained from all patients and parents before participation.

Study Visits and Data Collection/ Clinical Assessment

Demographic and clinical characteristics documented were age at diabetes diagnosis, type 1 diabetes duration, mode of diabetes management (MDI or CSII), insulin dose (units/kg/day), age at CD diagnosis, CD duration, CD-related symptoms (documented at the time of CD diagnosis), and anthropometric measurements (height, weight, and BMI), with *z*-scores computed using Centers for Disease Control and Prevention 2000 reference data. The most recent HbA_{1c} was documented, and lifetime mean HbA_{1c} was computed from all available data. Blood tests were performed at the study visit for 25-hydroxy vitamin D (25-OHD), albumin, thyroid function, and liver function. Deficiency of 25-OHD was defined as <50 nmol/L. Pubertal development was assessed and documented by the clinician and quantified by hormone levels (luteinizing hormone, follicle stimulating hormone, and testosterone or estradiol).

Gluten-Free Diet Adherence

Gluten-free diet (GFD) adherence was assessed clinically and serologically, as previously described (18). An accredited practicing dietitian documented families' usual dietary intake, precautions taken when eating out, and their perceived GFD adherence. Tissues transglutaminase IgA and deamidated IgG serology was measured to document adherence. Patients with tissue transglutaminase titers in the normal range (or declining titres if recently diagnosed) and GFD adherent (GFD^+), as assessed by the dietitian, were classified as GFD^+. Patients with elevated titers and GFD nonadherent (GFD^-), as assessed by the dietitian, were classified as GFD^-. There was complete concordance between dietetic assessment of GFD^+ or GFD^- and celiac titers. Assessment of GFD adherence by a dietitian is recognized as the best available measure (19).

Bone Densitometry

Total body, posteroanterior lumbar spine (LS), and femoral neck BMD and body composition were determined by DXA

using a GE-Lunar Prodigy (enCORE 8.6 software; GE Lunar Radiation Corp, Madison, WI), with positioning, scanning, and standard analysis according to the manufacturer's recommendations. These provided total body, LS, and femoral neck BMD and BMC adjusted for age and height, as previously described (20). Total BMC-to-LTM ratio and BMC adjusted for bone area (BA) (BMC-to-BA ratio) were also calculated. Volumetric LS BMD was calculated as per Carter et al. (21) to reduce the influence of height. Reduced bone mass and density for age and height was defined as *z*-score values of <-2.0, according to the International Society for Clinical Densitometry guidelines (22). Height *z*-scores for DXA measures were used to adjust for any variance in stature within and between groups, whereas age *z*-scores were used for pQCT because it is a true volumetric density measure.

Cross-sectional measurements of the nondominant lower leg and forearm were performed by pQCT using a Stratec XCT-2000 (Stratec Medizintechnik GmbH, Pforzheim, Germany). Measurements were made and analyzed using software version 6.0B. Epiphyseal scans were performed at the 4% site of the nondominant tibia and radius. Diaphyseal scans were undertaken at the 65% site of the radius and 66% of the tibia. Both the tibia and radius were acquired with a voxel size of 0.4 mm. A scan speed of 15 and 20 mm/s was used for the radius and tibia, respectively. The slice thickness of the machine was 2.4 mm, as previously described (23). Bone measurements included volumetric BMD (vBMD, mg/cm^3), vBMD trabecular bone, total and cortical cross-sectional area (CSA, mm^2), muscle CSA (mm^2), total and cortical BMC (mg/mm) and polar strength-strain indices (pSSI, mm^3). pSSI provides a good estimate of mechanical strength (24). Conversion from pQCT raw data to sex- and age-matched *z*-scores were based on published pediatric reference data (25).

Assessment of Glycemic Variability

Glycemic control was measured by HbA_{1c} using high-performance liquid chromatography (nondiabetic range 4–6%) (Diamat BioRad, Hercules, CA). Fluctuations in HbA_{1c} over the duration of diabetes was calculated as previously described (26). For each patient, the intrapersonal mean and SD of all recorded glycemic control measurements was calculated, and the SD-HbA_{1c} was considered a measure of glycemic variability (26). Because the number of individual visits (*n*) could influence the SD-HbA_{1c} (with fewer visits likely to artificially inflate SD), values for SD-HbA_{1c} were divided by *n* to adjust for this possibility. We also calculated coefficient of variation (CV), a normalized measure of glycemic variability. CV was computed as the division of SD-HbA_{1c} by a factor of mean HbA_{1c} (i.e., CV = SD − HbA_{1c}/[mean HbA_{1c}/10]).

Sample Size

In our previous study of BMD in patients with cystic fibrosis–related diabetes (27), we found a difference in the total BMD (TBMD) *z*-score of 0.99 ± 1.11 compared with cystic fibrosis alone and a difference in the LS vBMD *z*-score of 0.62 ± 0.76. We anticipated smaller but clinically significant differences may be observed for bone parameters measured in this study population and therefore aimed to recruit 40 patients per group (*z*-score difference, 0.5 ± 0.8, $\alpha = 5\%$, power = 90%).

Data Analysis

Descriptive statistics are reported as mean ± SD for continuous variables, which were normally distributed. Categorical variables were compared between groups using χ^2 tests. Continuous variables were compared between groups using Student *t* tests, because all data were normally distributed. Multivariable linear regression analysis was used to examine the association between bone health indices and explanatory variables, including presence of CD, diabetes duration, lifetime HbA_{1c}, and insulin dose/kg/day. Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY) and Stata 13.0 (StataCorp, College Station, TX) software.

RESULTS

Study Population and Characteristics

We recruited 82 youth with type 1 diabetes (42 with coexisting CD, 40 with type 1 diabetes alone). The total study population had a mean age of 14.3 ± 3.1 years, age at diabetes diagnosis of 6.7 ± 3.6 years, HbA_{1c} of 8.2 ± 1.5% (66 ± 5 mmol/mol), 25-OH of 68 ± 10.5 mmol/mol, and mean height *z*-score of 0.2 ± 1.2. Characteristics of participants stratified by presence or absence of CD are reported in Table 1. Youth with coexisting CD had a significantly higher prescribed insulin doses (0.95 ± 0.30 vs. 0.78 ± 0.21 units/kg/day, $P = 0.005$), but all other characteristics such as glycemic control and anthropometric measures were comparable. 25-OHD levels were significantly different between youth with type 1 diabetes and youth with coexisting CD; however, both values were clinically in the normal range, and the proportion of patients with 25-OHD deficiency did not differ. None of the participants had abnormal results on thyroid or liver function tests or evidence of active inflammation (based on full blood count, erythrocyte sedimentation rate, and C-reactive protein levels), and all patients with 25-OHD deficiency had normal alkaline phosphatase levels. None of the participants demonstrated delayed puberty.

DXA Scan Results

Youth with coexisting CD versus type 1 diabetes alone had a significantly lower BMC-to-LTM ratio ($P = 0.007$), suggesting an abnormal muscle and bone relationship. Both groups had similar-sized BA, height (Table 2), and TBMD. When youth with coexisting CD were stratified by GFD adherence (27 GFD^+ vs. 15 GFD^-), there were no statistically or clinically significant differences in any of the DXA measures (e.g., BMC-to-LTM ratio *z*-score −0.34 ± 0.85 vs. −0.42 ± 1.54, $P = 0.86$). Youth with coexisting type 1 diabetes and CD had lower TBMD for height (*z*-score −0.42, $P = 0.02$), BMC-to-LTM ratio (*z*-score, −0.37, $P = 0.04$), and BMC-to-BA ratio (*z*-score −0.69, $P = 0.001$) compared with the general population (results not shown). In multivariable linear regression, these associations remained significant after adjustment for total daily insulin dose and HbA_{1c}.

pQCT Results

Radial pQCT showed that youth with coexisting CD had lower cortical total BMC and lower trabecular bone vBMD ($P = 0.03$) than youth with type 1 diabetes (Table 3), despite similar muscle CSA ($P = 0.45$) and cortical CSA *z*-scores, $P = 0.12$). Lower pSSI *z*-scores in those with type 1 diabetes and CD ($P = 0.01$) indicate reduced bone strength. Youth with coexisting type 1 diabetes and CD had higher vBMD compared with the general population (*z*-score 0.42, $P < 0.001$),

Table 1—Clinical characteristics of patients stratified by presence or absence of CD

	Type 1 diabetes + CD (n = 42)	Type 1 diabetes (n = 40)	P value
Females	26 (62)	23 (58)	0.17
Age (years)	14.0 ± 3.3	14.7 ± 2.8	0.33
Age at diabetes diagnosis (years)	6.3 ± 3.9	6.5 ± 3.5	0.83
Diabetes duration (years)	7.8 ± 3.8	8.1 + 3.0	0.73
CD duration (years)	5.0 ± 3.6	—	
GFD adherent	27 (64)	—	
Median HbA_{1c} year before visit (%, mmol/mol)	8.5 ± 1.5 (69 ± 17)	8.0 ± 1.0 (64 ± 11)	0.10
HbA_{1c} at visit (%, mmol/mol)	8.4 ± 1.4 (68 ± 16)	8.1 ± 1.5 (65 ± 17)	0.26
Lifetime HbA_{1c} to visit (%, mmol/mol)	8.1 ± 0.9 (65 ± 10)	7.8 ± 0.8 (62 ± 9)	0.07
HbA_{1c} variability (SD-HbA_{1c})	0.86 ± 0.31	0.94 ± 0.30	0.21
Insulin (units/kg/day)	**0.95 ± 0.30**	**0.78 ± 0.21**	**0.005**
Height SDS	0.07 ± 1.26	0.34 ± 1.15	0.31
Weight SDS	0.60 ± 0.81	0.62 ± 0.97	0.93
BMI SDS	0.67 ± 0.71	0.51 ± 0.96	0.40
Overweight/obese	13 (31)	11 (28)	0.73
25-OHD at visit (nmol/L)	76 ± 22	65 ± 18	0.02
25-OHD deficient†	6 (14)	6 (15)	0.93
Alkaline phosphatase (ref: 50–350 units/L)	201 ± 119	195 ± 104	0.79

Data are mean ± SD or n (%). Values in boldface type are statistically significant. †25-OHD deficiency defined as <50 nmol/L.

whereas trabecular bone vBMD measures were lower in those with coexisting type 1 diabetes and CD versus the general population (z-score, −1.00; $P < 0001$) and total BMC (z-score, −1.02; $P < 0.001$). When youth with coexisting CD were stratified by GFD adherence, there were no statistically significant differences in any of the pQCT measures, although there was a trend to a lower 66% BMC cortical z-score in those GFD^- versus GFD^+ (−0.06 ± 0.78 vs. 0.64 ± 0.98, P = 0.08). In multivariable linear regression, lower total BMC remained significantly associated with coexisting CD and type 1 diabetes and was also associated with higher insulin dose (β = 0.28; 95% CI 0.12, 2.49; P = 0.03). Neither diabetes duration nor lifetime HbA_{1c} were significant in the model. Lower pSSI was associated with higher insulin dose (β = 0.32; 95% CI 0.37, 2.80; P = 0.01) and diabetes duration (β = −0.25; 95% CI −0.19, −0.007; P = 0.04) but not lifetime HbA_{1c}. Duration of CD was not associated with any bone health parameter.

CONCLUSIONS

This is the first study to examine the impact of biopsy specimen-proven CD on bone in youth with coexisting type 1 diabetes. We found abnormal bone structure in those with type 1 diabetes and CD, characterized by lower radial BMC, lower trabecular bone, and lower cortical BMC, despite similar-sized bone compared with youth with type 1 diabetes alone. Those with coexisting CD also had a lower BMC-to-LTM ratio with higher material density (vBMD), suggesting an impairment of bone development compared with those with type 1 diabetes alone. Compared with the general population, youth with coexisting type 1 diabetes and CD had abnormal bone structure, as demonstrated by lower TBMD, lower BMC-to-BA ratio, and lower BMC-to-LTM ratio. Moreover, a lower BMC-to-LTM ratio coupled with higher total vBMD indicates a state of lower bone turnover, resulting in older and stiffer bones (28).

The BMC-to-LTM ratio was significantly lower in those with coexisting type 1 diabetes and CD, even though neither LTM adjusted for height nor muscle size were significantly different between the two groups. Muscle is essential for bone development and maintenance, modeling, and remodeling: changes in bone follow changes in muscle mass (29) as bones adapt to muscle force (30). The low BMC-to-LTM in the setting of normal LTM for height suggests the skeleton is unable to adequately respond to the force applied to it through muscle pull and implies a primary bone abnormality (31). Alternatively, it may be that muscle force and

Table 2—DXA results comparing type 1 diabetes and CD versus type 1 diabetes alone youth

	Type 1 diabetes + CD (n = 42)	Type 1 diabetes (n = 40)	P value
Age (years)	14.0 ± 3.3	14.7 ± 2.7	0.52
Height SDS	0.07 ± 1.26	0.34 ± 1.15	0.36
Weight SDS	0.60 ± 0.81	0.62 ± 0.97	0.97
BMI SDS	0.67 ± 0.71	0.51 ± 0.96	0.57
TBMD height z-score	−0.42 ± 1.15	−0.19 ± 1.20	0.37
TBMC height z-score	−0.13 ± 1.29	0.24 ± 1.77	0.29
BMC-to-LTM ratio z-score	**−0.37 ± 1.12**	**0.73 ± 2.23**	**0.007**
BMC-to-BA ratio z-score	−0.69 ± 1.22	−0.99 ± 1.65	0.36
BA Height z-score	0.13 ± 1.30	0.69 ± 2.19	0.16
LTM height z-score	0.04 ± 1.22	−0.29 ± 1.19	0.21
LS 1–4 vBMD z-score	−0.59 ± 1.20	−0.30 ± 0.88	0.21

Data are presented as the mean ± SD. Values in boldface type are statistically significant.

