The Gastrointestinal Manifestations of Type One Diabetes Mellitus in Children

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Abstract

Introduction

Type one diabetes mellitus (T1DM) is one of the most common, serious chronic diseases of childhood. Hyperglycaemia causes well known micro- and macro-vascular complications. Less well explored are the ways the gastrointestinal (GI) system is affected. This research aimed to examine in depth three aspects of the gastrointestinal manifestations of T1DM.

Coeliac Disease

Coeliac Disease (CD) occurs more frequently in children with T1DM, the two diseases share genetic and environmental risk factors. To establish how clinicians in New Zealand screen for and manage CD in T1DM, a benchmark survey was performed. All paediatricians caring for children with T1DM in NZ were sent an online questionnaire with multi-choice and open questions regarding their individual practice.

Ninety-two percent of the clinicians replied. Most screen for coeliac disease in T1DM but approximately a third do not. Those that do not screen use poor control, poor growth and GI symptoms as a trigger for testing. All were sensitive to the burden of the double diagnosis.

Gastric emptying

Gastric emptying has been demonstrated to be delayed in adults with T1DM, which has potential adverse effects on blood sugar control and symptomatology. Evidence regarding the rate of gastric emptying in children with T1DM is conflicting and inconclusive. This pilot study aimed to investigate gastric emptying in children with T1DM and in health. Gastric emptying was measured using Carbon 13 (C13) breath testing, a non-invasive, very low risk procedure.

Nineteen cases and 15 age and sex matched controls underwent testing. The mean gastric emptying coefficient [mean (95% CI)] in cases was higher than in controls, indicating a shorter gastric emptying time (3.19 (2.97 – 3.41) vs 2.90 (2.74 - 3.10), p = 0.03). Mean
GET1/2 [mean (95% CI)] was not different between the two groups (cases 99 (68 - 128) mins vs 103 (88-118) mins, p = 0.8).

Secondary analysis suggested that there was a relationship between the duration of T1DM and the speed of gastric emptying but numbers were small and the result did not meet statistical significance.

**Gastrointestinal symptoms:**

Anecdotally children with T1DM are said to complain of more GI symptoms than their healthy peers. We aimed to prospectively establish the frequency and intensity of GI symptoms in a clinic population of New Zealand children with T1DM compared to an aged-matched group of healthy children. Caregivers were given a 10 item questionnaire about their child’s experience of GI symptoms in the previous month. Responses were marked on a Likert scale, from 0 (not at all) to 4 (a whole lot). Participant’s scores for each question were also summed together to give an overall score as a marker of the overall intensity of symptoms.

Two hundred and forty four children completed the questionnaire. Cases and controls had similar rates of any GI symptoms (80% of controls v 85% cases, OR 1.5 (95% CI: 0.7-3.1)). Children with T1DM had higher mean scores for abdominal pain (1.3 v 1.0, p = 0.02) and reflux (0.4 v 0.20, p = 0.02). The overall mean score was also higher in cases (4.9 v 3.4, p = 0.02) indicating the intensity of their complaints was higher than healthy controls.

**Conclusion:**

This thesis shows the importance of the gastrointestinal manifestations of T1DM in children. Further research to expand upon our knowledge of these manifestations will allow for improved management of T1DM in children.
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Many friends, my parents and parents-in-law have provided practical help to enable me to complete this research; I hope I will be able return the support one day.

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Lastly I would like to say thank you to the children and their families who so willingly took part in my research, giving up their free time to help me.

*Na to rourou na taku rorrou-
ka ora ai te iwi*

*With your food basket and my food basket-
The people will thrive*
Publications

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Presentations

Oral

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Paediatric Society of New Zealand Annual Scientific Meeting 2013 -
Oral presentation: “Gastric emptying in Children with T1DM” (Winner: Paediatric Young Investigator of the Year)
Rapid Fire Presentation: “Gastrointestinal symptoms in children with T1DM”.

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Paediatric Society of New Zealand Annual Scientific Meeting 2013 – "Gastrointestinal symptoms in children with T1DM".
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<th>Description</th>
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<tbody>
<tr>
<td>AGA</td>
<td>Anti-gliadin antibodies</td>
</tr>
<tr>
<td>AN</td>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BSL</td>
<td>Capillary blood glucose</td>
</tr>
<tr>
<td>C\textsubscript{13}</td>
<td>Carbon 13</td>
</tr>
<tr>
<td>C\textsubscript{14}</td>
<td>Carbon 14</td>
</tr>
<tr>
<td>CD</td>
<td>Coeliac Disease</td>
</tr>
<tr>
<td>CO\textsubscript{2}</td>
<td>Carbon Dioxide</td>
</tr>
<tr>
<td>DAISY</td>
<td>Diabetes Auto Immunity Study in the Young</td>
</tr>
<tr>
<td>EEG</td>
<td>Electrogastrography</td>
</tr>
<tr>
<td>EMA</td>
<td>Anti-endomysial antibodies</td>
</tr>
<tr>
<td>FGID</td>
<td>Functional Gastrointestinal Disease</td>
</tr>
<tr>
<td>FH</td>
<td>Family History</td>
</tr>
<tr>
<td>GAD</td>
<td>Glutamic acid decarboxylase</td>
</tr>
<tr>
<td>GEC</td>
<td>Gastric Emptying Coefficient</td>
</tr>
<tr>
<td>GET\textsubscript{\textfrac{1}{2}}</td>
<td>Gastric half emptying time</td>
</tr>
<tr>
<td>GET\textsubscript{lag}</td>
<td>Gastric emptying lag time</td>
</tr>
<tr>
<td>GET\textsubscript{max}</td>
<td>Maximum gastric emptying time</td>
</tr>
<tr>
<td>GFD</td>
<td>Gluten free diet</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GIP</td>
<td>Glucose dependent insulinotrophic peptide</td>
</tr>
<tr>
<td>GLP</td>
<td>Glucagon like peptide</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health related Quality of Life</td>
</tr>
<tr>
<td>IA2A</td>
<td>Insulinoma-associated autoantigen 2</td>
</tr>
<tr>
<td>IAA</td>
<td>Insulin auto antibodies</td>
</tr>
<tr>
<td>ICC</td>
<td>Interstitial cells of cajal</td>
</tr>
<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
</tr>
<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
</tr>
<tr>
<td>NOD</td>
<td>Non-obese diabetic mice</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>OBT</td>
<td>Carbon 13 oral breath test</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PMH</td>
<td>Past medical history</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>T1DM</td>
<td>Type one diabetes mellitus</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type two diabetes mellitus</td>
</tr>
<tr>
<td>TEDDY</td>
<td>The Environmental Determinants of Diabetes in the Young</td>
</tr>
<tr>
<td>TTG</td>
<td>Tissue transglutaminase</td>
</tr>
<tr>
<td>ZnT8A</td>
<td>Zinc transporter 8</td>
</tr>
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</table>
Chapter One: Introduction

Autoimmune Type one diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood (1). Destruction of the pancreatic islet cells results in an absence of circulating endogenous insulin (2). Glucose cannot be utilised by cells, resulting in hyperglycaemia and intra cellular starvation (2). Exogenous insulin injections allow for survival but so far cannot replicate a smooth physiological homeostasis of blood glucose levels, with most patients spending at least part of the day out of the physiological range (3). The resulting hyperglycaemia causes well-documented complications, involving the eye, kidney, heart and brain, as well as peripheral nerve damage (4-7).

Often mentioned by clinicians, but not as well documented in the literature, are effects on the gastrointestinal (GI) system. The gut is intrinsically involved in the delivery of the components of food to the blood stream and in turn its mechanism of action is affected by the blood glucose level (8). Coeliac disease (CD) occurs more commonly in children with T1DM (9), the two disease states have common genetic predispositions and hypothesised causal mechanisms, which raises the question of the utility of screening (10). The rate of gastric emptying is known to be altered in T1DM (11). Children with T1DM have reason to complain more of GI symptoms, and anecdotally do.

This thesis aims to explore the gastrointestinal manifestations of T1DM with particular reference to CD, GI symptoms and gastric emptying.

1.1 Diabetes mellitus type one

1.1.1 Definition

Diabetes mellitus is diagnosed when an individual’s blood glucose is persistently elevated in the presence of hyperglycaemic symptoms. The current consensus is a fasting blood glucose of $\geq 7.0$ mmol, or a random blood glucose of $\geq 11.1$ mmol in a patient with classic symptoms of hyperglycaemia or a blood glucose of greater than 11.5 mmol during a standardised oral glucose tolerance test (12). Diabetes mellitus is classified as “Type one” when there is an absence of circulating insulin and can be further classified either as autoimmune, with evidence of autoimmunity to the pancreatic beta cells, or less commonly idiopathic, when there are no diabetes-associated autoantibodies detectable in the blood (2).
1.1.2 Epidemiology of T1DM

The International Diabetes Federation (13) estimates that approximately 500,000 children are living with T1DM worldwide.

The International Diabetes Federation has published worldwide incidence rate estimates. However, prevalence and incidence rates vary in different geographical areas around the world. The estimated rates are highest in developed European and Northern American countries but estimated rates in New Zealand and Australia are almost as high (13, 14) (Figure 1.1).

![Figure 1.1: Estimated new cases of T1DM (<15yrs) per 100,000 children per year, 2015, used with permission IDF (13)](image)

Most epidemiological data in New Zealand has been collected from Auckland or Canterbury populations and the overall trend is to increasing numbers of children diagnosed and living with T1DM.

A New Zealand wide, prospective case reporting study found an annual incidence of 17.9/100,000 in children 0-14 years old during 1999-2000 (15). A more recent estimate comes from a report from a national “virtual register” collected from DHB records, which reported 1103 children younger than 15 living with T1DM in 2011, giving a nationwide prevalence of 127/100,000 (16).
Regional studies within New Zealand have also demonstrated increasing incidence and prevalence rates. Examination of a comprehensive database of children with T1DM in the Auckland region showed that incidence rates had increased over time. In 2009, the Auckland regional incidence of T1DM was reported as 22.5/100000 in children younger than 15 years old compared to 10.9 per 100,000 in 1990, \( p < 0.0001 \) (17) (Figure 1.2). A Canterbury study showed an incidence of 28.6/100,000 in 2004, the highest since 1970, although significant year-to-year variation over the 20 years of data collection should be noted (18).

![Figure 1.2: Change in incidence over time in Auckland children. From Derraik (17).](image)

A prevalence study in Canterbury youth found a prevalence of 443/100000 in 15 – 19 year olds in 2010 (19). This represented a 20% rise in absolute numbers from a study seven years earlier, which reported prevalence rates of 369/100000 (20), however the increase did not meet statistical significance (19).

Although the exact numbers vary, and have varied over time, the lowest reported prevalence rate predicts that approximately 1/500 school children in NZ have a diagnosis of T1DM (13). This represents a significant burden of disease both in terms of
numbers of children living with a chronic illness and in monetary value as it has been estimated that each person with T1DM in NZ requires a healthcare spend of approximately 4962 US dollars per person per year (13).

1.1.3 Pathophysiology

The underlying deficit in T1DM is insulin deficiency due to endocrine pancreatic failure, however the exact process that leads to this is an area that has generated much investigation. In autoimmune T1DM, it is clear that there is a complex interaction of genetic and environmental factors that eventually leads to autoimmune destruction of the insulin secreting islet cells of the pancreas.

The autoimmunity is evidenced by antibodies directed against the beta cells. Ninety percent of newly diagnosed individuals with T1DM have at least one of either: auto antibodies to insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated autoantigen 2 (IA2A), and/or zinc transporter 8 (ZnT8A) (21). A cohort study with 20 years of follow up has demonstrated that antibodies may precede the development of clinical diabetes by many years, however the presence of the antibodies does not necessarily mean that the disease state will follow (22).

1.1.4 Genetics

There is a clear familial predisposition to developing T1DM. First-degree relatives have a 1-15% chance of developing T1DM compared to 0.1% risk in the general North American population, while identical twins have a 23-50% lifetime risk (23, 24).

The biggest genetic susceptibility appears to come from the major histocompatibility complex (MHC) on chromosome 6 (25). The MHC includes the genetic code for Human Leucocyte Antigens (HLA), cell surface glycoproteins that are involved in antigen presentation to T cells. There are two classes of HLA. Class II HLA are mostly expressed on B lymphocytes, dendritic cells, macrophages and activated T lymphocytes, they are recognised by CD4 helper/inducer T cells (23). Polymorphisms of these class II HLA are linked to T1DM. Changes in the structure of the HLA alter autoantigen binding and are thought to increase and decrease susceptibility to T1DM (26, 27).

Two specific HLA polymorphisms are found in 90% of patients with T1DM: HLA-DR3,DQB1*0201 (also known as DR3-DQ2) and/or HLA-DR4,DQB1*0302 (also known as DR4-DQ8). This carriage rate is more than double that of controls with either haplotype,
who have been demonstrated to have carriage rates of around 40% (28). Carrying both versions of the allele confers the biggest risk. For example, a population in Denver with a high proportion of DR3-DQ2 and DR4-DQ8 carriage rates, found that children with both alleles had a 5% chance of developing T1DM compared to 0.3% in the general population (29, 30).

HLA genes are inherited in an autosomal fashion, but as the incomplete concordance of the diabetes phenotype in carriers of the at-risk HLA genes demonstrates, T1DM is a polygenic condition. At least 40 other loci have been identified as involved in T1DM risk (23). Genes that have generated interest include, the insulin gene on chromosome 11 and genes that are involved in antigen presentation, CTLA4, PTPN22 and Cd25 (23). Several other genes are of interest: some of these loci are common to CD and T1DM (31).

1.1.5 Environmental factors

Whilst most children with T1DM carry at least one HLA gene that confers risk, most children who carry the risk genes do not develop diabetes, and 80% of cases of T1DM do not occur in individuals with an affected family member (25). This degree of variability suggests that environmental factors must impact on the expression of the genetic information that then results in the T1DM phenotype.

As discussed earlier, incidence studies have repeatedly shown that the incidence of T1DM is rapidly on the rise (3, 13). This change is too rapid to be attributable to genetic changes and suggests that environmental factors play a significant role in the development of T1DM. A proposed a model for how T1DM develops is that while a genetic susceptibility is key, environmental factors are probably important throughout the entire natural history of the disease (3). Proposed environmental factors include, viruses, diet and the interplay of the gut microbiota and exposure to antigens.