Table 3—Radial pQCT results stratified by absence or presence of CD

	Type 1 diabetes + CD (n = 39)	Type 1 diabetes (n = 39)	P value
CSA cortical	−0.25 ± 1.21	0.13 ± 0.91	0.12
CSA muscle	−0.89 ± 1.56	−0.64 ± 1.23	0.45
4% BMC total	**−0.92 ± 1.40**	**−0.26 ± 1.23**	**0.03**
4% CSA total bone	−0.63 ± 1.40	−0.39 ± 1.40	0.45
4% vBMD trabecular	**−1.00 ± 1.49**	**−0.36 ± 1.09**	**0.03**
66% BMC cortical	**−0.26 ± 0.88**	**0.21 ± 0.92**	**0.02**
66% BMC total	**−1.02 ± 1.20**	**−0.44 ± 1.12**	**0.03**
66% cortical thickness	−0.03 ± 0.73	0.02 ± 0.81	0.78
66% CSA cortical	−0.26 ± 1.21	0.12 ± 0.91	0.13
66% CSA relative cortical	0.20 ± 0.81	0.00 ± 0.92	0.34
66% CSA total bone	−0.40 ± 1.48	0.13 ± 1.20	0.08
66% pSSI	**−0.39 ± 1.31**	**0.32 ± 1.18**	**0.01**
66% vBMD cortical	0.42 ± 2.03	1.04 ± 1.00	0.09
66% vBMD total	0.47 ± 1.24	0.49 ± 1.29	0.93

Data are presented as the z-score ± SD. Values in boldface type are statistically significant.

power are additionally reduced in those with coexisting type 1 diabetes and CD, because adolescents with type 1 diabetes alone have decreased muscle power and force as evaluated by jumping mechanography (32). Exercise, particularly resistance training, increases muscle strength (33) and BMD (34) in children. However, we did not document activity levels in this population or undertake measures of muscle force, so it is unknown whether there are differences in these factors between the two groups.

Total body BMC as assessed by DXA reflects cortical BMC. The lower total BMC in youth with coexisting CD therefore indicates lower cortical bone content, despite similar muscle and cortical bone size. The similar total and cortical bone size in our study supports the finding of bone size normalization in youth with type 1 diabetes of similar age (35). Two studies of youth with type 1 diabetes, from Finland (36) and France (37), demonstrated lower BMC compared with healthy control subjects despite similar anthropometrical measurements, suggesting that diabetes impairs bone mass accrual during skeletal growth. Youth with coexisting CD had higher insulin requirements, and similarly, those with lower BMC had higher insulin requirements in the French study (37). In type 1 diabetes, adolescence is associated with an exaggerated dysregulation of the growth hormone IGF-I/IGF-binding protein axis, contributing to a puberty-associated deterioration in glycemic control and worsening of insulin resistance (2) and resulting in higher insulin requirements. Although HbA_{1c} was not different between groups in our study and was not correlated with BMC in the French study (37), we speculate that functional insulopenia at the bone level (2) may impair bone formation.

Glycemic control and overall glycemic variability were similar between those with type 1 diabetes alone and coexisting CD in our study, despite higher total daily insulin doses. The limited existing data on youth with diabetes and celiac autoimmunity are conflicting: one study found no association between glycemic control and BMD (38), while two studies demonstrated a relationship between higher HbA_{1c} and lower BMD (11,39). However, in contrast to our population, none of the patients in these studies had biopsy specimen-confirmed CD, which limits the generalizability of the data. We previously showed that glycemic control was also not associated with early evidence of renal disease in adolescents with coexisting type 1 diabetes and CD (40). Together, this suggests the mechanism for low BMD in CD is multifactorial and not dependent on glycemic control alone. Although the higher insulin requirements in those with CD may also reflect dietary differences, in our previous study of the same population, we did not find differences in total daily carbohydrate intake in those with coexisting type 1 diabetes and CD versus type 1 diabetes alone (41).

The risk of fractures is higher in patients with type 1 diabetes and microvascular complications (42). Adults with type 1 diabetes and microvascular complications have deficits in cortical and trabecular bone vBMD as examined by pQCT, which may partly explain the excess skeletal fragility (43). In contrast, the bone microarchitecture in adults with type 1 diabetes without microvascular complications was not different from control subjects. The increased risk of microvascular complications in those with coexisting CD (44,45) identifies a subgroup of patients with type 1 diabetes who require ongoing monitoring, particularly as life expectancy increases (46).

We have shown for the first time, using pQCT, that youth with CD and diabetes had lower radial trabecular bone and lower pSSI, indicating both abnormal bone structure and reduced bone strength. Diabetes-induced changes in BMD are expected to be first noted in the metabolically active trabecular bone (2), which is best visualized by pQCT. However, only two studies have used pQCT in patients with type 1 diabetes (3,4), and none have used this tool in those with coexisting CD. In the only study using pQCT in children and adolescents with type 1 diabetes alone, trabecular bone density was lower than in age- and sex-matched control subjects (3). Hence, our data suggest that the coexistence of CD confers an additional burden on trabecular bone.

Nutritional, metabolic, and demographic factors may influence BMD, size, and content. There were no clinically significant differences in 25-OHD levels between those with coexisting CD and type 1 diabetes alone, and in our analysis of micro- and macronutrients in this study population, we found no differences in intake of calcium, carbohydrate, protein, or dietary fat (18). The standardized BMI score (SDS) was also not different between groups. Although none of the patients had evidence of inflammation at the time of assessment (based on full blood court, erythrocyte sedimentation rate. and C-reactive protein), we cannot exclude the possibility that patients with coexisting CD may have a heightened inflammatory state that influences bone metabolism (10). Notably, however, BMD and other bone measures did not differ between GFD^+ and GFD^- youth.

The strengths of our study include the use of pQCT, which enables assessment of bone structure, in addition to DXA, and the confirmation of CD based on a biopsy specimen.

Limitations include lack of data on exercise, which influences muscle and bone formation. A lower BMC-to-LTM ratio coupled with higher total vBMD

indicates a state of lower bone turnover, but this is best evaluated by bone histomorphometry. Although most were in late puberty, follow-up of the study population later in adolescence will be important to examine whether differences are sustained. Owing to the small sample size of GFD^- individuals (n = 15), the study was underpowered. Given the observed association between GFD^+ and diabetes complications, the association between GFD^+ and bone outcomes should be explored in future studies.

We cannot exclude the possibility that genetics plays a role in bone development; however, this has yet to be examined in youth with type 1 diabetes. In a community cohort study of adults, osteoporosis was associated with positive tissue transglutaminase antibodies but not HLA DQ2 or DQ8 (47).

Longitudinal analysis from before puberty would enable examination of the impact of puberty on differences in bone structure development throughout childhood and adolescence. We did not have fracture data in this cohort of patients; however, this is currently being investigated in a larger study from our center. Recruitment of a larger sample size may have enabled adjustment for potential confounding variables; however, the study groups were matched for age, diabetes duration, HbA_{1c}, and sex (48).

In conclusion, we have shown youth with type 1 diabetes and CD appear to have abnormal bone structure, with deficits in cortical and trabecular bone, and a low bone turnover state, resulting in high BMD compared with those with diabetes alone. Youth with coexisting type 1 diabetes and CD also demonstrated lower radial trabecular bone and BMC compared with those with diabetes alone. These structural differences are independent of LTM, glycemic control, and dietary calcium intake, but insulin doses were higher in those with CD. We recommend regular monitoring of bone health to monitor changes and implementing early interventions, such as regular weight-bearing exercise, to optimize bone health, particularly as longer diabetes duration is associated with increased fracture risk (49).

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CHAPTER 9 DISCUSSION

This body of work presents six original studies that were conducted with the aim of examining the broad impact of coexisting CD among young people with T1D. Within this research theme, the studies demonstrated that CD in T1D is common, especially in children with T1D onset before age 5 years (Chapter 3); requires regular screening (Chapter 4), influences risk of microvascular complications (Chapter 5), affects QoL and wellbeing (Chapter 6), increases glycaemic variability, and is associated with inadequate micronutrient intake (Chapter 7), and is associated with adverse bone health (Chapter 8). The importance of adherence to the GFD was highlighted in Chapters 5 and 6; whereby non-adherence to the GFD was associated with early signs of nephropathy (Chapter 5), QoL and lower general well-being (Chapter 6), as well as suboptimal glycaemic control (Chapter 6). These findings support the importance of screening for CD (Chapters 3 and 4) to identify those at risk, and emphasize the need to provide dietary and psychological support to maximise health outcomes. The coexistence of CD and T1D, independent of glycaemic control and GFD adherence was associated with increased glycaemic variability (Chapter 7) and abnormal bone health (Chapter 8), reinforcing the need to identify CD in youth with T1D through screening, particularly as most are asymptomatic at the time of small bowel biopsy (Chapter 4).

9.1 SCREENING FOR CD IN T1D

The first study (Pham-Short et al. 2012), reported in Chapter 3, reported the incidence of CD in a 20-year longitudinal observational study of 4,379 youth was 7.7 per 1,000 person years. Incidence was 60% higher in children aged < 5 years at diabetes onset; novel findings from this study demonstrated that this subgroup were more likely to seroconvert after T1D

diagnosis, and be diagnosed with CD after longer T1D duration (3.3 years vs 0.7 years in children aged $\geq$ 5 years at T1D diagnosis, $p < 0.001$). The prevalence of CD in our clinic population was 7.1%, in keeping with subsequently published nationwide data in youth from ADDN (7.7%) (Craig 2017). The high prevalence of CD in T1D supports the importance of continued screening for CD throughout childhood, particularly in children diagnosed with T1D before age 5 years.

The higher rate of CD at the time of diagnosis of T1D in older children in our cohort emphasizes the importance of screening at T1D diagnosis, as well as education and initiation of the GFD to maximize growth and BMD, particularly as preclinical CD may have been present prior to diabetes diagnosis. Recognized adverse effects of untreated CD include iron deficiency, anaemia, growth retardation, and osteoporosis (Matysiak-Budnik et al. 2007). The impact of GFD non-adherence is further examined in Chapters 5, 6, 7 and 8.

The findings from Chapter 3 in youth from NSW informed the next study, a systematic review of the epidemiology of CD in T1D, with subgroup analysis by age, gender, and duration of diabetes (Pham-Short et al. 2015), reported in Chapter 4. The second specific aim of the systematic review was to examine the risk of CD in people at diagnosis of T1D and at specific time intervals after diagnosis, to determine the optimal frequency of screening. The systematic review of 11,157 young people with T1D diagnosed < 21 years of age, from nine longitudinal cohort studies with median follow up of 10 years (range 5-18 years), demonstrated a weighted pooled CD prevalence of CD of 5.1% (range 1.6% to 9.7%).

The risk of CD was highest within the first year after T1D diagnosis: 40% were diagnosed within 1 year, 55% within 2 years, and 79% within 5 years of diabetes duration. Of note, 85% of patients were asymptomatic at the time of CD diagnosis. The findings from this review suggested that screening for CD should be performed at the time of diagnosis, and within 2 and 5 years thereafter. In addition, CD should be considered at any time in patients with symptoms suggestive of CD.

The systematic review has been cited 71 times since its publication in 2015 (Google Scholar), including guidelines from the ADA (American Diabetes Association 2018) and ISPAD (Mahmud et al. 2018); both societies updated their 2018 screening recommendations to state that 'screening for CD should be performed at the time of diabetes diagnosis, and at 2 and 5 years thereafter, as it is frequently asymptomatic', cited as level B evidence. The translation of these guidelines to inform clinical practice will enable improved estimates of CD incidence and prevalence in youth with T1D, as well as evaluation of early diagnosis and treatment in this at-risk population.

9.2 THE ROLE OF GFD ADHERENCE IN T1D AND CD

The studies reported in Chapters 5 and 6 highlight the importance of GFD adherence in youth with T1D and biopsy-proven CD. The burden of coexisting T1D and CD may be expected to result in suboptimal glycaemic control, conferring a greater risk of complications. However, in our study of 2639 young people with T1D (Chapter 5), glycaemic

control was better in the 129 individuals with CD, despite younger age at diabetes onset and longer diabetes duration. Reassuringly, CD was not associated with higher rates of any microvascular complications, lower height SDS or adverse lipid profiles. However, adherence to the GFD was associated with early evidence of renal disease. This was the first study in youth with coexisting T1D and CD to compare complication rates stratified by GFD adherence. In contrast, a case–control study demonstrated that mean albumin:creatinine ratio was lower in youth with T1D and CD who adhered to the GFD versus those without CD (Malalasekera et al. 2009). However, there was no comparison group with CD that did not to the GFD. The authors speculated that the lower mean albumin:creatinine ratio was attributable to consumption of less high-temperature processed foods in the GFD, as evidenced by lower plasma advanced glycation end-product fluorescence in those with CD vs. without CD. Whilst we did not assess dietary intake, we speculate that patients who did not adhere to a GFD may have consumed more highly processed gluten-containing foods, along with higher salt and high-fat intake. We also did not measure inflammatory markers such as erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP), however it is plausible that lack of adherence to the GFD may be associated with chronic low-grade inflammation, which may also play a role in early elevation of AER. Collectively, these data support further investigation of dietary factors, including advanced glycation end-products, on complications risk, particularly among individuals with coexisting T1D and CD.

In summary, Chapter 5 demonstrated that GFD non-adherence is associated with early elevation of AER, which is a recognized risk factor for future development of microalbuminuria in T1D (Schultz et al. 2000, Stone et al. 2006, Dunger et al. 2007,

Donaghue et al. 2009). While the relationship between poor glycaemic control and microvascular complications is well-established (DCCT 1993), non-adherence to the GFD was associated with elevated AER, independent of HbA1c. Our findings support the need for education to support adherence to the GFD in people with CD and regular dietetic review to ensure adequate dietary education. This study also provides further rationale for CD screening in T1D as presented in Chapters 3 and 4.

The GFD, which is pervasive and life long, coupled with the demands of managing T1D, may be expected to result in lower QoL in youth living with both conditions, as shown in adults (Bakker et al. 2013). In Chapter 6 the results of a case-control study demonstrated that the additional diagnosis of CD did not impair QoL in youth and their parents, although differences emerged when stratifying youth by GFD adherence. This was the first study to demonstrate that youth who did not adhere to the GFD had lower well-being and diabetes specific QoL, accompanied by suboptimal glycaemic control. Youth who were symptomatic at the time of diagnosis of CD were more likely to adhere to the GFD and reported better QoL. There was no difference in diabetes-specific QoL in youth with CD treated with CSII vs MDI; however, the CD–specific scale suggested a greater burden of having to follow a lifelong diet in those treated with CSII.