Investigating the potential role viruses may play has been a major area of attention, particularly enterovirus and norovirus. These common pathogens are postulated to either directly infect the pancreas and cause destruction or trigger autoimmunity. Viruses have been demonstrated in animal models and humans to cause lymphopenia (32) and have been found in pancreatic cells (33-35). Norovirus is one of the four most common pathogens found in an observational study of genetically at risk toddlers, although an association with disease has yet to be demonstrated (36).
Another area of intense focus has been diet. Longitudinal cohort studies - such as the Diabetes Auto Immunity Study in the Young (DAISY) (37), Babydiet (38) and The Environmental Determinants of Diabetes in the Young (TEDDY) (39) have followed children at risk of T1DM and examined many environmental and anthropometric data. Areas of interest include breastfeeding, introduction of solids, dietary glucose, cow’s milk intake and introduction of gluten. No single food has been shown to “cause” T1DM although the research has given rise to recommendations: 4-5 months of age is safe for the introduction of solids (37), gluten exposure is not related to the development of T1DM (40, 41) and that breastfeeding maybe protective (42). Reducing exposure to cow’s milk protein in infancy initially looked promising, but an intervention study, with 7 years of follow up has not demonstrated a change in incidence (43).

Vitamin D has also been of interest; a large cohort study in Finnish children did show an association between vitamin D supplementation and lower rates of T1DM (44). However no association was found between measured vitamin D levels and the risk of T1DM in another study (45).

Individuals with T1DM show greater levels of certain bacteria compared to healthy controls (46-48). Animal models have shown that exposure to certain bacteria is protective against the development of diabetes in non-obese diabetic (NOD) and biobreeding diabetes-prone mice (48). Other investigators have demonstrated that when a strain of bacteria capable of disrupting intestinal barrier function was introduced to NOD mice the rate of progression to insulinitis increased (49).

Many of the postulated mechanisms for the development of T1DM could potentially mediate their effect via the gut. Food is obviously digested in the gut, enterovirus and norovirus are gut pathogens. Certain patterns of gut microbiota are associated with T1DM, it is postulated that strains of flora are associated with pro inflammatory environments, leading to the introduction of antigens to the submucosa and the subsequent development of autoimmunity (48).
1.2 Coeliac Disease

1.2.1 Definition

CD is the most widely recognised and commonly seen co-morbid GI condition seen in T1DM.

CD is a chronic enteropathy of the small bowel. In genetically predisposed individuals, exposure to dietary gluten causes an immune response in the villi of the small bowel, the ongoing villous atrophy and crypt hyperplasia lead to nutrient malabsorption (50). It can be classified as classical, non-classical and the increasingly recognized subclinical, which is defined as evidence of autoimmunity with no or few clinical findings or symptoms (51).

The disease is typically diagnosed by finding evidence of autoimmunity to either gluten or an enzyme involved in the digestion of gluten, tissue trans-glutaminase (TTG) (50). A biopsy to confirm small bowel inflammation has generally been gold standard for diagnosis, and remains so for the population of children with T1DM (50).

1.2.2 Epidemiology

It is commonly accepted that CD occurs in the general population with a prevalence rate of around 1% (52). There is significant geographical variation, with community prevalence ranging from 0.3% in Germany, to > 2% in Finland (53). A population based screening study in Christchurch, New Zealand in the 1990s indicated that the prevalence rate of CD was 1.2% in Canterbury adults (54). Recent work retrospectively reviewing the paediatric population of Canterbury could not make prevalence estimates but found a rate of diagnosis of 32 biopsy proven cases per year, a rate that had increased from 13 per year over an 11-year period (55). A New Zealand cohort study found a prevalence of 1% in New Zealand children, although they were relying on parental report (56).

Studies from around the world have repeatedly shown that CD occurs more commonly in people with T1DM than in the general population. Prevalence rates vary from 1.6% (57) to 16.4% (58). There is a large range of definitions and methodologies in the numerous studies. A comprehensive meta-analysis of only longitudinal studies with robust methodology found a quality-weighted prevalence of 5.1% (CI 3.1-7.4%) in the European and Australian populations included in their review (9).
Pham Short et al. (9) also reported incidence rates showing that 40% of cases of CD diagnosed in T1DM are diagnosed in the first year of T1DM diagnosis and 79% are found within 5 years.

### 1.2.3 Pathophysiology

CD is an immune mediated condition. A strong underlying genetic basis has been recognised for many years, but environmental factors are also important in the pathogenesis.

### 1.2.4 Genetics

Like T1DM, CD is far more common in individuals with certain HLA subtypes. Ninety to ninety-five per cent of individuals with CD are positive for the HLA molecule DQ2.5, which is encoded by the genes HLA.DQA1*5.01 and HLA.DQB1*2.01, almost all other cases are either HLA DQ8 or DQ 2.2 (59-61). As in T1DM these genotypes do not pre-determine disease expression, but are necessary to be present for the disease to manifest. (These high-risk HLA subtypes, HLA-DQ2 and HLA-DQ8, are the same as those that put an individual at risk of developing T1DM.) It is thought that the molecular structure of these higher risk HLA molecules allow for enhanced binding of CD4 T-cells in the small bowel mucosa to de-aminated gliadin molecules, a product of the digestion of gluten (59).

Variations in HLA subtype are not adequate to explain the immune processes observed in CD and much effort has been spent identifying other genes involved in the pathogenesis. As technology to map the genome and search for genes associated with disease have advanced, the areas of genetic code suspected to be associated with autoimmune disease have increased in number. The TEDDY group has recently published work examining the HLA associated regions (62) as well as non-HLA (63) associated with CD. Many areas that have been identified add weight to the immune mediated model of CD as they are involved in cell selection, regulation, survival and stimulation of T-cells (61, 64).

Genetic discoveries have led to a hypothesis that helps explain the relationship between CD and T1DM. The immune mediated inflammatory process driven by CD autoimmunity results in impaired intestinal barrier function (64), which allows the introduction of environmental factors to the submucosa which may then lead to the autoimmune process which results in the development of T1DM.
1.2.5 Environmental factors

As in T1DM, whilst there is no doubt that there is a genetic risk, the lack of complete concordance in twin and family studies strongly suggests that environmental factors play a role in the development of CD (65).

The most obvious factor is gluten. CD is more common in areas where gluten is consumed heavily and barely recordable in geographic areas where gluten is not ingested in large amounts (61).

This dietary link has lead researchers to look at the timing of introduction of gluten as a potentially modifiable risk factor. Observational work from Sweden where a change in infant feeding advice coincided with increasing incidence of CD made this hypothesis seem more likely (66). However, prospective observation studies did not show this (67, 68) and two randomised controlled trials also failed to show any change in incidence with delaying or advancing the introduction of gluten to breast fed or formula fed infants (69, 70). The most recent work suggests that the timing of gluten introduction does not impact on subsequent risk of CD (71).

Observational work has also been done to see if any perinatal factors affect the subsequent risk of CD. The most convincing factor is elective caesarean-section, which was associated with a small increase in OR 1.15 (1.04-1.26), a hypothesis to explain this is variation in the microbiota due to the lack of exposure to the flora in the birth canal (72).

As with T1DM the role that viral infection may play in triggering autoimmunity has been investigated, although results have not been conclusive. One prospective study following children with high risk HLA subtypes did show that there was a trend to increasing risk with increasing occurrence of rotavirus infection, but this was not significant at each individual time point and the occurrence of infection was only inferred from serological changes (73). The role of gastrointestinal infection is also supported by work that has shown increased prevalence of CD in children born in summer months (74). One hypothesis mooted to explain this finding is that these children are introduced to solids at a time when gastrointestinal infections are at their peak.

Taking the viral work a step further than inference, a group has identified a subset of anti-TTG antibodies that recognise rotaviral proteins. The presence of these anti-rotaviral antibodies was far more common in children with CD, but were not exclusively
found in the disease state. Further molecular work demonstrated that the antibody did modify the expression of genes involved in CD pathogenesis, for example genes that alter epithelial function (75).

Again, similar to the body of work in T1DM, the intestinal microbiota in individuals with CD has been investigated, as was well summarised in a recent review (76). The microbiota in individuals with CD and those in the normal population does differ, but no “typical” CD microbiota has been found. The changes include a decrease in protective bacteria and an increase in the amounts of bacteria thought to favour a pro-inflammatory state. A hypothesis to explain an observed peak in incidence in Sweden was that the changes in dietary practice could be changing the microbiota, by selecting for bacteria that favoured those dietary changes. As summarised earlier, the suggested dietary changes however have not been consistently linked to CD (67, 68). It has also not been established which came first, the pro-CD microbiota or if the pathophysiology of CD promotes certain bacteria.

### 1.2.6 Similarities between the pathogenesis of DM and CD

There are many parallels between the pathogenesis of CD and T1DM. Much of the research has followed similar avenues: genetic, viral and the interplay of the intestinal microbiome and autoimmunity.

An animal model demonstrated a link between a gluten containing diet and the development of hyperglycaemia. NOD mice fed a GFD from birth had a different faecal microbiota and a reduced rate of hyperglycaemia, which reversed when gluten was introduced (77).

The interplay between the immune system and the gut microbiota offers an explanation for some of the increase in CD seen in T1DM. There are probably several factors at work, obvious shared genetic susceptibility, mediated through altered immune function, shared environmental risk factors and almost certainly impaired gut intestinal barrier function that allows the exposure of antigens to immune cells and the subsequent development of autoimmunity to gluten and or insulin.

The close relationship becomes important clinically when considering the question of screening in T1DM for CD, as it may have important implications for growth, diabetes control and quality of life. It is also of importance when thinking of primary prevention
of both illnesses, as perhaps there is some environmental modification that could be made to prevent the development of the disease state.

1.3 Gastric emptying in T1DM

Gastric emptying is complex; many factors influence the rate that food is emptied from the stomach. There is a substantial body of evidence in the adult literature and growing in paediatrics, that gastric emptying is altered in T1DM. Many physiological factors that are impacted by the pathology of T1DM are related to the complex neuronal and hormonal control of gastric emptying. Knowledge of gastric emptying rates is important as altered gastric emptying may be associated with GI symptoms (8). In T1DM the rate of gastric emptying is of even more relevance as the rate that the stomach empties is linked to the delivery of food and therefore glucose to the rest of the digestive system, which can impact on blood glucose levels (78).

1.3.1 Physiology of gastric emptying

Gastric emptying is the rate that food leaves the stomach. The way that food is broken down and then allowed through the pylorus is essentially a function of the motor activity of the three parts of the stomach – the proximal stomach, the antrum and the pylorus - as well as the proximal intestine (8).

While fasting, the stomach goes through 3 phases of contractions, which together are called the “migrating motor complex” (79). When food is ingested this resting pattern changes to a post-prandial pattern of irregular contractions. The stomach must relax to allow the food into the proximal stomach where it is stored, before it moves into the antrum to be ground up into tiny particles, then emptied incrementally through the antrum (8).

The rate that the stomach empties alters according to the make-up of the meal. The calorie value, fibre content and texture of a meal determine the emptying speed (8). Liquids with no calorie value empty exponentially, liquids with more calorie value empty in a more linear fashion and solids are emptied last, as they need to be churned before they can be emptied (8). The phase of a meal where the solids are retained is called the lag phase. Most solid meals have been emptied by 3 – 4 hours post ingestion (8).
Coordinated relaxation and contraction of the three parts of the stomach is under both neural and hormonal control (79). The enteric nervous system, which has plexi in the sub mucosal and myenteric layers of the stomach, along with the autonomic nervous system, which also innervate the gastric wall, are involved in the coordination of muscle contractions (80).

The interstitial cells of cajal (ICC) are ‘pacemaker” cells which produce the electrical signals that drive the maximum contraction rate of the stomach (80). Once food arrives in the small intestine, inhibitory pathways work to reinforce motor activity that slows gastric emptying, by relaxing the antrum and fundus but strengthening the pyloric contractions (79). The rate of gastric emptying usually varies between 1-4 kcal/min (79). Gastric emptying activity is mediated directly by the vagus nerve as well as hormones secreted by the gut: Glucagon-like peptide – 1(GLP-1), cholecystokinin, peptide YY and amylin (also called human islet amyloid peptide), which is co-secreted with insulin (81).

1.3.2 Gastric emptying in T1DM

It has been recognised since at least 1958 that gastric emptying is altered in adults with diabetes (11).

Diabetic gastroparesis is a clinical syndrome where there is a symptomatic delay in gastric emptying, in the absence of physical obstruction and in the presence of euglycaemia (82). How many adults with T1DM are affected by gastroparesis is not clear, as definitions have varied and achieving euglycaemia during testing is not easily accomplished (81). Prevalence in some tertiary centres has been reported as 40%, but community estimates put it closer to 5% in T1DM, and under 0.5% of controls (83).

Gastroparesis is not the only abnormality of gastric emptying demonstrated in diabetes mellitus. A retrospective case review of 129 patients with diabetes mellitus (about 50% had T1DM) who had scintography performed for various clinical indications showed that while 36% of the patients had delayed gastric emptying, 22% had rapid gastric emptying. The study aimed to establish a diabetes “phenotype” of symptoms, however the only predictor of accelerated gastric emptying was neuropathy (OR, 3·60, 95% CI, 1·007–12·89) and weight loss for delayed gastric emptying (OR, 2·81, 95% CI, 1·09–7·23). Insulin therapy was associated with a lower risk for rapid GE (OR, 0·08; 95% CI, 0·01–0·53) but otherwise no other indicators of control or duration of diabetes were
useful to discriminate if gastric emptying would be abnormal. The applicability of this study to paediatric clinical practice and children with T1DM is hampered by the patient group – adults, nearly 96% who had GI symptoms at inclusion in the study (84).

A study with small numbers, but interesting findings about gastric emptying in different physiological states, performed scintography under varying conditions in 15 patients with T1DM and 10 matched controls (85). Patients were shown to have faster gastric emptying that controls 90–120 mins post meal (p = 0.03). This finding became more pronounced when the controls were kept hyperglycaemic; they had a marked slowing of their gastric emptying, which was not seen in cases. The groups were then given pramilinitide (an amylin analogue) and the T1DM patients’ gastric emptying then slowed to match that of controls. It was not clear what the duration of T1DM was in the patients, but they were well selected to have no signs of autonomic dysfunction.

Gastric emptying has also been demonstrated to be accelerated in T2DM. Two scintography studies with small groups of patients demonstrated accelerated gastric emptying (86, 87). Both of the studies were in patients with relatively newly diagnosed T2DM, with few complications perhaps indicating that gastric emptying itself was a factor in the hyperglycaemia seen clinically.