We have demonstrated a subgroup of youth with CD identified through screening who have difficulty implementing the GFD. This highlights the impact of screening for CD in T1D particularly given CD often presents asymptomatically (Pham-Short et al. 2014). However,

symptoms may be identified retrospectively; more than one-half of asymptomatic children diagnosed with CD indicated (on a Likert scale) feeling “much better” or “somewhat better” after starting the GFD compared with beforehand. The majority of patients (69%) in this study adhered to the GFD, with adherence influenced by parental support, CD awareness, and availability of GF products (Rosen et al. 2011). As screening is now recognized as a standard of care in T1D (American Diabetes Association 2018, Mahmud et al. 2018), strategies are needed to intervene in those who resist the GFD. In our study, those who adopted the GFD within the first year of CD diagnosis were more likely to maintain GFD adherence. This identifies a crucial time for follow-up of the GFD and to discuss barriers the family may face.

Adherence to a GFD was higher in those displaying CD-related symptoms before being diagnosed with CD. Interestingly, however, parents of symptomatic youth reported a greater strain on their family relationships, and emotional and social well-being. This may be owing to parents actively supporting the GFD for their children by educating others and preplanning for meals eaten outside of the home. Although burdensome, this extra support has proven beneficial for the well-being and GFD adherence of adolescents (Olsson et al. 2008). Youth who adhere to the GFD and their parents were more likely to consider the diet beneficial, a finding that mirrors studies of youth with CD only (van Doorn et al. 2008). Youth who were GFD adherent and their family were more likely to eat together, which is a recognized indicator of greater nutritional quality in the general population (Hammons et al. 2011), as well as in T1D (Kornides et al. 2014). This greater level of parental involvement may also extend to T1D management, which is reflected in the better glycaemic control in

the patients who adhered to the GFD, as we and others have previously reported (Sanchez-Albisua et al. 2005, Pham-Short et al. 2013). The lower general well-being reported by youth who did not adhere to the GFD and their parents may be owing to perceived greater difficulty with the GFD, because youth who did not adhere expressed extreme sadness at having to follow a diet for CD , which has also been reported in CD alone (Wagner et al. 2008, Barratt et al. 2011).

We have shown that living with T1D and CD is not associated with lower QoL. However, we identified that youth who do not adhere to the GFD have lower well-being and diabetes-specific QoL, along with suboptimal glycaemic control than youth who adhere to the GFD. This places them at risk of vascular complications (Pitocco et al. 2011, Mollazadegan et al. 2013, Pham-Short et al. 2013, Rohrer et al. 2015). Regular monitoring of adherence in youth with coexisting T1D and CD will enable identification of the subgroup who do not adhere, who may benefit from more intensive clinical and psychosocial support.

9.3 THE IMPACT OF THE GFD ON GLYCAEMIC EXCURSIONS

The GFD has a high GI and low-fibre content, which potentially influences glycaemic excursions in T1D and CD. Our case-control study (Chapter 7) of youth with coexisting T1D and CD, compared to T1D alone utilised CGMS worn uninterrupted for six days. This was the first study to examine the impact of the GFD in youth with coexisting CD and T1D on glycaemic variability and nutrient intake. The GFD was associated with greater glycaemic excursions, characterized by a faster time to peak BGL, higher peak and higher two-hour

post prandial BGLs, despite similar exogenous insulin requirements. The GFD and the gluten-containing diet had similar macronutrient distributions that met national nutritional guidelines, however the intake of saturated fat and sodium were above national and international recommendations, while the intake of dietary fibre and calcium was inadequate.

The test meal of GF cereal consumed by all study participants was associated with greater glycaemic excursions in youth with T1D and CD compared with their T1D alone peers. The observation of faster glucose absorption in those with CD expands on a physiological study in which solutions of increasing glucose concentrations were infused into the small intestine and glucose absorption measured by the production of electrical activity (Apparent Km) (Read et al. 1976). Interestingly, higher Apparent Km was correlated with longer duration of GFD consumption in patients with CD and was higher than in controls. Similarly, we found a positive relationship between longer CD duration and higher 2 hour postprandial BGL. This suggests that chronic exposure to the GFD, which has a higher GI, modifies glucose transport and results in more rapid glucose absorption. In support of this hypothesis, three molecules that transport glucose (SGLT1, PEPT1 and NHE3) were higher in patients with treated vs untreated CD (Laforenza et al. 2010), implying that carbohydrates specific to the GFD may alter intra-intestinal gene transcription. The consideration of insulin timing given 10-15mins pre-prandially and lower GI choices, in addition to stronger insulin to carbohydrate ratios may minimise glycaemic excursions reported in our study.

GF pasta consumed by healthy adults also results in elevated postprandial glucose excursions (Johnston et al. 2017). This American study reported 57% higher plasma glucose concentrations for GF rice and corn pasta, compared to wheat pasta. Glycaemic variability associated with the GF diet may have further health implications and disease risk that warrants investigation, particularly as the GFD gains popularity in the general population (Kim et al. 2016), and as CD prevalence increases (Liu et al. 2017).

The dietary intake of youth with T1D alone and those with both conditions was at the lower end of both national and international guideline recommendations for carbohydrates, inadequate for fibre and calcium and high for saturated fats (Schofield 1985, NHMRC 2012, Smart et al. 2014). The latter finding is consistent with dietary data in youth with T1D from the US and Europe (Schober et al. 1999, Helgeson et al. 2006, Lodefalk et al. 2006, Overby et al. 2007), while the inadequate fibre intake is consistent with data in T1D or CD populations (Thompson et al. 2005, Hopman et al. 2006), but not coexisting T1D and CD. Although fibre intake was inadequate for those on the GFD, they consumed more fruit, which is a naturally GF carbohydrate food. This may have offset the expected reduction in carbohydrate grain-based products that is often seen in studies of individuals with CD alone (Thompson et al. 2005), but was not observed in our study group. The detailed dietary histories obtained from all patients in this study, irrespective of coexisting CD, indicate there is scope for improvement in dietary quality and reinforces the importance of dietary education in their management.

Our free-living study enables a more accurate depiction of life in youth with T1D and those with coexisting CD. Correction doses of insulin were administered pre-meal, thereby providing an unbiased assessment of post-meal glucose excursions. All but one of our patients adhered to the GFD and therefore our results may not be applicable to those who do not adhere to the GFD; this is a population that warrants further study given we and others have demonstrated they have suboptimal glycaemic control (Chapter 5), lower QoL (Chapter 6) and are at greater risk of microvascular complications (Chapter 5). To further develop the findings of Chapter 5, and investigate any additional clinical effects of the coexistence of T1D and CD, we also examined bone health in Chapter 8.

9.4 ABNORMAL BONE STRUCTURE IN YOUTH WITH T1D AND CD

Utilising both DXA and pQCT, we assessed bone structure in youth with coexisting T1D and CD compared to T1D alone in a case-control study (Chapter 8). This was the first study to examine the impact of biopsy proven CD on bone in youth with coexisting T1D and CD. We found abnormal bone structure in those with both conditions, characterized by lower radial BMC, and lower radial cortical BMC, despite similar sized bone to youth with T1D alone. Those with coexisting T1D and CD also had a lower BMC:LTM, with higher material density, suggesting an impairment of bone development compared to those with T1D alone. Moreover, lower BMC:LTM coupled with higher total vBMD indicates a state of lower bone turnover, resulting in older and stiffer bones.

BMC:LTM was significantly lower in those with coexisting T1D and CD, even though neither LTM adjusted for height nor muscle size were significantly different between the two groups. Low BMC:LTM in the setting of normal LTM for height suggests the skeleton is unable to adequately respond to the force applied to it through muscle pull and implies a primary bone abnormality (Hogler et al. 2003). Alternatively, it may be that muscle force is reduced in those with T1Dand CD despite normal muscle size, since muscle power correlates with bone strength in healthy adolescents (Janz et al. 2015). Exercise, particularly resistance training, increases muscle strength (Faigenbaum et al. 1999) and BMD (Gutin et al. 1999) in children. However, we did not document activity levels in this population or undertake measures of muscle force, so it is unknown whether there are differences in these factors between the two groups.

In conclusion, the final study in this body of work demonstrated that youth with T1D and CD have a low bone turnover state, resulting in high BMD with reduced response to muscle pull, compared to those with T1D alone. Youth with coexisting T1D and CD also demonstrated lower radial trabecular bone and BMC compared with those with T1D alone. These structural differences were independent of LTM, glycaemic control and dietary calcium intake, but insulin doses were higher in those with CD. The findings suggest that regular monitoring of bone health is needed in youth with both conditions to enable early interventions such as regular weight bearing exercise and support GFD adherence to optimize bone health. These recommendations are particularly important in those with longer T1D duration, which is associated with increased fracture risk (Botushanov et al.

2009), and because GFD adherence for five years was associated with full recovery of BMD in those with CD alone (Grace-Farfaglia 2015).

9.5 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

A summary of the main findings, clinical implications and recommendations from this body of work is shown in Figure 9.1. Clinical practice recommendations based on the studies that comprise this thesis include:

- Screen for CD at the time of diabetes diagnosis and at two and five years thereafter. This recommendation has been incorporated into clinical practice guidelines by ADA (American Diabetes Association 2018) and ISPAD (Mahmud et al. 2018), with both societies updating their 2018 screening recommendations, citing our systematic review as level B evidence. Screen for CD beyond 10 years of T1D duration, especially for those diagnosed with T1D < 5 years of age.
- Support adherence to the GFD by regular dietary review and serological testing, as adherence is associated with lower AER, better glycaemic control and higher QoL.
- Address the greater glycaemic variability in youth with coexisting T1D and CD, through adjustment of insulin regimens, including insulin to carbohydrate ratios.
- Educate and monitor for inadequate nutritional intake in youth with coexisting T1D and CD.
- Regularly monitor bone health in youth with coexisting T1D and CD, due to the additive risk for adverse measures of bone health.

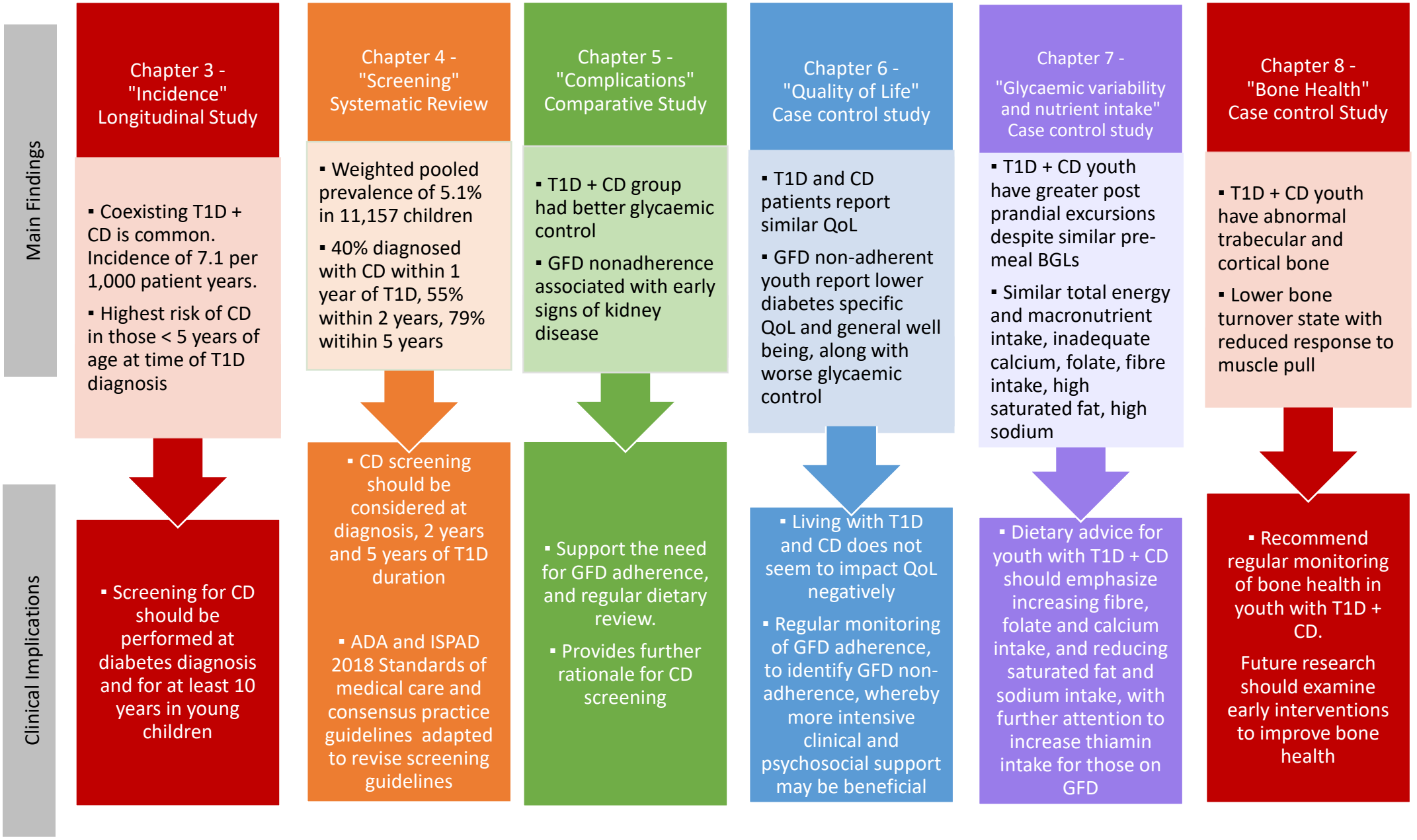
Future studies should include prospective cohorts with at least five years of diabetes duration, to enable reliable assessment of the impact of screening after T1D diagnosis. Studies incorporating both children and adults will enable further evaluation of the frequency of CD screening in T1D, as well as examination of the effect of age and gender at diabetes diagnosis on the development of CD. Large observational cohort studies, such as ADDN, DPV and T1DX, should consider examining glycaemic variability, QoL and bone health in the broader T1D population, particularly among those with longer disease duration. CD specific studies, in those with or without coexisting T1D, should examine factors associated with GFD adherence and results should be stratified by GFD adherence. Studies of complications in people with T1D and CD should investigate the role of dietary factors including AGEs, and the impact of CSII vs MDI on complications risk, given CSII reduces complications in T1D (Zabeen et al. 2016). Assessment of glycaemic variability should incorporate CGM over longer periods of time, and consider whether variability can be reduced by dietary changes such as increased fibre, or different insulin administration algorithms, rates or volumes as suggested. Finally, intervention studies will provide the highest level of evidence to address these research questions; for example use of MDI vs CSII/hybrid closed loop, or interventions to improve bone health in people with T1D and CD.