### 1.3.3 Gastric Emptying in children with T1DM

All of the above studies were performed in adults with diabetes. Some studies have been done to evaluate gastric emptying in children and young people with T1DM. The following table summarises these diverse studies.
<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Subjects mean(SD)</th>
<th>Duration of T1DM</th>
<th>Autonomic neuropathy</th>
<th>Results</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>(88)</td>
<td>Electrogastrography</td>
<td>49 cases 10yrs(4.4) 17 controls (age matched)</td>
<td>Early</td>
<td>No evidence of AN</td>
<td>Increased rate of EGG abnormalities in cases (p = 0.011)</td>
<td>No correlation</td>
</tr>
<tr>
<td>(89)</td>
<td>Electrogastrography</td>
<td>42 cases 12.9yrs (+/-3.1) 35 controls 13.4 (+/-3.6)</td>
<td>Less than one year</td>
<td>CVS methods – none found</td>
<td>Increased rate abnormalities 29% cases 91% controls normal EGG (p&lt; 0.05)</td>
<td>No correlation</td>
</tr>
<tr>
<td>(90)</td>
<td>Electrogastrography and ultrasound</td>
<td>40 cases 9yrs(6-14) 15 controls 7yrs(4-15)</td>
<td>No correlation with duration</td>
<td>CVS methods – none found</td>
<td>26/40 delay on ultrasound (p&lt;0.01) increased prevalence of abnormal EGG in cases (p &lt;0.05)</td>
<td>Higher HbA1c correlated with delay</td>
</tr>
<tr>
<td>(91)</td>
<td>Scintography</td>
<td>33 cases 12.2yrs (4.3) 26 controls 11.4 yrs(2.1)</td>
<td>No correlation with duration</td>
<td>Microalbuminuria not correlated with gastric emptying</td>
<td>151.7 (154.5) v 109.8 (60.5) (p =0.885)</td>
<td>No correlation</td>
</tr>
<tr>
<td>(92)</td>
<td>Scintography</td>
<td>33 cases 15.3 yrs (4.9) 36 controls 15.4 yrs (1.9)</td>
<td>Not specified</td>
<td>CVS methods – none found</td>
<td>No difference 114.4(30.2) v 94.3(32.5) (p &lt; 0.2)</td>
<td>no correlation</td>
</tr>
<tr>
<td>(93)</td>
<td>C13 Breath testing</td>
<td>7 cases 16.0yrs(1.9) 7 controls 15.4yrs(1.9)</td>
<td>Correlation not examined</td>
<td>Not specified &quot;no complications&quot;</td>
<td>Area under curve significantly longer in cases (p =0.0001)</td>
<td>Selected for good control</td>
</tr>
<tr>
<td>Author</td>
<td>Method</td>
<td>Subjects mean(SD)</td>
<td>Duration of T1DM</td>
<td>Autonomic neuropathy</td>
<td>Results</td>
<td>HbA1c</td>
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<tr>
<td>--------</td>
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<td>-------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>(94)</td>
<td>Electrical impedance tomography</td>
<td>40 cases 17.6yrs(4.6) 20 (age matched)</td>
<td>No correlation</td>
<td>CVS methods - no difference</td>
<td>Slower in cases 54.8 (26.63) v 40.37 (8.62), (p &lt; 0.05)</td>
<td>No correlation</td>
</tr>
<tr>
<td>(95)</td>
<td>$^{13}$C Breath testing</td>
<td>30 15.1yrs (2.5) 10 14yrs (3.5)</td>
<td>No correlation</td>
<td>CVS methods - no difference</td>
<td>Rapid: 78(IQR 61-99)cases 109 (IQR 71-124)controls</td>
<td>No correlation</td>
</tr>
</tbody>
</table>

Key: AN = autonomic neuropathy, CVS = cardiovascular, EGG = electrogastrography, IQR = Interquartile range
The studies have used various methods to measure gastric emptying. There is no unifying agreement on what constitutes delayed or rapid gastric emptying, so simple comparison or meta-analysis is not possible. The two with possibly the most robust method of measurement – scintigraphy – show no difference in the rate of gastric emptying between cases and controls (91, 92), although in both, the cases had a tendency to a longer GE time. All of the other studies did show differences in gastric emptying rates between cases and controls (88-90, 93-95).

Most of the studies tried to look for factors hypothesised to be associated with altered gastric emptying. None of the children who had investigations performed had evidence of autonomic dysfunction. Most of the studies used HbA1c to measure control and none demonstrated a difference in gastric emptying that could be related to this marker. When recorded the duration of diabetes did not seem to impact on results.

Drawing overall conclusions from this body of research is difficult due to the heterogeneity of the studies. Also numbers in each study were relatively small, indicative of the difficulty performing invasive and time consuming test on children. Despite the current body of evidence, it is not clear what the pattern of gastric emptying is in children with T1DM.

**1.3.4 Pathophysiology of gastric emptying differences**

Most of what is known about the pathophysiology of gastric emptying differences in T1DM comes from adult studies. As discussed above, gastric emptying is influenced by many factors. Hyper and hypoglycaemia certainly play a role in reversible alterations.

The mechanisms that explain pathologically altered gastric emptying in T1DM include alterations in the gastric hormones, signalling peptides and changes in Nitric oxide levels (96). Cell damage to the smooth muscle layer and reduced numbers of ICC, have been demonstrated (97, 98). Neuronal changes also probably play a part, particularly damage to the vagal nerve (99).

Understanding the changes in gastric motility provoked by the hyper- and hypoglycaemia that occur with eating are important when considering gastric emptying, particularly in T1DM, when it is likely there will be marked changes in the blood glucose after ingestion of a meal. Elevated blood glucose results in a reduction in the speed of gastric emptying (100). Acute changes are seen in the muscle activity of the stomach – the fundus and antrum relax while the pyloric contractions are attenuated (79).
Hypoglycaemia in contrast results in a marked increase in gastric emptying (101). These changes are still seen within the physiological range (102).

It has not been fully established exactly how physiological or pathological changes in gastric emptying are mediated – gastric emptying is a complex process and therefore it can be expected that many factors are involved. Interest has focused on hormonal changes, where there is potential to use pharmacological methods to alter gastric emptying (96). The figure adapted from Marathe et al. (103) summarises some of the feedback loops at play when there are changes in blood glucose.

Figure 1.3: The inter-relationship of gastric emptying, incretin hormones and post-prandial blood glucose. Glucagon like protein-1 (GLP-1), glucose dependent insulinotrophic peptide (GIP), adapted from Marathe (103).

Amylin (islet amyloid polypeptide) a hormone co-secreted with insulin from the beta cells of the pancreas is likely to be involved (8). Release of amylin results in slowing of the gastric emptying rate (102). Reduced levels of amylin have been consistently seen in children with T1DM (104-106). Heptulla et al. (106) demonstrated that this reduction in amylin was associated with slower gastric emptying, contrary to her hypothesis that it
would accelerate gastric emptying, and possibly illustrating the complexity of gastric emptying and successfully measuring it.

Grehlin is another hormone that has effects on gastric motility. It is synthesised in the gut and has receptors throughout the body \(8\). One of grehlin’s actions is to accelerate gastric emptying \(107\). Elevated levels of grehlin have been found in children with T1DM \(104, 108\).

Other peptides released by the gut, such as GLP-1 and glucose-dependent insulinotropic peptide (GIP) are released by the intestine when in contact with food and these also work to slow gastric emptying \(103\).

While it has been demonstrated that gastric emptying is altered by the level of glucose in the blood, the rate that glucose is delivered to the gut for absorption also affects the blood glucose. A group in Australia have shown that alterations in gastric emptying accounts for up to 30% of the variability in blood glucose in health \(109\).

Post-prandial blood glucose has been a focus of research as the typical rise in blood glucose after a meal is a significant contributor to over-all diabetes control \(78, 103\). Monnier \(110\) showed that the contribution of post-prandial blood glucose was between 30-70% of the overall time an individual was hyperglycaemic, when they analysed diurnal blood glucose in a group of 240 people with T2DM. Post-prandial blood glucose had the biggest impact on over-all area under the curve in those with the highest average HbA1c \(110\).

There is also a body of evidence that suggests that much of the oxidative damage to nerves and vessels that result in the long term complications of T1DM is caused by the post prandial fluctuations in blood glucose \(111\).

How control of T1DM in turn affects gastric emptying is not straightforward as so many factors impact on overall control, and a clear relationship has not been found \(112\). The landmark cohort study that determined that tight blood glucose control resulted in better outcomes, the Diabetes Control and Complications Trial (DCCT) \(113\), was continued as the Epidemiology of Diabetes Interventions and Complications (EDIC) study, this group evaluated gastric emptying in a cohort of 78 cases. At year 20 since entry into the study, 50% had normal gastric emptying, 47% had delayed and 3% had rapid gastric emptying. Those with delayed gastric emptying had higher HbA1c at the
time of testing, a higher average HbA1c over the year and there was also an association with severe nephropathy and higher upper GI symptom score (114).

1.3.5 Relevance of Gastric emptying in clinical practise

Because of this interwoven relationship of gastric emptying and glycaemic control, the more we understand about the mechanisms of gastric emptying the better our understanding of blood glucose control. Given that peaks of blood glucose are times when oxidative damage is done, interventions that aim to smooth these peaks would appear to be of benefit to patients (78). Before interventions can take place there is still more to be learnt about the pathophysiology of gastric emptying.

1.4 Measurement of gastric emptying

1.4.1 Development of the Carbon 13 oral breath test

The generally accepted gold standard to measure gastric emptying is scintography. The subject ingests a meal labelled with a radioactive marker, usually technetium and a gamma camera is used to measure the removal of the trace from the stomach. This necessitates a dose of radioactivity, time in front of the camera, cooperation of the subject and expensive machinery. For many reasons this test has not been deemed desirable or accessible for research studies in children (115). In the 1990s investigators, chiefly at Leuven in Belgium and the Mayo clinic in the United States began to develop a new method of measuring gastric emptying using isotopes of carbon.

Test subjects are fed a meal rich in carbon 13 (C\textsubscript{13}), a stable isotope. Samples of their breath are then captured over a certain period of time. The breath is analysed by mass spectrometry and the amount of carbon dioxide (CO\textsubscript{2}) rich in C\textsubscript{13} (13-CO\textsubscript{2}) excreted over time can be measured. Two curves are produced: one describing the measured 13-CO\textsubscript{2} recovered in the breath, the percentage of excretion per hour of the total C\textsubscript{13} dose, (see figure 1.4) the other is the percentage the total C\textsubscript{13} dose excreted in the breath over time (see figure 1.5). Four parameters are generally calculated: gastric emptying half time (GET\textsubscript{½}) when half the substrate has been metabolised, lag time (GET\textsubscript{lag}), the time of maximum gastric emptying speed, maximum gastric emptying time (GET\textsubscript{max}), the peak of the percentage excretion curve and a gastric emptying coefficient (GEC) which describes the shape of the entire percentage excretion curve (see figure 1.4).
The breath test is based on the fact that medium and short chain fatty acids are very quickly absorbed from the duodenum, transported to the liver for metabolism, converted to CO$_2$ and then excreted in the breath (116). Assuming that post absorptive processes are constant the rate-limiting step is gastric emptying (117, 118).

In 1993 Ghoos (116) from the Leuven group in Belgium, published the first report comparing scintigraphically measured gastric emptying with C$_{13}$ and the very similar C$_{14}$ labelled sodium octanoate breath tests (OBT). 36 subjects were given a meal
labelled with both C\textsubscript{14} and technetium. GET\textsubscript{1/2}, GET\textsubscript{lag} and GEC were calculated using non-linear regression. They found excellent correlation (r = -0.88 for GEC, 0.89 for GET\textsubscript{1/2}, and r = -0.92 for GET\textsubscript{lag}) between scintographic data and the oral breath test (OBT). In vitro studies were also performed to assess the label’s stability in the stomach. They found the label was stable and no statistically significant intra-individual or inter-individual variation.

The Mayo group also validated C\textsubscript{13} breath testing against scintography (119-122). They developed various models using generalised regression, which calculated the breath test emptying parameters using differently weighed 13-CO\textsubscript{2} concentrations from various time points. The hypothesis was that the post absorption metabolism was too different between individuals to apply the same correction for all subjects. If they applied the original non-linear regression model to their data, estimated steady state 13-CO\textsubscript{2} excretion (M) was often not steady even when all of the food had been shown to leave the stomach with technetium scanning (121, 122). They found M was sometimes overestimated which would therefore lead to inaccuracies in the calculated gastric emptying time. Even extending the time collection period did not truly correct for this (119, 120). They proposed a generalised regression model that didn’t rely on M, using only three time points. In a comparison study of Ghoos’s method, scintigraphy and their new model they found good agreement with scintography using the more simple approach (121).

Since that time other generalised regression models have been devised using many different time points, mostly collecting data over 4 hours (121-124). All have validity and good correlation for the meals that they have been tested against but applying the models to different meals without a validation process is unreliable (118).

1.4.2 Application of the OBT test to children

The OBT has since original inception been identified as a test desirable for use in children. Studies have been done in both the liquid and solid phases to evaluate the reliability and suitability for children. Most have followed the original paper by Ghoos and used nonlinear regression to calculate GET\textsubscript{1/2}, T\textsubscript{lag} T\textsubscript{max} and GEC (125-128).

Not surprisingly there are limited studies that compare the OBT with “gold standard” scintography in children. In one of the only studies validating a solid sodium octanoate meal against technetium, 25 healthy children were given a meal containing both C\textsubscript{13} and
technetium. GET\(_{1/2}\), T\(_{lag}\) and GEC were measured, using Ghoo’s non-linear regression model. Very good correlation was found for GET\(_{1/2}\) (r 0.92) and less strong but statistically significant correlation was found for T\(_{lag}\).

Hauser performed a recent study to first of all correlate scintography with a pancake OBT, then performed the OBT in 120 healthy children, to try and establish a normal range. They showed good correlation between the scintography and C\(_{13}\) test, (r 0.748), and also established a mean GET\(_{1/2}\) of 157.7 +/- 54 (71-415). They performed regression for gender, weight, height and body mass index (BMI), none of which affected gastric emptying, but with increasing age gastric emptying did increase (129).

1.4.3 The OBT in T1DM

Little has been published about children with diabetes using the OBT. Some work has been done to investigate gastric emptying in adult diabetics using this method.

An early study (130) evaluated the OBT in adults with both T1DM and T2DM. The OBT and scintography were measured on two different days. The OBT had as sensitivity of 75% and specificity of 85% to detect delayed gastric emptying. There was no statistically significant correlation between blood glucose levels, HbA1c or duration of diabetes.

1.4.4 Using the OBT

The OBT has been repeatedly shown to be comparable to scintography. It can detect changes in gastric emptying with sensitivities approaching 100% in some studies. It can reliably be used in children and in T1DM. Interpretation must be tempered against the known drawbacks, including a lack of standardisation, not just of the meal but the method for interpreting the values generated. It does represent a safe, repeatable, acceptable measure of gastric emptying.