9.6 CONCLUSIONS

In conclusion, screening for CD within the first 10 years of T1D diagnosis will yield the highest prevalence of CD. The additional diagnosis of CD is not associated with lower QoL among youth with T1D, however non-adherence to the GFD is associated with lower QoL and early signs of nephropathy. The GFD is associated with greater glycaemic variability,

despite similar macronutrient profiles to the gluten-containing diet. Overall, the dietary quality of youth with T1D, with or without coexisting CD, is suboptimal, with inadequate calcium, folate and fibre intake, as well as excessive saturated fat and sodium. The coexistence of CD and T1D confers an additional burden on bone health, resulting in abnormal cortical and trabecular bone. Clinical management should address adherence to the GFD, glycaemic variability and dietary quality. Current evidence suggests there is no benefit of CSII vs MDI in youth with T1D and CD, however CSII negatively impacts on some aspects of QoL.

Figure 9.1 Summary of main thesis findings, clinical implications and recommendations



CHAPTER 10. REFERENCES

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APPENDIX

Conference poster presentations

Questionnaires used in Chapter 6

APPENDIX A. POSTER PRESENTATIONS

i. ISPAD Annual Conference 2011, Miami, USA, *"Young people with coeliac disease are not at increased risk of microvascular complications",* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME,

ii. APEG Annual Scientific Meeting 2012, Queenstown, New Zealand, *"Increased risk of microalbuminuria in young people with diabetes and coeliac disease with poor gluten free diet adherence"* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME,

iii. ADA Annual Scientific Sessions 2013, Chicago, USA, *"Early elevations of albumin excretion rate is associated with poor gluten free diet adherence in young people with coeliac disease and diabetes"* **Pham-Short A,** Donaghue KC, Ambler G, Chan A, Hing S, Cusumano J, Craig ME,

iv. ADA Annual Scientific Sessions 2014, San Francisco, USA, *"Abnormal cortical bone and muscle in celiac disease and type 1 diabetes*

v. ISPAD Annual Conference 2014, Toronto, Canada, "*Screening intervals for coeliac disease in youth with type 1 diabetes: Systematic Review",* **Pham-Short A**, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME

vi. ISPAD Annual Conference 2016, Valencia, Spain, "*Quality of life in type 1 diabetes and Celiac Disease: Role of the Gluten Free Diet",* **Pham-Short A,** Donaghue KC, Ambler G, Garnett S, Craig ME

Young people with coeliac disease are not at increased risk of microvascular complications despite longer diabetes duration

Anna Pham[1,2], Kim C. Donaghue[1,2], Geoff R Ambler[1,2], Albert K Chan[1], Janine Cusumano[1], Stephen Hing[1], Maria E Craig[1,2]

1. The Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia
2. Discipline of Paediatrics and Child Health, The University of Sydney, Sydney, Australia

Introduction

The coexistence of type 1 diabetes mellitus (T1DM) and coeliac disease (CD) is well documented, with prevalence rates varying from 1-10% worldwide.

Non-adherence with treatment causes different problems in T1DM and CD. The burden of two chronic diseases may make complications more likely.

Established risk factors for complications of T1DM include longer disease duration, older age and puberty, with improved glycaemic control conferring significant risk reduction for microvascular complications.

Left untreated, patients with CD are at increased risk of iron deficiency, anaemia, fertility problems, gastrointestinal malignancy and mortality.

Furthermore individuals with T1DM and CD may be at increased risk of microvascular complications due to chronic inflammation . To date, there are no published studies examining whether CD increases rates of microvascular complications in T1DM.

Aims

1. To examine glycaemic control, anthropometry and microvascular complications in those with T1DM and CD (T1DM+CD) vs T1DM (T1DM).
2. To determine whether adherence with the gluten free diet (GFD) impacts on glycaemic control, anthropometry or microvascular complications.

Patient Group

Comparative study of T1DM (n=2551) and T1DM+CD (n=145) individuals aged 9 to <20 years attending complications assessment between 1990–2011 at their most recent visit.

For comparison, those with biopsy confirmed CD were further stratified by gluten free diet (GFD) accordance. TTG antibody titres within the normal range at time of visit were defined as GFD compliance (GFDComp) or otherwise defined as GFD Non-compliance (GFDNon).

Methods

Investigations included:

- Albumin excretion rate (AER) by times overnight urine collections
- Early retinopathy was detected using 7-field fundal photography

Results

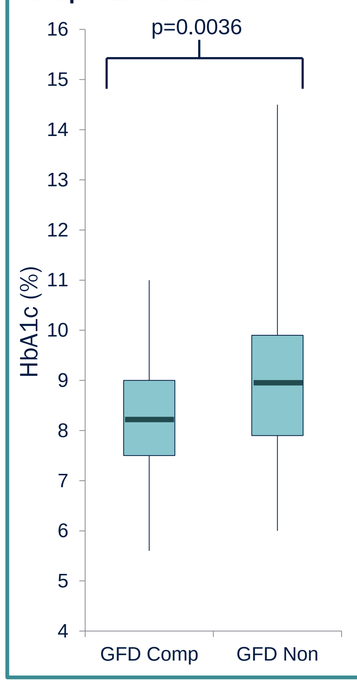
- Trend to better glycaemic control in those with CD (p = 0.084)
- Compliance to GFD associated with better glycaemic control than those GFD non-compliant, or without CD (p=0.0031)
- Non-compliance to GFD associated with worst glycaemic control compared to those GFD compliant, or without CD
- Trend to lower BMI SDS in those GFD compliant compared to than those GFD non-complaint (p = 0.056)
- Trend to lower insulin dose/weight in those GFD compliant compared to those GFD non-compliant
- Presence of CD in T1DM does not increase risk of microvascular complications

Table 2. Characteristics of those with, or without coeliac disease

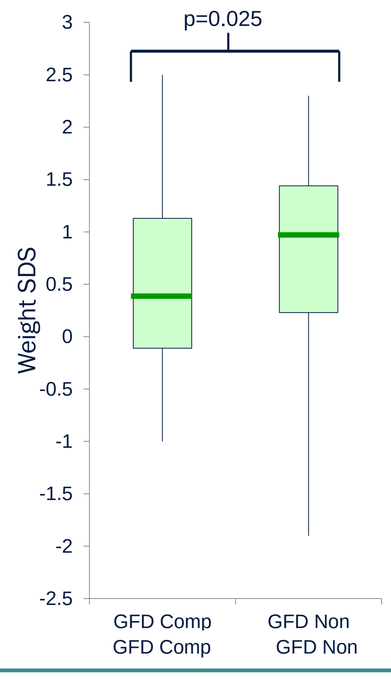
	T1DM (n = 2449)	T1DM+CD (n = 139)	p-value
Age at visit	16.3 [14.7 – 17.8]	15.9 [14.3 – 17.7]	0.12
Age at diabetes diagnosis	8.6 [5.4-11.3]	7.1 [3.1 – 10.0]	< 0.0001
HbA1c (%)	8.6 [7.1 – 9.6]	8.3 [7.7-9.3]	0.084
Height SDS	0.23 [-0.45 – 0.89]	0.19 [-0.60 – 0.85]	0.36
Weight SDS	0.77 [0.18-1.26]	0.68 [0.14-1.24]	0.56
BMI SDS	0.71 [0.16-1.20]	0.76 [0.11 – 1.25]	0.77
Cholesterol (mmol/L)	4.4 [3.9 – 5.0]	4.4 [3.9 – 5.1]	0.55
Insulin dose/weight (unit/kg/day)	1.06 [0.88 – 1.28]	1.14 [0.92 – 1.35]	0.019
Retinopathy	541/2296 (24%)	27/132 (20%)	0.41
Microalbuminuria (AER)	46/1025 (4%)	1/56 (2%)	0.51

Results. Comparison by GFD Compliance

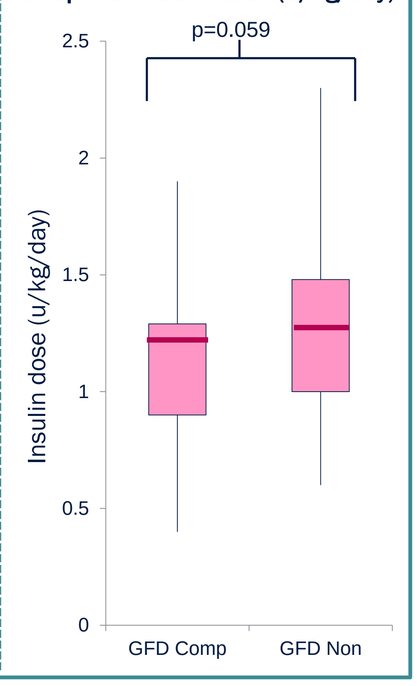
Graph 1. HbA1c



Graph 2. Weight SDS



Graph 3. Insulin dose (U/kg/day)



Results - Table 1. Comparison of those without coeliac disease, and by GFD accordance

	T1DM (n=2449)	GFDComp (n=71)	GFDNon (n=56)	p-value*
Age at visit	16.4 [14.7 – 17.8]	16.4 [14.7 – 17.9]	15.3 [13.9 – 17.3]	0.030
Age at diabetes diagnosis	8.6 [5.4 – 11.3]	6.5 [2.8 – 9.7]	7.5 [3.1 – 10.9]	<0.0001
HbA1c (%)	8.6 [7.7-9.6]	8.2 [7.5 – 9.0]	8.8 [7.9 – 9.9]	0.0031
Height SDS	0.23 [-0.45 - 0.89]	0.02 [-0.63 - 0.72]	0.27 [-0.58 - 0.81]	0.21
Weight SDS	0.77 [0.18 - 1.26]	0.48 [-0.11 - 1.13]	0.98 [0.23 - 1.44]	0.051
BMI SDS	0.71 [0.16 - 1.20]	0.61 [0.06 - 1.12]	1.07 [0.25 - 1.33]	0.13
Cholesterol (mmol/L)	4.4 [3.9 - 5.0]	4.2 [3.9 - 5.0]	4.4 [3.9 - 5.3]	0.76
Insulin dose/weight (unit/kg/day)	1.06 [0.88 - 1.28]	1.11 [0.9 - 1.29]	1.17 [1.00 - 1.48]	0.028
Retinopathy	541/2296 (24%)	9/68 (13%)	15/53 (28%)	0.097
Microalbuminuria (AER)	46/1025 (4%)	0/28 (0%)	1/24 (4%)	0.52

**p-value from analysis of variance, comparing the three groups*

Conclusions

- Young people with T1DM and CD who adhere to the GFD have better glycaemic control, lower weight SDS and lower BMI SDS and less retinopathy.
- We speculate that young people who struggle with CD also struggle with diabetes management and may benefit from further support and education.
- CD does not appear to negatively influence anthropometry or microvascular complications risk

Contact: Anna Pham annap3@chw.edu.au

Increased risk of microalbuminuria in young people with diabetes and coeliac disease with poor gluten free diet adherence

Anna Pham-Short[1,2], Kim C. Donaghue[1,2], Geoff R Ambler[1,2], Albert K Chan[1], Janine Cusumano[1], Stephen Hing[1], Maria E Craig[1,2]

1. The Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia
2. Discipline of Paediatrics and Child Health, The University of Sydney, Sydney, Australia

Introduction

The coexistence of type 1 diabetes mellitus (T1DM) and coeliac disease (CD) is well documented, with prevalence rates varying from 1-10% worldwide.

As individual conditions, T1DM and CD have their own sets of complications. The impact of two chronic diseases may increase the risk of complications.

Established risk factors for complications of T1DM include longer disease duration, older age and puberty, with improved glycaemic control conferring significant risk reduction for microvascular complications.

Left untreated, patients with CD are at increased risk of iron deficiency, anaemia, fertility problems, gastrointestinal malignancy and mortality.

Furthermore individuals with T1DM and CD may be at increased risk of microvascular complications due to chronic inflammation . To date, there are no published studies examining whether CD increases rates of microvascular complications in T1DM.

Aims

1. To examine glycaemic control, anthropometry and microvascular complications in those with T1DM and CD (T1DM+CD) vs T1DM (T1DM).
2. To determine whether adherence with the gluten free diet (GFD) impacts on glycaemic control, anthropometry or microvascular complications.

Patient Group

Comparative study of T1DM (n=2511) and T1DM+CD (n=145) individuals aged 9 to <20 years attending complications assessment between 1990–2011 at their most recent visit.

For comparison, those with biopsy confirmed CD were further stratified by gluten free diet (GFD) accordance. TTG antibody titres within the normal range at time of visit were defined as GFD compliance (GFDComp) or otherwise defined as GFD Non-compliance (GFDNon).

Methods

Investigations included:

- Glycaemic control measured by HbA1c
- Albumin excretion rate (AER) by timed overnight urine collections
- Early retinopathy was detected using 7-field fundal photography

Results

- Trend to better glycaemic control in those with CD (p = 0.08)
- Non-compliance with GFD is associated with a higher risk of early elevation of AER (p = 0.043)
- Compliance to the GFD is not associated with height, weight, nor BMI SDS
- Presence of CD in T1DM does not increase risk of neuropathy or retinopathy development despite longer diabetes duration
- Young people with CD and T1DM are diagnosed with T1DM at an earlier age (p < 0.0001)

Table 2. Characteristics of those with, or without coeliac disease

	T1DM (n = 2511)	T1DM+CD (n = 145)	p-value
Age at visit (yrs)	16.5 [14.8 – 17.8]	16.1 [14.3 – 17.8]	0.13
Age at diabetes diagnosis (yrs)	8.3 [5.3-11.3]	6.7 [3.0 – 10.0]	< 0.0001
Diabetes duration (yrs)	7.2 [4.9 -10.3]	9.6 [6.3 -12.2]	<0.0001
HbA1c (%)	8.6 [7.7 – 9.6]	8.3 [7.6-9.3]	0.08
Height SDS	0.23 [-0.45 - 0.89]	0.24 [-0.60 - 0.87]	0.54
Weight SDS	0.77 [0.15-1.20]	0.67 [0.08-1.21]	0.51
BMI SDS	0.70 [0.16-1.20]	0.76 [0.11 – 1.25]	0.89
Cholesterol (mmol/L)	4.3 [3.8 – 5.0]	4.4 [3.8 – 5.0]	0.97
Insulin dose/weight (unit/kg/day)	1.05 [0.87 – 1.28]	1.14 [0.92 – 1.35]	0.02
Retinopathy	556/2382 (23%)	31/140 (22%)	0.74
Mean AER ≥ 7.5µg/min	601/2119 (28%)	39/130 (30%)	0.69
Mean ACR	0.76 [0.55 – 1.23]	0.79 [0.61 – 1.26]	0.43
Peripheral nerve abnormality	627/2426 (26%)	40/144 (28%)	0.61

Table 3. Characteristics stratified by GFD accordance

	GFDComp (n=76)	GFDNon (n=51)	p-value
Age at visit	15.6 [14.1 – 17.3]	16.6 [15.0 – 18.1]	0.12
Age at diabetes diagnosis	6.4 [2.6 – 9.5]	8.1 [3.1 – 11.1]	0.20
Diabetes duration (yrs)	9.4 [6.6 – 12.2]	9.3 [6.3 – 12.3]	0.71
HbA1c (%)	8.3 [7.7 – 9.0]	8.5 [7.6 – 9.4]	0.40
Height SDS	0.20 [–0.60 to 0.72]	0.29 [–0.58 to 1.00]	0.67
Weight SDS	0.63 [0.15 – 1.14]	0.97 [0.22 – 1.33]	0.14
BMI SDS	0.62 [0.04 – 1.21]	1.05 [0.38 – 1.30]	0.14
Cholesterol (mmol/L)	4.4 [3.7 – 5.0]	4.4 [4.0 – 5.0]	0.44
Insulin dose/weight (unit/kg/day)	1.08 [0.90 – 1.34]	1.16 [0.91 – 1.34]	0.42
Retinopathy	13/74 (18%)	14/49 (29%)	0.15
Mean AER ≥ 7.5µg/min	17/70 (24%)	19/45(42%)	0.04
Mean ACR	0.79 [0.64 – 1.26]	0.96 [0.47 – 1.30]	0.86
Peripheral nerve abnormality	19/75 (25%)	17/51 (33%)	0.33

Conclusions

- Increased risk of microalbuminuria in young people with diabetes and CD with poor gluten free diet adherence
- CD does not appear to negatively influence anthropometry, glycaemic control, neuropathy or nephropathy complication risk despite longer diabetes duration.
- We speculate that the development of microvascular complications is influenced by more than glycaemic control and diabetes duration

Contact: Anna Pham anna.pham@health.nsw.gov.au

Early Elevation of AER Associated with Poor Gluten Free Diet Adherence in Young People with Diabetes and Coeliac Disease

Anna Pham-Short[1,2], Kim C. Donaghue[1,2], Geoff R Ambler[1,2], Albert K Chan[1], Janine Cusumano[1], Stephen Hing[3], Maria E Craig[1,2,4]

1. The Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia 2. Discipline of Paediatrics and Child Health, The University of Sydney, Sydney, Australia
3. Ophthalmology Department, The Children's Hospital at Westmead, Sydney, Australia 4. School of Women's and Children's Health, University of New South Wales, Sydney, Australia

Background

There are conflicting data on the risk of microvascular complications among individuals with type 1 diabetes (T1D) and coeliac disease (CD).

Some studies show that coexisting CD (CD+) is associated with increased risk of retinopathy and vascular disease, whilst others show reduced risk of nephropathy and retinopathy.

Risk factors are likely to be multifactorial, although the role of glycemic control has not been consistently associated with complications risk in CD+.

Furthermore, the role of long-term gluten free diet adherence (GFD+) on complications risk has not been examined.

Hypothesis

We hypothesized that for young people with T1D, CD+ and poor GFD adherence (GFD-) would have higher complications rates, independent of glycemic control

Methods

- Comparative study of 2510 young people with T1D (CD-), and 129 biopsy proven CD+ aged <20 years at their most recent to the Diabetes complications screening visit from 1990 – 2010
- GFD adherence defined as EMA or TTG titres within the normal range (GFD+), or elevated (GFD-) at time of visit.

Complications Screening:

- Retinopathy by 7-field stereoscopic fundal photography
- Timed overnight urine collections for AER. Early elevation defined as AER > 7.5µg /min
- Peripheral neuropathy – by thermal threshold and vibration perception at the foot and pupillometry for autonomic neuropathy

Statistical Analysis - Analyses performed using SPSS, version 20.

- Continuous variables compared between groups using analysis of variance and categorical variables using χ^2- tests.
- Binary logistic regression used to examine association between complication outcomes (presence or absence) and explanatory variables including GFD+ vs GFD-, age, HbA1c, gender, BMI SDS, insulin/kg/day and use of continuous subcutaneous insulin infusion therapy (CSII).
- Interaction terms such as HbA1c x GFD- were examined in multivariate models.

Table 1. Characteristics and complications rates in those with diabetes with, or without coexisting coeliac disease

	CD- (n=2510)	CD + (n = 129)	p-value
Age at diabetes diagnosis (years)	8.6 [5.3 – 11.4]	7.1 [2.9 – 10.0]	< 0.001
Current age	16.5 [14.8 – 17.9]	16.1 [14.3 – 17.8]	0.13
Diabetes duration (years)	7.2 [4.9 – 10.4]	9.3 [6.3 –12.2]	<0.001
Coeliac disease duration (years)	-	6.6 [3.0 – 10.3]	
Male gender (%)	1206/2510 (48%)	55/129 (43%)	0.24
HbA_{1c} (%)	8.6 [7.7 – 9.6]	8.3 [7.6 – 9.3]	0.04
Mean HbA1c last 12 months (%)	8.6 [7.8 – 9.6]	8.3 [7.8 – 9.4]	0.08
HbA1c > 9.0%	927 / 2447 (38%)	33/127 (26%)	0.03
Insulin Pump therapy	322/2468 (13%)	25/126 (20%)	0.04
Height SDS	0.23 [-0.45 – 0.90]	0.20 [-0.58 – 0.85]	0.28
Weight SDS	0.78 [0.17 – 1.26]	0.75 [0.15 – 1.22]	0.86
BMI SDS	0.70 [0.15 – 1.20]	0.81 [0.16 -1.26]	0.59
Cholesterol (mmol/l)	4.3 [3.8 – 5.0]	4.4 [3.8 – 5.0]	0.54
Insulin dose (unit/kg/day)	1.05 [0.87 – 1.28]	1.08 [0.91 – 1.34]	0.08
AER ≥ 7.5 µg/min	600/2118 (28%)	36/117 (31%)	0.60
Peripheral nerve abnormality	627/2425 (26%)	36/128 (28%)	0.61
Retinopathy	556/2381 (23%)	27/125 (22%)	0.75
Pupillary abnormality	1020/1771 (58%)	63/105 (60%)	0.69

Table 2. Characteristics and complications rates stratified by GFD adherence

	GFD + (n=69)	GFD - (n=60)	p-value
Age at diabetes diagnosis (years)	6.7 [2.9 – 9.6]	7.3 [2.8 – 1.0]	0.48
Current age	15.8 [14.4 – 17.8]	16.4 [14.3 – 17.9]	0.43
Diabetes duration (years)	9.2 [6.60 – 12.22]	9.4 [6.3 – 12.3]	0.81
Coeliac disease duration (years)	6.2 [3.1 – 9.6]	6.7 [2.8 – 11.5]	0.54
Male gender (%)	26/69 (38%)	29/60 (48%)	0.22
HbA_{1c} (%)	8.2 [7.6 – 9.0]	8.7 [7.8-10.0]	0.003
Mean HbA1c last 12 months (%)	8.2 [7.8 – 8.8]	8.8 [7.8 – 10.0]	0.009
HbA1c > 9.0%	10/69 (14%)	23/58 (40%)	0.002
Insulin Pump therapy	15/68 (22%)	10/58 (17%)	0.50
Height SDS	0.75 [-0.60 – 0.72]	0.29 [-0.58 – 1.00]	0.51
Weight SDS	0.59 [0.13 – 1.13]	0.95 [0.22 – 1.33]	0.39
BMI SDS	0.61 [0.06 – 1.10]	1.00 [0.28 – 1.30]	0.61
Cholesterol (mmol/l)	4.20 [3.70 – 5.00]	4.45 [3.93 – 5.1]	0.08
Insulin dose (unit/kg/day)	1.03 [0.88 – 1.27]	1.15 [0.99 – 1.46]	0.002
AER ≥ 7.5 µg/min	15/65 (23%)	21/52 (40%)	0.04
Peripheral nerve abnormality	17/68 (25%)	19/60 (32%)	0.40
Retinopathy	12/67 (18%)	15/58 (26%)	0.38
Pupillary abnormality	32/55 (58%)	31/50 (62%)	0.69

Results Summary

CD – vs CD+	GFD + vs GFD -
• CD+ cases were significantly younger at diabetes diagnosis, and therefore had longer diabetes duration • HbA1c was significantly lower in CD+ (8.3% vs 8.6%) • CSII use was higher in CD+ (20% vs 13%) • There were no differences in anthropometry, cholesterol or complications rates in CD- vs CD+	• There were no differences in current age, gender, diabetes duration or CD duration • GFD+ had significantly better glycemic control than GFD- at most recent visit (8.2% vs 8.7%) • The frequency of early elevation of AER was significantly higher in GFD- vs GFD+ (40% vs 23%). • In multivariate logistic regression, elevated AER was associated with GFD- (odds ratio 2.37, 95% CI *P*=0.039) and diabetes duration (OR 1.13, 95% CI *P*=0.026). • HbA1c was not significant in univariate analysis (OR 1.24, p=0.1) or in the multivariate model. • The interaction between HbA1c and GFD- was also not significant (p=0.13).

Discussion

- To our knowledge, this is the first study to compare complication rates in young people with co-existing T1D and CD, stratified by GFD adherence
- GFD- is associated with early evidence of renal disease, independent of glycemic control
- The GFD, which contains less high temperature processed foods and hence less advanced glycation end-product (AGEs), may play a role in reduced complications risk – this warrants further investigation
- A potential limitation of our study include the use of cross-sectional analysis, however median diabetes duration was > 9 years and data were analysed to the last study visit to enable longest diabetes and CD duration

Clinical Indications

- Our findings support the need for adherence to the GFD in people with CD and regular dietetic review to ensure adequate dietary education.
- Our findings also support guidelines for CD screening in type 1 diabetes.

Abnormal Cortical Bone and Muscle In Celiac Disease and Type 1 Diabetes

Anna Pham-Short[1,2], Kim C., Donaghue[1,2], Geoffrey Ambler[1,2], Julie Briody[1,3], Robert Howman-Giles[1,2,3], Craig Munns[1,2], Maria E Craig [1,2,4]

1. The Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia 2. Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia
3. Department of Nuclear Medicine, The Children's Hospital at Westmead, Sydney, Australia 4. School of Women's and Child's Health, University of New South Wales, Sydney, Australia

Introduction

The coexistence of type 1 diabetes mellitus (T1D) and coeliac disease (CD) is well documented, but data on the effects on bone health are limited. In CD, there is increased fracture risk in both children and adults, whilst in T1D, there is increased fracture risk in adults. As childhood and adolescence are important times for attaining peak bone mass during growth, assessing bone health in children is important.

Various factors in adolescents with T1D may contribute to overall poor bone health and lower peak bone mass. These include non-adherence with diabetes management such as insulin omission, insufficient dietary calcium intake and increased calcium excretion.

Dual energy X-ray absorptiometry (DXA) is the gold standard in assessing bone mineral density (BMD) and bone mineral content (BMC). Peripheral quantitative computed tomography (pQCT) is another tool that allows for determination of trabecular and cortical vBMD and provides data on bone size and shape which allow for determination of bone strength.

Hypothesis

Children and adolescents with T1D and CD will have lower BMD and abnormal bone development compared to age and sex matched controls

Aim

To examine bone and muscle parameters in children and adolescents with T1D and CD from a tertiary pediatric centre using DXA and pQCT.

Methods

Observational study of 32 children and adolescents with T1DM and biopsy proven CD.

DXA provided measurements of total BMD, bone mineral content (BMC), lumbar spine volumetric BMD (vBMD), lean tissue mass (LTM) and reported as z-scores for age.

pQCT of the radius and tibia was also performed in 25; reported as z-score for age in metaphyseal and diaphyseal bone (4% and 66% of bone length, respectively) . pQCT measurements included volumetric BMD (vBMD), cortical BMC, cross sectional area (CSA) of total bone, *CSA cortical bone*, CSA relative cortical bone, CSA muscle, cortical BMC/ muscle CSA.