1.5 Gastrointestinal symptoms

1.5.1 Symptoms in Children with T1DM

Given the increased prevalence of coeliac disease and the potential for altered gastric emptying, it seems likely children with T1DM would experience gastrointestinal symptoms. Anecdotally clinicians report increased complaints of GI symptoms in
children with T1DM. It was this clinical observation that partly prompted the thesis question, however robust research examining this hypothesis is not abundant.

There have been two studies that looked at the prevalence of GI symptoms in children with T1DM. Both studies found similar rates of GI symptoms in children with T1DM and healthy controls. The prevalence rates varied between the two studies, one reported a rate of around 30% (131) in both cases and controls and the other a rate around 70% (132). Methodology and control groups differed between the two studies.

1.5.2 Prevalence of symptoms in healthy children

Overall, gastrointestinal symptoms in children are common (133-135). A community based study, using a similar questionnaire to that used in this study, found weekly prevalence rates of 45% of any GI symptom and found that during the study period 90% of school aged children complained at some time of any GI complaint (133).

Much of the work looking for symptoms has focused on finding the prevalence of Functional Gastrointestinal Disorders (FGID): GI symptom complexes that cause significant functional impairment (136). As with symptom complaints, FGID are also common in children. An excellent recent meta-analysis tried to pool data from around 20,000 patients in regards to abdominal pain FGID (137). They demonstrated a prevalence of 13.5% (95% CI 11.8-15.3), although prevalence did vary greatly, from 1.6% - 41.2% (137).

As well as examining prevalence, the meta-analysis looked at factors associated with higher rates of pain. Girls had higher rates than boys, pooled OR 1.5 (95% CI 1.3-1.7, p 0.01). Anxiety and depression were more frequent. Depression predicted a higher likelihood of a pain FGID, and a FGID predicted higher rates of depression. Pain disorders were also more likely in those who had experienced adverse life events (137).

1.5.3 Measuring symptoms

To assess GI symptoms in children most research has used questionnaire-based assessments. The two studies done in children with T1DM used different methods. Vazeou et al. (131) used an unidentified standardised questionnaire, administered by a single researcher. Lodefalk et al. (132) used postal questionnaires designed for use in adults, with 87 questions, some of which related to GI symptoms.
A large body of work has gone into developing questionnaires that are based on the Rome criteria for diagnosis of FGID (138). These are very long detailed questionnaires designed to make a diagnosis of functional gastrointestinal syndromes such as abdominal migraine, functional constipation or functional dyspepsia.

None of these tools suited the population or aim of the current research. The tool that best matched was that used by Saps et al. (139). It was a simple questionnaire designed to establish the prevalence of GI symptoms in the previous week. It was designed to be filled in by school students each week, with an overall aim of determining intensity of symptoms. The questions from this questionnaire were in turn based on the Child Somatisation Inventory, a well-validated tool for identifying somatic conditions in children (140).

### 1.5.4 Pathophysiology of GI symptoms in Children

As described in the preceding sections, children with T1DM have higher rates of GI pathology that potentially could cause an increase in associated symptoms. However as demonstrated by the prevalence of symptoms in controls and community “well child” studies (133-135), in the majority of cases, children with gastrointestinal symptoms, particularly pain symptoms, do not have serious underlying pathology. In the absence of concerning signs (such as weight loss, bloody stool, physical findings) most abdominal pain in children does not have a serious cause (136). A cost analysis study of the investigations used for FGID showed that for $6000 of blood tests, radiology and endoscopy, almost no serious pathology was discovered (141).

Children all over the world describe recurrent GI symptoms (135). The underlying reasons for the high prevalence of complains but lack of underlying pathology is multifactorial. Children have a limited vocabulary and ways to describe what they feel. Some may interpret feelings in their abdomen as pain where as others may use different words to describe the sensation (142). Parents interpret and react to complaints of pain in different ways (143).

The pathogenesis of functional pain disorders is thought to be associated with altered gut motility, visceral hypersensitivity, abnormal brain/gut interaction, psychosocial disturbance and immune activation. The above factors are thought to work in conjunction to influence how the body feels pain, interprets and reacts to it (142). Notably early life
experiences and life stressors are a major influencing factor on the development of FGID (144).

The gut is a complex organ system. It has important barrier and immune functions, which need to balance with its vital role in the digestion and absorption of nutrients (145). A network of reflex circuits and afferent pathways to the central nervous system interact to control these various functions. The pathways have receptors throughout the enteric system that respond to physical and chemical stimuli – such as distension and absorbed nutrients (146, 147). The receptors are modulated by many factors – they can be upregulated by inflammation and injury to become more sensitive, so that stimuli that may not cause a sensation of pain in one individual is interpreted as a negative sensation in another (146). One of the mediators of this upregulation is hypothesised to be the hypothalamic-pituitary-adrenal axis, which helps explain the consistent link between psychosocial stress and increased complaints of gastrointestinal symptoms, as this axis is switched on during times of stress (142, 145).

Abnormal motility is involved in gastrointestinal symptoms. Psychosocial stress is a factor as emotional disturbance has been demonstrated to cause slowed gastric emptying but also stimulate colonic motor function (142). These symptoms include nausea and vomiting, abdominal pain and diarrhoea/constipation (146). In one study of children with functional dyspepsia, around 60% of the children had slower gastric emptying and/or abnormal gastrography, suggesting altered gastric emptying was a mechanism in the pathophysiology of this group of disorders (148).

1.5.5 Relevance of GI symptoms to clinical practise

The research undertaken in children with T1DM has not demonstrated any difference in prevalence of gastrointestinal symptoms, but the studies have been small and there are methodological difficulties particularly in terms of the control group and the selection of subjects – neither is truly representative of the general population of children with T1DM (131, 132). There are plausible mechanisms to explain the anecdotal findings of clinicians that children with T1DM suffer more GI symptoms, for instance increased psychological stress and altered gastric emptying, but evidence is preferable to anecdote. Knowledge of the rate and intensity of symptoms is important if clinicians are to adequately and competently address these complaints, both to identify pathology as well avoid unnecessary investigation.
1.6 Hypothesis/research questions:

This thesis aims to explore the gastrointestinal manifestations of T1DM. Three areas were chosen for particular study: CD, GI symptom complaints and gastric emptying rates.

1.6.1 Coeliac Disease Screening Benchmark

CD and T1DM are common co-diagnoses and probably have common causal mechanisms. Screening for CD in T1DM has been mooted as worthwhile by many international bodies (50, 149). However, clinical experience suggested that clear guidance was not easily accessible, and different clinicians had different practise. To help clarify a standard approach, this thesis aimed to create an accurate picture of current practice for screening and management of CD amongst clinicians caring for children with T1DM in New Zealand (NZ).

1.6.2 Gastric Emptying Rates in children with T1DM

Gastric emptying impacts on blood glucose control and blood glucose levels influence gastric emptying. To understand this relationship, a good knowledge of gastric emptying is required. Adults have high rates of gastroparesis but rates of gastric emptying have not clearly been demonstrated to be either rapid or delayed. This thesis hypothesised that gastric emptying will be delayed in children with T1DM.

We aimed to compare gastric emptying in children with T1DM to that in healthy controls. Secondary objectives are to determine the impact of Body Mass Index (BMI), glucose control, age, gender and duration of disease upon emptying in children with T1DM.