Results

Table 1. Patient characteristics

	Mean ± SD
Median age at visit (years)	13.9 ± 3.5
Age at T1D diagnosis (years)	6.3 ± 4.0
Age at CD diagnosis (years)	9.3 ± 4.1
Duration of T1D (years)	7.6 ± 3.9
Duration of CD (years)	4.6 ± 3.4
HbA1c at visit (%)	8.3 ± 1.2
Height z-score	0.04 ± 1.3

Table 2. DXA (n=32), pQCT (radial and tibial , n=25)

		Z-score (95% CI)	p-value
DXA results	Total BMD (DXA)	-0.21 (-0.60 to 0.18)	0.29
	Total BMC (DXA)	0.10 (-0.36 to 0.55)	0.66
	L1 – 4 vBMD (DXA)	-0.57 (-1.00 to -0.14)	0.01
	LTM for height	0.09 (-0.34 to 0.53)	0.67
	BMC/LTM	-0.15 (-0.55 to 0.25)	0.44
Radial pQCT results	4% BMC total	-0.90 (-1.46 to -0.35)	<0.01
	4% vBMD trabecular	-1.24 (-1.84 to -0.64)	< 0.001
	4% CSA total bone	-0.33 (-0.74 to 0.08)	0.03
	66% BMC cortical	-1.62 (-2.17 to -1.07)	<0.001
	66% Cortical thickness	0.03 (-0.28 to 0.34)	0.83
	66% vBMD cortical	0.31 (-0.70 to 1.32)	0.54
	66% CSA total bone	-0.41 (-1.07 to 0.24)	0.21
	66% CSA cortical	-0.22 (-0.74 to 0.30)	0.40
	CSA muscle	-0.89 (-1.53 to -0.25)	<0.01
	Cortical BMC/muscle CSA	-0.82 (-1.32 to -0.33)	<0.01
Tibial pQCT results	4% vBMD trabecular	-0.59 (-0.88 to -0.30)	< 0.001
	66% BMC cortical	-0.22 (-0.68 to 0.23)	0.32
	66% Cortical thickness	-0.66 (-0.89 to -0.43)	< 0.001
	66% vBMD cortical	0.44 (0.17 – 0.70)	0.02
	66% CSA total bone	0.65 (0.02 – 1.28)	0.04
	66% CSA cortical	-0.38 (-0.80 o 0.04)	0.07
	CSA muscle	-0.20 (-0.71 to 0.31	0.43
	Cortical BMC/muscle CSA	-0.10 (-0.52 to 0.32)	0.63

Images of radial pQCT results from a 17 year old boy with T1DM + CD

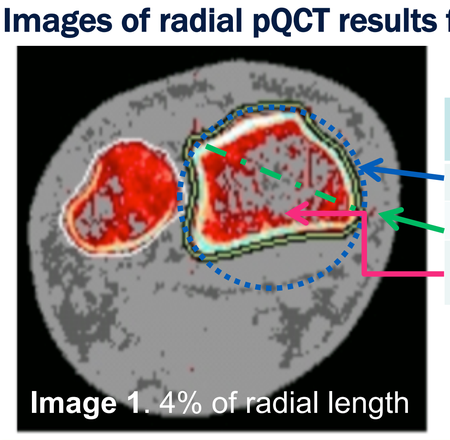


Image 1. 4% of radial length

Variable
BMC total
CSA total bone
vBMD Trabecular

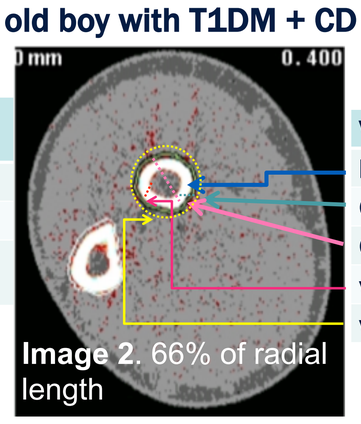


Image 2. 66% of radial length

Variable
BMC Cortical
Cortical thickness
CSA total bone
vBMD Cortical
vBMD Total

Interpretation

- Reduced trabecular bone density is evident – with reduced lumbar spine vBMD, and reduced trabecular vBMD in both the radius and tibia.
- Radial cortical bone essentially normal, as was total body BMD.
- Tibial bone results indicate increased size, with thin and dense cortices.
- Muscle mass and muscle bone health in relation for total body and tibia are normal, with reduced muscle CSA in the radius.

Conclusions

- Patient group has overall normal bone, ie. > -2.0 SD
- Statistically significant reduction in trabecular bone mass in all areas measured
- pQCT data suggest discrepency between cortical bone development in radius and tibia which requires further investigation

Future Research

- Prospective studies (DEXA and pQCT scans every 1-2 years) in youth with T1D and CD, and T1D (control data) are needed to understand the natural history of bone density in to adulthood. In addition, the relationship between optimal management of T1D and CD, and bone outcomes, should be examined.

Screening Intervals For Coeliac Disease In Youth With Type 1 Diabetes: Systematic Review

Anna Pham-Short[1,2], Kim C Donaghue[1,2], Geoffrey Ambler[1,2], Helen Phelan[3], Stephen Twigg[2,4], Maria E Craig [1,2,5]

1. The Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia
2. Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia
3. John Hunter Children's Hospital, Newcastle, Australia
4. Royal Prince Alfred Hospital, Sydney, Australia
5. School of Women's and Child's Health, University of New South Wales, Sydney, Australia

Background

The co-existence of type 1 diabetes (T1D) and coeliac disease (CD) has been recognised since the 1960s but data on the optimal screening frequency for CD in T1D are limited. Prevalence rates from cross sectional and longitudinal studies range from 1.6% to 16.4% worldwide.

Recognized side effects of untreated CD include iron deficiency, anaemia, and growth retardation. In T1D, non-adherence to the gluten free diet has been associated with early elevation of albumin excretion rate, whilst CD duration beyond 10 years irrespective of GFD adherence, has been associated with diabetic retinopathy. The rationale for CD screening in T1D is to prevent these complications and to maximise growth.

Seroconversion from negative to positive CD autoantibodies can occur beyond 10 years of T1D duration, further supporting the importance of repeated screening for CD.

Despite the well-recognised increased risk of CD in T1D and the potential for increased morbidity, there are no systematic reviews examining incidence of CD nor the optimal screening frequency for CD in T1D. The recommended screening frequency is variable and not evidence based. Thus, we systematically reviewed incidence and prevalence of CD in people with T1D in order to inform screening guidelines.

Objectives

To systematically review the incidence and prevalence of coeliac disease (CD) in type 1 diabetes (T1D) and determine the optimal screening frequency for CD.

Study Aims

1. Systematically review the epidemiology of biopsy proven CD in people with T1D, with subgroup analysis by age, gender and duration of diabetes.

2. Review the risk of CD in people at the time of T1D diagnosis, and specific time points after diagnosis to determine optimal screening frequency.

Methods

Inclusion Criteria:

- Longitudinal studies
- Screened for CD using either endomysial antibodies (EMA), or tissue transglutaminase autoantibodies (TTG) at least twice
- Children, adolescents of adults with T1D
- Human studies
- Reported in English
- CD confirmed by small bowel biopsy

Databases used: EMBASE, Medline, Cochrane to 30th June 2014

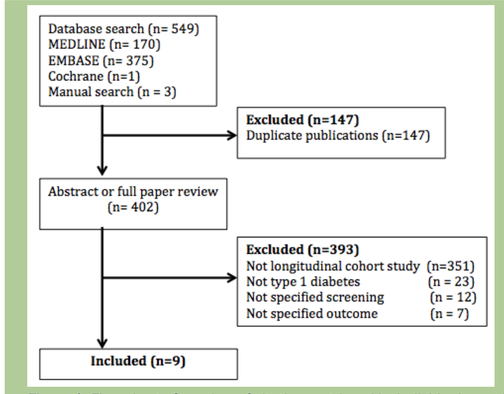
Study quality assessed by Newcastle-Ottawa quality assessment scale

Outcomes examined: prevalence, incidence, cumulative incidence

Pooled prevalence calculated as the total number of CD cases divided by the total number of patients screened (n=11,156)

Incidence density: calculated as total number of diagnosed cases divided by the number of patients screened up to point of interest (n = 4839, 8789, and 20,299 at 1,2 and 5 years respectively).

Results



Included studies:

- Barera, Pediatrics 2002
- Cerutti, Diabetes Care 2004
- Crone, J Ped Gastr Nutr 2003
- Glastras, Diabetes Care 2005
- Larsson, Paed Diabetes 2008
- Pham-Short , Diabetic Medicine 2012
- Poulain, Diabetes Metab 2007
- Salardi, J Ped Gast Nutr 2008
- Uibo, Ped Intern 2010

Figure 1. Flow chart of number of citations retrieved by individual searches and number of studies included in review

Results

- 9 studies – 7 from Europe, 2 from Australia
- Total population: 11,156 young people diagnosed with T1D < 21 years
- Median follow up time 10 years (range 5 – 18 years)
- 587 cases of biopsy proven CD – 41 CD cases diagnosed prior to T1D]
- Pooled prevalence – 5.3%
- Seroconversion ranged from 2 – 10.2 years
- No relationship between age at diabetes diagnosis, nor gender
- Five studies reported CD symptomology in those with T1D and CD (n=308), 85% of cases asymptomatic and identified via screening
- Screening recommendations from studies variable – ranging from at DM diagnosis, to annually for 'several' years

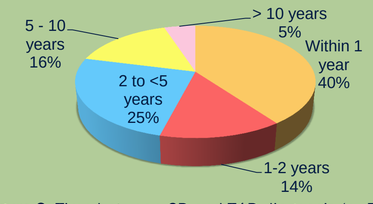


Figure 2. Time between CD and T1D diagnosis (n=536)

Table 1. Pooled incidence density calculated from available data in publications

Diabetes duration	Incidence / 1,000 patient years
1 year	43.3
2 years	32.7
5 years	20.0

Conclusions

CD is relatively common in young persons under 21 years of age with T1D; greatest risk is within 1 year of diabetes onset but 21% are diagnosed after more than 5 years diabetes duration.

We recommend screening at diabetes diagnosis, annually for the first 2 years, and again at least once before 5 years of diabetes duration.

Whilst CD can be diagnosed beyond 10 years after diabetes diagnosis, more research is required to establish the optimal screening frequency beyond 5 years of diabetes duration as well as the optimal screening frequency in adults with T1D.

Correspondence: Maria Craig: m.craig@unsw.edu.au, Anna Pham-Short: anna.pham@health.nsw.gov.au

Quality of Life in Type 1 Diabetes and Celiac Disease: Role of the Gluten Free Diet

Anna Pham-Short[1,2], Kim C Donaghue[1,2], Geoffrey Ambler[1,2], Sarah Garnett[1,2], Maria E Craig[1,2,3]

[1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Australia [2] Discipline of Child and Adolescent Health, University of Sydney

[3] School of Women's and Child's Health, University of New South Wales

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Background

Evidence of long-term negative outcomes for individuals living with type 1 diabetes (T1D) and celiac disease (CD) are emerging; these include an increased risk of retinopathy, nephropathy, and subclinical atherosclerosis, at times independent of glycemic control. This suggests that those who struggle with the coexistence of both chronic conditions are at higher risk of complications; however, there is a paucity of data on the impact of living with both conditions on quality of life (QoL) and general well-being.

T1D negatively impacts QoL, particularly among girls and prepubertal children. Mealtime behaviour problems in T1D are commonly reported, compounded by the demands of carbohydrate counting and eating to manage blood glucose levels independent of hunger. CD is managed by a GFD, which requires the substitution of commonly available carbohydrate foods such as wheat-based breads, cereal, and pasta. Continuous subcutaneous insulin infusion (CSII) allows for flexibility with meal times and food choices, and thus can alleviate the restrictive nature of the GFD. However, the impact of CSII on QoL in those with T1D+CD has not been studied.

QoL studies in those with T1D + CD are scarce and conflicting. The only pediatric study found no difference in generic or diabetes-specific QoL in those with T1D + CD compared to T1D alone. In contrast, adults with T1D + CD reported lower generic and diabetes specific QoL. Given these conflicting findings, we examined the effect of the 'double diagnosis' on QoL, well-being and eating behaviours in youth and their parents.

Objectives

To evaluate quality of life (QoL) and glycemic control in youth with T1D + CD vs T1D only. We hypothesize that QoL scores would be lower in youth with T1D + CD and those non-adherent to the gluten free diet (GFD) compared with their peers with T1D only.

Methods

Patient population

- Cross-sectional case control study of youth with T1D + CD (n=35) and T1D alone (n=35) attending routine diabetes outpatient clinic appointments.
- **Inclusion criteria:** • 8-18 years • T1D ≥ 1 year • CD ≥ 6 months
- Cases matched by age (± 1 year), diabetes duration (± 1 year), most recent HbA1c (± 0.5%) and mode of diabetes management (MDI or CSII). Controls had at least one negative CD screen in previous 12 months

Questionnaires

- Youth and their parents/guardians completed age-specific questionnaires and proxy questionnaires at the study visit
- Generic QoL measured by: PedsQL Generic Core Scale (version 4.0), General Well-Being Scale (GWBS, Standard Version)
- Diabetes specific QoL measured by: PedsQL Diabetes Module (version 3.2)
- Eating behaviours measured by: Locally modified Eating Behaviours questionnaire
- Parents/guardians also completed the PedsQL Family Impact Scale
- Celiac disease specific QoL measured by: Celiac disease DUX (CDDUX)

Respondents asked to rate how frequently each item was problematic over the past 1 month Each questionnaire assigned a total and subdomain score ranging from 0 to 100, with higher scores reflecting higher QoL/general wellbeing or healthier eating behaviours.

GFD Adherence

- Assessed both clinically and serologically

Results

- Generic, diabetes-specific, general well being, family impact, and eating behaviour QoL scores did not differ between those with T1D + CD vs T1D only
- GFD- youth reported lower general well-being (P=0.2), and diabetes-specific QoL (P=0.003) than youth GFD+
- GFD- youth and their parents were less likely to find the diet beneficial than their GFD+ peers (P = 0.04 and P=0.03)
- CSII and MDI patients with T1D + CD reported similar overall QoL scores for all questionnaires. CSII youth indicated on the CDDUX they were unhappier about having to follow a life-long diet (P=0.01), with their parents reporting greater diabetes treatment barriers (P=0.35) on the diabetes-specific QoL questionnaire.
- Duration of CD or T1D (either as continuous or categorical variable) was not associated with any QoL measures.

Table 1. Clinical characteristics of patient groups stratified by presence or absence of celiac disease and GFD adherence in those with celiac disease

	T1D only (n=35)	T1D + CD (n=35)	*P*	GFD+ (n=24)	GFD- (n=11)	*P*
Female n (%)	19 (54)	20 (57)	0.81	12 (50%)	8 (73)	0.21
Age at study visit (y)	13.6 ± 3	13.7 ± 3.1	0.93	13.5 ± 3.1	14.2 ± 3.1	0.52
Age at diabetes diagnosis (y)	6.1 ± 3.8	6.1 ± 3.9	0.9	6.3 ± 4.1	5.7 ± 3.6	0.68
Diabetes duration (y)	7.5 ± 3.9	7.6 ± 3.3	0.57	7.2 ± 3.4	8.5 ± 3.0	0.26
HbA1c at visit (%)	8.4 ± 1.6	8.5 ± 1.6	0.99	**8.0 ± 1.2**	**9.6 ± 1.9**	**0.02**
Lifetime HbA1c (%)	7.8 ± 0.8	8.0 ± 0.7	0.21	**7.8 ± 0.7**	**8.5 ± 0.6**	**0.007**
CSII, n (%)	26 (74)	23 (66)	0.43	16 (67)	7 (64)	0.86
Insulin, U/kg/d	0.9 ± 0.3	0.9 ± 0.2	0.50	0.9 ± 0.2	0.9 ± 0.3	0.9
Age at CD diagnosis (y)	-	9.1 ± 3.5		9.1 ± 3.6	9.1 ± 3.6	0.98
Duration of CD (y)		4.6 ± 2.7		4.4 ± 2.7	5.2 ± 2.7	0.42
Symptomatic before CD diagnosis		21 (60%)		**18 (75%)**	**3 (27%)**	**0.007**
GFD adopted within first year		25 (71%)		**24 (100%)**	**1 (9%)**	**<0.001**

Data are n (%) or mean + SD. Bold signifies results of significance, P < 0.05

Conclusions

- The additional diagnosis of CD does not impair QoL in youth nor their parents
- Youth non-adherent to the GFD have lower general well-being, and lower diabetes specific QoL, accompanied by worse glycemic control.
- Youth who displayed CD symptoms prior to diagnosis, or noted in retrospect were more likely to adhere to GFD and reported better QoL
- CSII and MDI patients reported similar diabetes specific QoL scores, however the CD specific questionnaire identifed CSII youth report greater burden with having to follow a lifelong diet
- GFD+ influenced by family support, CD awareness, and availablity of GF foods.
- As screening is now recognised as a standard of care in T1D, strategies are needed to intervene in those who resist the GFD. Regular monitoring of adherence in youth with coexisting T1D and CD will enable idenfication of the GFD- subgroup, who may benefit from more intensive clinical and pyschosocial support.

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Table 2. Total QoL questionnaire scores for youth with T1D vs youth T1D + CD, and GFD adherent vs GFD non-adherent T1D + CD youth

		T1D		T1D + CD		*P*	GFD+		GFD-		*P*
	Items	Mean ± SD	α	Mean ± SD	α		Mean ± SD	α	Mean ± SD	α	
GWBS – Child report	7	64 ± 26	0.90	70 ± 24	0.90	0.44	**76 ± 23**	**0.91**	**57 ± 20**	**0.86**	**0.02**
GWBS – Parent proxy report	7	72 ± 25	0.84	65 ± 22	0.84	0.29	**73 ± 22**	**0.83**	**50 ± 12**	**0.89**	**0.001**
PedsQL Generic – Child	23	83 ± 12	0.87	81 ± 12	0.88	0.34	84 ± 10	0.86	75 ± 14	0.88	0.11
PedsQL Generic – Parent proxy	23	76 ± 12	0.94	76 ± 13	0.89	0.98	77 ± 10	0.88	73 ± 17	0.9	0.39
PedsQL Diabetes Module - Child	33	73 ± 14	0.84	70 ± 16	0.95	0.36	**75 ± 13**	**0.95**	**58 ± 16**	**0.87**	**0.003**
PedsQL Diabetes Module – Parent proxy	33	70 ± 17	0.94	66 ± 15	0.91	0.29	68 ± 13	0.9	61 ± 17	0.92	0.25
Eating behaviour specific – Child	24	64 ± 9	0.6	62 ± 13	0.82	0.34	64 ± 14	0.85	57 ± 9	0.66	0.08
Eating behaviour specific – Parent	**24**	**68 ± 10**	**0.73**	**62 ± 13**	**0.78**	**0.045**	64 ± 13	0.84	57 ± 11	0.79	0.11
Family Impact Scale – Parent report	36	70 ± 17	0.97	68 ± 18	0.96	0.93	69 ± 17	0.96	65 ± 21	0.97	0.67

APPENDIX B. QUALITY OF LIFE QUESTIONNAIRES USED IN CHAPTER 6

i. 8-12 year old Child QoL questionnaires
ii. 8-12 year old Parent QoL questionnaires
iii. 13-18 year old Child QoL questionnaires
iv. 13-18 year old Parent QoL questionnaires
v. CDDUX – Coeliac Disease questionnaire

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Questionnaires

This survey aims to find out how different aspects of life effect of you and your family. The information we gather from this will help us understand how type 1 diabetes affects you and your family's life, shopping habits and your family's eating patterns.

On the following pages is a list of things that might be a problem for **you.** Please tell us **how much of a problem** each one has been for **you** during the **past ONE MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

Please take time to answer all the questions.

It will take about 20-30 minutes.

Thanks for your help in completing this survey.

If you have any questions, please contact Anna Pham-Short (02) 9845 3073

PedsQL – Pediatric Quality of Life Inventory Version 4.0 Child Report (ages 8 - 12)

In the past **ONE month**, how much of a **problem** has this been for you..

ABOUT MY HEALTH AND ACTIVITIES (*problems with…)*	Never	Almost never	Some times	Often	Almost always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS (*problems with…)*	Never	Almost never	Some times	Often	Almost always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

ABOUT SCHOOL (*problems with…)*	Never	Almost never	Some times	Often	Almost always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

Directions

Children with diabetes sometimes have special problems. Please tell us **how much of a problem** each one has been for **you** during the past ONE month by circling.

In the past **ONE month**, how much of a **problem** has this been for you…

ABOUT MY DIABETES (*problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel hungry	0	1	2	3	4
2. I feel thirsty	0	1	2	3	4
3. I have to go to the bathroom too often	0	1	2	3	4
4. I have tummy aches	0	1	2	3	4
5. I have headaches	0	1	2	3	4
6. I feel like I need to throw up	0	1	2	3	4
7. I go “low”	0	1	2	3	4
8. I go “high”	0	1	2	3	4
9. I feel tired	0	1	2	3	4
10. I get shaky	0	1	2	3	4
11. I get sweaty	0	1	2	3	4
12. I feel dizzy	0	1	2	3	4
13. I feel weak	0	1	2	3	4
14. I have trouble sleeping	0	1	2	3	4
15. I get cranky or grumpy	0	1	2	3	4

TREATMENT – I (*problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It hurts to get my finger pricked	0	1	2	3	4
2. It hurts to get insulin shots	0	1	2	3	4
3. I am embarrassed by my diabetes treatment	0	1	2	3	4
4. My parents and I argue about my diabetes care	0	1	2	3	4
5. It is hard for me to do everything I need to do to care for my diabetes	0	1	2	3	4
6. It hurts to get my finger pricked	0	1	2	3	4

Whether you do these things **on your own or with the help of your parents**, please answer how hard these things were to do in the past **ONE month**

Treatment – II (*problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to take blood glucose levels	0	1	2	3	4
2. It is hard for me to take insulin shots	0	1	2	3	4
3. It is hard for me to exercise or do sports	0	1	2	3	4
4. It is hard for me to keep track of carbohydrates	0	1	2	3	4
5. It is hard for me to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for me to snack when I go “low”	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you…

Worry (*problems with…)*	Never	Very seldom	Some times	Often	All the time
1. I worry about going “low”	0	1	2	3	4
2. I worry about going “high”	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you…

Worry (*problems with…)*	Never	Very seldom	Some times	Often	All the time
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4
4. I am embarrassed about having diabetes	0	1	2	3	4

Directions

These questions are about meals and eating for you and your family. Please tell us which statement applies to you and your family by circling the numbers.

I FIND…	Never	Almost Never	Some-times	Often	Almost Always
1. I like eating meals	0	1	2	3	4
2. I eat the same meals as the rest of the family	0	1	2	3	4
3. I get to choose what I want to eat	0	1	2	3	4
4. Eating what the hospital has told me to is easy to follow	0	1	2	3	4
5. I think my parents don’t give me enough food	0	1	2	3	4
6. I think my parents give me too much food	0	1	2	3	4
7. I like trying new foods	0	1	2	3	4
8. My parents tell me when and how much to eat	0	1	2	3	4
9. I decide how much and when to eat	0	1	2	3	4

FAMILY AND FRIENDS	Never	Almost Never	Some-times	Often	Almost Always
10. I help prepare meals	0	1	2	3	4
11. Our family likes eating the same foods together	0	1	2	3	4
12. Our family eats dinner together	0	1	2	3	4
13. I help shop for food	0	1	2	3	4
14. Friends are interested in what I eat	0	1	2	3	4
15. Friends tease me about what I eat	0	1	2	3	4
16. Choosing foods is easy when going out with family/friends	0	1	2	3	4
17. The TV is on during meals	0	1	2	3	4
18. I find it hard to eat at school	0	1	2	3	4
19. My family argues about what I should eat	0	1	2	3	4
20. I think what I eat is important	0	1	2	3	4
21. Outside of home, we ask how people make food	0	1	2	3	4

CARBOHYDRATE COUNTING	Never	Almost Never	Some-times	Often	Almost Always
22. My parents count carbohydrates for me	0	1	2	3	4
23. I count carbohydrates	0	1	2	3	4
24. Before I eat, my parents use things to figure out how much I can eat	0	1	2	3	4
We use: Measuring cups/Kitchen scales/Traffic Light Guide To Food Carbohydrate Counter/Calorie King / Other: _____	0	1	2	3	4

Tell us what you think…

25. What do you like **most** about meals and eating?

_____

_____

26. What do you like **least** about meals and eating?

_____

_____

27. How many times a week does your family eat dinner together?

_____

Please tick:

I have ☐ Type 1 diabetes for _____ years ☐ Coeliac Disease for _____ years

THANK YOU FOR YOUR TIME

****

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Questionnaires

This survey aims to find out different aspects of life effect of your child and family. The information we gather from this will help us understand how type 1 diabetes affects you and your family's life, shopping habits and your family's eating patterns.

On the following pages is a list of things that might be a problem for **your child.**

Please tell us **how much of a problem** each one has been for **your child** during the **past ONE MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

Please take time to answer all the questions.

It will take about 20-30 minutes.

Thanks for your help in completing this survey.

If you have any questions, please contact Anna Pham-Short (02) 9845 3073

In the past ONE month, **how much of a** problem **has your child had with…**

DIABETES *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Feeling hungry	0	1	2	3	4
2. Feeling thirsty	0	1	2	3	4
3. Having to go to the bathroom too often	0	1	2	3	4
4. Having tummy aches	0	1	2	3	4
5. Having headaches	0	1	2	3	4
6. Feeling like he/she needs to throw up	0	1	2	3	4
7. Going "low"	0	1	2	3	4
8. Going "high"	0	1	2	3	4
9. Feeling tired	0	1	2	3	4
10. Getting shaky	0	1	2	3	4
11. Getting sweaty	0	1	2	3	4
12. Feeling dizzy	0	1	2	3	4
13. Feeling weak	0	1	2	3	4
14. Having trouble sleeping	0	1	2	3	4
15. Getting cranky or grumpy	0	1	2	3	4

In the past ONE month, **how much of a** problem **has your child had with…**

TREATMENT – I *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Finger pricks causing him/her pain	0	1	2	3	4
2. Insulin shots causing him/her pain	0	1	2	3	4
3. Getting embarrassed about his/her diabetes treatment	0	1	2	3	4
4. Arguing with me or my spouse about diabetes care	0	1	2	3	4
5. It is hard for my child to do everything he/she needs to do to care for his/her diabetes	0	1	2	3	4

Whether your child does these things **independently or with your help**, please answer how difficult these things were to do in the past **ONE month.** (Note: This section is **not** asking about your child's independence in these areas, just how hard they were to do).

TREATMENT – II *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. It is hard for my child to take blood glucose levels	0	1	2	3	4
2. It is hard for my child to take insulin shots	0	1	2	3	4
3. It is hard for my child to exercise or do sports	0	1	2	3	4
4. It is hard for my child to track carbohydrates	0	1	2	3	4
5. It is hard for my child to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for my child to snack when he/she goes "low"	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has your child had with…

WORRY *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Worrying about going "low"	0	1	2	3	4
2. Worrying about going "high"	0	1	2	3	4

In the past **ONE month,** how much of a **problem** has your child had with…

COMMUNICATION *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Asking the doctors and nurses questions	0	1	2	3	4
3. Explaining his/her illness to other people	0	1	2	3	4
4. Getting embarrassed about having diabetes	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has your child had with…

PHYSICAL FUNCTIONING *(problems with…)*	**Never**	**Almost never**	**Some times**	**Often**	**Almost always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or sad	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Directions

Families of children sometimes have special concerns or difficulties because of the child's health. Below is a list of things that might be a problem for **you.** Please tell us **how much of a problem** each one has been for **you** during the past ONE month.

In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with**…**

Physical Functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

Emotional Functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I get frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

Social functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

Cognitive functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

Communication (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

Worry (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

Directions

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for your family during the **past ONE month**.

In the past **ONE month**, as a result of your child's health, how much of a problem has **your family** had with…

Daily activities (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

Family relationships (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

In the past **ONE month**, how often has your **child** had difficulty with…

Gastrointestinal Symptoms (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Pain in his/her abdomen or stomach	0	1	2	3	4
2. Diarrhoea	0	1	2	3	4
3. Constipation	0	1	2	3	4
4. Nausea	0	1	2	3	4
5. Vomiting	0	1	2	3	4
6. Discomfort in his/her abdomen or stomach	0	1	2	3	4
7. Passing gas	0	1	2	3	4
8. Not feeling hungry	0	1	2	3	4
9. Bloating	0	1	2	3	4

Directions

These questions are about meals and eating for your child and family. Please tell us which statement applies to you and your family by circling the numbers.

FOR YOUR CHILD'S EATING PATTERNS, YOU FIND…	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Meal times are enjoyable.	0	1	2	3	4
2. They eat the same meals as the rest of the family	0	1	2	3	4
3. They feel in control of their eating habits	0	1	2	3	4
4. The recommended meal plan is easy to follow	0	1	2	3	4
5. I give my child less food than they say they want	0	1	2	3	4
6. They like trying new foods	0	1	2	3	4
7. I decide how much and when my child eats	0	1	2	3	4
They decide how much and when to eat	0	1	2	3	4
8. Meal times are enjoyable.	0	1	2	3	4

FAMILY AND FRIENDS	Never	Almost Never	Some-times	Often	Almost Always
9. Preparation of family meals is difficult	0	1	2	3	4
10. Meals are accepted by family members.	0	1	2	3	4
11. Shopping for food is difficult	0	1	2	3	4
12. Shopping for food is expensive	0	1	2	3	4
13. Friends are interested in my child's eating pattern	0	1	2	3	4
14. Friends are not supportive of my child's eating pattern	0	1	2	3	4
15. Choosing foods is easy when going out with family/friends☐	0	1	2	3	4
16. It is difficult to find foods my child likes to eat	0	1	2	3	4
17. Meal times are difficult at school	0	1	2	3	4
18. Family members argue about what to feed my child	0	1	2	3	4
19. The diet is beneficial to my child.	0	1	2	3	4
20. Outside of home, we ask what ingredients are in meals	0	1	2	3	4

CARBOHYDRATE COUNTING	Never	Almost Never	Some-times	Often	Almost Always
21. I count carbohydrates for my child	0	1	2	3	4
22. My child counts carbohydrates	0	1	2	3	4
23. We use tools to help count carbohydrates	0	1	2	3	4
We use: Measuring cups/Kitchen scales/Traffic Light Guide To Food Carbohydrate Counter/Calorie King / Other: _____	0	1	2	3	4

Comment about your child's usual eating patterns

24. What does your child like **most** about meals and eating?

_____

_____

25. What does your child like **least** about meals and eating?

_____

_____

26. How many times a week does your family eat dinner together?

_____

My child has : ☐ Type 1 diabetes for _____ years ☐ Coeliac Disease for _____ years

THANK YOU FOR YOUR TIME

****

the children's hospital at Westmead

Questionnaires

This survey aims to find out how different aspects of life effect of you and your family. The information we gather from this will help us understand how type 1 diabetes affects you and your family's life, shopping habits and your family's eating patterns.

On the following pages is a list of things that might be a problem for **you.** Please tell us **how much of a problem** each one has been for **you** during the **past ONE MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

Please take time to answer all the questions.

It will take about 20-30 minutes.

Thanks for your help in completing this survey.

If you have any questions, please contact Anna Pham-Short (02) 9845 3073

In the past **ONE month**, how much of a **problem** has this been for you…

About my diabetes (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I feel hungry	0	1	2	3	4
2. I feel thirsty	0	1	2	3	4
3. I have to go to the bathroom too often	0	1	2	3	4
4. I have stomachaches	0	1	2	3	4
5. I have headaches	0	1	2	3	4
6. I feel like I need to throw up	0	1	2	3	4
7. I go “low”	0	1	2	3	4
8. I go “high”	0	1	2	3	4
9. I feel tired	0	1	2	3	4
10. I get shaky	0	1	2	3	4
11. I get sweaty	0	1	2	3	4
12. I feel dizzy	0	1	2	3	4
13. I feel weak	0	1	2	3	4
14. I have trouble sleeping	0	1	2	3	4
15. I get cranky or grumpy	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you…

Treatment – I (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. It hurts to get my finger pricked	0	1	2	3	4
2. It hurts to get insulin shots	0	1	2	3	4
3. I am embarrassed by my diabetes treatment	0	1	2	3	4
4. My parents and I argue about my diabetes care	0	1	2	3	4
5. It is hard for me to do everything I need to do to care for my diabetes	0	1	2	3	4

Whether you do these things **on your own or with the help of your parents**, please answer how hard these things were to do in the past **ONE month**

Treatment – II (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. It is hard for me to take blood glucose levels	0	1	2	3	4
2. It is hard for me to take insulin shots	0	1	2	3	4
3. It is hard for me to exercise or do sports	0	1	2	3	4
4. It is hard for me to keep track of carbohydrates	0	1	2	3	4
5. It is hard for me to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for me to snack when I go “low”	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you…

Worry (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I worry about going “low”	0	1	2	3	4
2. I worry about going “high”	0	1	2	3	4
3. I worry about long-term complications from diabetes	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you…

Communication (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4
4. I am embarrassed about having diabetes	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has this been for you..

About my health and activities (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About my feelings (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I get along with others (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About school (*problems with…)*	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I find it hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

In the past **ONE month**, how much does this **sound like you…**

About Me	**Never**	**Very seldom**	**Some times**	**Often**	**All the time**
1. I feel happy	0	1	2	3	4
2. I feel good about myself	0	1	2	3	4
3. I feel good about my health	0	1	2	3	4
4. I get support from my family or friends	0	1	2	3	4
5. I think good things with happen to me	0	1	2	3	4
6. I think my health will be good in the future	0	1	2	3	4

In the past **ONE month…**

In General	**Bad**	**Fair**	**Good**	**Very Good**	**Excellent**
1. In general, how is your health?	0	1	2	3	4

Directions

These questions are about meals and eating for you and your family. Please tell us which statement applies to you and your family by circling the numbers.

I FIND…	Never	Almost Never	Some-times	Often	Almost Always
1. I like eating meals	0	1	2	3	4
2. I eat the same meals as the rest of the family	0	1	2	3	4
3. I get to choose what I want to eat	0	1	2	3	4
4. Eating what the hospital has told me to is easy to follow	0	1	2	3	4
5. I think my parents don't give me enough food	0	1	2	3	4
6. I think my parents give me too much food	0	1	2	3	4
7. I like trying new foods	0	1	2	3	4
8. My parents tell me when and how much to eat	0	1	2	3	4
9. I decide how much and when to eat	0	1	2	3	4

FAMILY AND FRIENDS	Never	Almost Never	Some-times	Often	Almost Always
10. I help prepare meals	0	1	2	3	4
11. Our family likes eating the same foods together	0	1	2	3	4
12. Our family eats dinner together	0	1	2	3	4
13. I help shop for food	0	1	2	3	4
14. Friends are interested in what I eat	0	1	2	3	4
15. Friends tease me about what I eat	0	1	2	3	4
16. Choosing foods is easy when going out with family/friends	0	1	2	3	4
17. The TV is on during meals	0	1	2	3	4
18. I find it hard to eat at school	0	1	2	3	4
19. My family argues about what I should eat	0	1	2	3	4
20. I think what I eat is important	0	1	2	3	4
21. Outside of home, we ask how people make food	0	1	2	3	4

CARBOHYDRATE COUNTING	Never	Almost Never	Some-times	Often	Almost Always
22. My parents count carbohydrates for me	0	1	2	3	4
23. I count carbohydrates	0	1	2	3	4
24. Before I eat, my parents use things to figure out how much I can eat	0	1	2	3	4
We use: Measuring cups/Kitchen scales/Traffic Light Guide To Food Carbohydrate Counter/Calorie King / Other: _____	0	1	2	3	4

Tell us what you think…

25. What do you like **most** about meals and eating? _____
26. What do you like **least** about meals and eating? _____
27. How many times a week does your family eat dinner together? _____

Please tick: I have ☐ Type 1 diabetes for _____ years ☐ Coeliac Disease for _____ years

THANK YOU FOR YOUR TIME

****

the children's hospital at Westmead

Questionnaires

This survey aims to find out how different aspects of life effect of your child and family. The information we gather from this will help us understand how type 1 diabetes affects you and your family's life, shopping habits and your family's eating patterns.

On the following pages is a list of things that might be a problem for **your teen.**

Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

Please take time to answer all the questions.

It will take about 20-30 minutes.

Thanks for your help in completing this survey.

If you have any questions, please contact Anna Pham-Short (02) 9845 3073

In the past ONE month, **how much of a** problem **has your teen had with…**

DIABETES *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Feeling hungry	0	1	2	3	4
2. Feeling thirsty	0	1	2	3	4
3. Having to go to the bathroom too often	0	1	2	3	4
4. Having tummy aches	0	1	2	3	4
5. Having headaches	0	1	2	3	4
6. Feeling like he/she needs to throw up	0	1	2	3	4
7. Going "low"	0	1	2	3	4
8. Going "high"	0	1	2	3	4
9. Feeling tired	0	1	2	3	4
10. Getting shaky	0	1	2	3	4
11. Getting sweaty	0	1	2	3	4
12. Feeling dizzy	0	1	2	3	4
13. Feeling weak	0	1	2	3	4
14. Having trouble sleeping	0	1	2	3	4
15. Getting cranky or grumpy	0	1	2	3	4

In the past ONE month, **how much of a** problem **has your teen had with…**

TREATMENT – I *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Finger pricks causing him/her pain	0	1	2	3	4
2. Insulin shots causing him/her pain	0	1	2	3	4
3. Getting embarrassed about his/her diabetes treatment	0	1	2	3	4
4. Arguing with me or my spouse about diabetes care	0	1	2	3	4
5. It is hard for my teen to do everything he/she needs to do to care for his/her diabetes	0	1	2	3	4

Whether your teen does these things **independently or with your help**, please answer how difficult these things were to do in the past **ONE month.** (Note: This section is **not** asking about your teen's independence in these areas, just how hard they were to do).

TREATMENT – II *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. It is hard for my teen to take blood glucose levels	0	1	2	3	4
2. It is hard for my teen to take insulin shots	0	1	2	3	4
3. It is hard for my teen to exercise or do sports	0	1	2	3	4
4. It is hard for my teen to track carbohydrates	0	1	2	3	4
5. It is hard for my teen to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for my teen to snack when he/she goes "low"	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has your teen had with…

WORRY *(problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost always**
1. Worrying about going "low"	0	1	2	3	4
2. Worrying about going "high"	0	1	2	3	4

In the past **ONE month,** how much of a **problem** has your teen had with…

COMMUNICATION *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Telling the doctors and nurses how he/she feels	0	1	2	3	4
2. Asking the doctors and nurses questions	0	1	2	3	4
3. Explaining his/her illness to other people	0	1	2	3	4
4. Getting embarrassed about having diabetes	0	1	2	3	4

In the past **ONE month**, how much of a **problem** has your teen had with…

PHYSICAL FUNCTIONING *(problems with…)*	**Never**	**Almost never**	**Some times**	**Often**	**Almost always**
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling afraid or sad	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up when playing with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Directions

Families of children sometimes have special concerns or difficulties because of the child's health. Below is a list of things that might be a problem for **you.** Please tell us **how much of a problem** each one has been for **you** during the past ONE month.

In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with**…**

Physical Functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

Emotional Functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I get frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

Social functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

Cognitive functioning (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

Communication (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

Worry (*problems with…)*	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

Directions

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for your family during the **past ONE month**.

In the past **ONE month**, as a result of your child's health, how much of a problem has **your family** had with…

Daily activities (*problems with…*)	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

Family relationships (*problems with…*)	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

In the past **ONE month**, how often has your **child** had difficulty with…

Gastrointestinal Symptoms (*problems with…*)	**Never**	**Almost Never**	**Some times**	**Often**	**Almost Always**
1. Pain in his/her abdomen or stomach	0	1	2	3	4
2. Diarrhoea	0	1	2	3	4
3. Constipation	0	1	2	3	4
4. Nausea	0	1	2	3	4
5. Vomiting	0	1	2	3	4
6. Discomfort in his/her abdomen or stomach	0	1	2	3	4
7. Passing gas	0	1	2	3	4
8. Not feeling hungry	0	1	2	3	4
9. Bloating	0	1	2	3	4

Directions

These questions are about meals and eating for your child and family. Please tell us which statement applies to you and your family by circling the numbers.

FOR YOUR CHILD'S EATING PATTERNS, YOU FIND…	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Meal times are enjoyable.	0	1	2	3	4
2. They eat the same meals as the rest of the family	0	1	2	3	4
3. They feel in control of their eating habits	0	1	2	3	4
4. The recommended meal plan is easy to follow	0	1	2	3	4
5. I give my child less food than they say they want	0	1	2	3	4
6. They like trying new foods	0	1	2	3	4
7. I decide how much and when my child eats	0	1	2	3	4
They decide how much and when to eat	0	1	2	3	4
8. Meal times are enjoyable.	0	1	2	3	4

FAMILY AND FRIENDS	Never	Almost Never	Some-times	Often	Almost Always
9. Preparation of family meals is difficult	0	1	2	3	4
10. Meals are accepted by family members.	0	1	2	3	4
11. Shopping for food is difficult	0	1	2	3	4
12. Shopping for food is expensive	0	1	2	3	4
13. Friends are interested in my child's eating pattern	0	1	2	3	4
14. Friends are not supportive of my child's eating pattern	0	1	2	3	4
15. Choosing foods is easy when going out with family/friends☐	0	1	2	3	4
16. It is difficult to find foods my child likes to eat	0	1	2	3	4
17. Meal times are difficult at school	0	1	2	3	4
18. Family members argue about what to feed my child	0	1	2	3	4
19. The diet is beneficial to my child.	0	1	2	3	4
20. Outside of home, we ask what ingredients are in meals	0	1	2	3	4

CARBOHYDRATE COUNTING	Never	Almost Never	Some-times	Often	Almost Always
21. I count carbohydrates for my child	0	1	2	3	4
22. My child counts carbohydrates	0	1	2	3	4
23. We use tools to help count carbohydrates	0	1	2	3	4
We use: Measuring cups/Kitchen scales/Traffic Light Guide To Food Carbohydrate Counter/Calorie King / Other: _____	0	1	2	3	4

Comment about your child's usual eating patterns

24. What does your child like **most** about meals and eating?

_____

_____

25. What does your child like **least** about meals and eating?

_____

_____

26. How many times a week does your family eat dinner together?

_____

My child has : ☐ Type 1 diabetes for _____ years ☐ Coeliac Disease for _____ years

THANK YOU FOR YOUR TIME

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the children's hospital at Westmead

Coeliac Disease Questionnaire

This survey aims to find out how you feel about living with coeliac disease.

For each of the sentences, circle the face that best explains how you feel.

There are no right or wrong answers. If you do not understand a question, please ask for help.

Please take time to answer all the questions.

It will take about 5-10 minutes.

Thanks for your help in completing this survey.

If you have any questions, please contact Anna Pham-Short (02) 9845 3073

Communication

1. Talking about coeliac disease, I find…	
2. When I have to explain to others what coeliac disease is, I feel…	
Talking about my coeliac disease with others my age, I find…	

Having Coeliac Disease

4. When at school if I am given food containing gluten, I find it…	
5. When someone offers me food that I can't have, I feel…	
6. When I think of food containing gluten, I feel…	

Diet

7. Not being able to eat anything I want, I find…	
8. Having to follow a lifelong diet, I find…	
9. Having to pay attention to what I eat, I find…	
10. Having coeliac disease is…	
11. Not being able to eat all the things other people eat, I find…	
12. Following a diet for my coeliac disease is…