1.6.3 GI symptoms in children with T1DM

There are plausible reasons that children with T1DM should have high rates of GI symptoms, both due to increased rates of CD, potentially altered gastric emptying as well as possible psychological differences. Evidence demonstrating a difference in symptoms is minimal.

This thesis hypothesised that children with T1DM would have increased rates of GI symptoms.
We aimed to prospectively establish the rate and intensity of GI symptoms in a clinic population of New Zealand children with T1DM compared to an aged-matched group of healthy children.
Chapter Two: Screening for Coeliac Disease in Type One Diabetes

2.1 Introduction

In New Zealand the incidence of T1DM has been observed to be 17.9/100000 (15), which is one of the highest rates in the world (18, 150). T1DM is strongly associated with certain HLA subtypes (31) although other genes as well as environmental factors have potential causal roles (10). T1DM is associated with increased risk of other autoimmune diseases, including coeliac disease (CD) (149).

CD is also strongly associated with certain HLA subtypes and is caused by a complex interaction of genetic and environmental factors (50). CD may present in several ways: the “classical” picture of malabsorption; the “non-classical” scenario, which may include various symptoms such as chronic abdominal pain, short stature or anaemia; and the increasingly recognised ‘subclinical” disease, which is asymptomatic on routine clinical assessment (51).

Prevalence studies from around the world have established that CD is more frequent in T1DM (58, 151-155). Rates vary from 2.4% (58) to 16.4% (154). A meta-analysis including Australian children found a pooled prevalence rate of 5.1% (CI 3.1-7.4%) (9), illustrating a substantial increase from the 1% rate of CD in the general population (54).

The two diseases share HLA subtypes. CD is potentially involved in the aetiology of T1DM, it has been postulated that increased intestinal permeability seen in CD could allow environmental antigens access to spark the immune processes leading to T1DM (10, 31).

In the last decade the presentation patterns of CD have changed greatly, with more non-classical or subclinical cases diagnosed and fewer classical presentations (156, 157). This is especially true in children with T1DM where up to 71% are reported to be asymptomatic at presentation (157). This pattern of CD in T1DM reflects in part the introduction of active screening programmes in some diabetes clinics. However the role of screening and the optimal screening system remain controversial (50, 149, 158).

Most international bodies recommend screening, but how and how often is not clear, as summarised in Table 2.1. The 2011 Australian Paediatric Endocrine Group diabetes management guideline suggests screening at diagnosis and once in the next 5 years but offer no suggestion as to which antibodies to use (149), whereas the 2012 European
Society for Paediatric Gastroenterology, Hepatology and Nutrition Celiac Disease management guidelines suggest establishing the HLA subtype at diagnosis and proceeding to screen at diagnosis and every 2 – 3 years subsequently only if at risk (50).

Due to the conflicting nature of this advice it is unclear how clinicians actually approach the issue. A recent North American postal survey of health professionals looking after adults found very varied screening practices (159). We aimed to create an accurate picture of current practice for screening and management of CD amongst clinicians caring for children with T1DM in New Zealand (NZ).
<table>
<thead>
<tr>
<th>Specialist Group</th>
<th>Publication year</th>
<th>Timing of screening recommended</th>
<th>Recommended screening test</th>
<th>Frequency of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Society for Paediatric and Adolescent Diabetes (160)</td>
<td>2014</td>
<td>At diagnosis</td>
<td>TTG and/or EMA, IgA</td>
<td>Annually for first 5 years, then every second year. More frequently if first degree relative with CD or suggestive symptoms</td>
</tr>
<tr>
<td>Australian Paediatric Endocrine Group (149)</td>
<td>2011</td>
<td>Screen at diagnosis in children and adolescents</td>
<td>Not specified</td>
<td>If negative, should be rescreened, at least once in the first 5 years after diagnosis</td>
</tr>
<tr>
<td>European Society for Paediatric Gastroenterology, Hepatology and Nutrition (50)</td>
<td>2012</td>
<td>Not specified</td>
<td>Start with HLA type, if positive then TTG and IgA, EMA if weak positive</td>
<td>Retest at intervals, no firm evidence but opinion is every 2 to 3 years</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (158)</td>
<td>2009</td>
<td>Not specified</td>
<td>TTG initially, check IgA if serology negative</td>
<td>Insufficient evidence to make a recommendation</td>
</tr>
</tbody>
</table>

Key: tTG = anti-tissue transaminase, EMA = anti-endomysial antibodies, IgA = total immunoglobulin A, HLA = human leukocyte antigen
2.2 Materials and Methods

2.2.1 Participants and inclusion criteria

Consultant paediatricians and adult physicians who cared for children under 15 years with T1DM in secondary or tertiary hospital clinics around NZ were invited to complete a questionnaire. A comprehensive list of consultants caring for children with T1DM was compiled. The list was created from the Novonordisk Endocrine Workshop 2010 invitees list. Every District Health Board’s Paediatric Outpatient Department was contacted to enquire who ran diabetes clinics. Invitees were also asked to recommend other consultants who should be on the list. The list was also discussed with a paediatric endocrinologist to ensure there were no omissions.

Each consultant was sent an email inviting participation in the study. Non-responding consultants were sent a further email reminding them of their invitation. Subsequently, the respondents who still had not responded were sent a paper copy of the questionnaire and asked to return it by mail or hand.

2.2.2 Survey Design

An online questionnaire was designed by the investigator using Surveygizmo (www.surveygizmo.com). The questions were written to discover the participants’ current practise regarding screening and management of CD in NZ children with T1DM. Areas covered were departmental screening procedures, the individual’s own screening practices and the management of CD after diagnosis. The questionnaire was a mixture of multiple choice and open-ended questions. Answers to open ended questions were grouped for interpretation. (Appendix A). The survey was reviewed by supervisors and an impartial clinician and feedback was incorporated. The survey was open from October 2010 until January 2011.

2.2.3 Ethical Approval

Ethical approval was not sought as this was a benchmarking exercise. Similarly consent was implied by participation in the survey.
2.3 Results

2.3.1 Respondents

Of the 37 consultants invited, 34 responded (Table 2.2).

Table 2.2: Clinical role of respondents to questionnaire

<table>
<thead>
<tr>
<th>Clinical role</th>
<th>Number of respondents (n=34)</th>
<th>Number invited to participate (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric endocrinologist</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>General paediatrician</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Adult physician</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neonatologist</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

2.3.2 Demographics

The reported number of children with T1DM cared for by individual participants ranged from 6 to 400. The respondents estimated that between 0 and 30% of children in their T1DM clinic had been diagnosed with CD.

2.3.3 Screening protocols

Twenty-one of the respondents have a formal departmental protocol for screening for CD in their population of children with T1DM. Regardless of departmental protocol the respondents were asked about their individual practice. Twenty-five of the consultants screen for CD at diagnosis of T1DM. Of those who do screen, all use anti-tissue transglutaminase antibodies (TTG), some also use anti-endomysial antibodies (EMA) and a few use other antibodies.

Twenty-one of the respondents who screen at diagnosis subsequently screen for CD every 1-2 years. The other four use symptoms and/or the patient’s age as a trigger to rescreen.

The nine consultants who don’t regularly screen at diagnosis were asked what if anything did trigger them to screen (Table 2.3). All use tTG to test for CD when they do screen, with most also using EMA, one adding antigliadin antibodies and one clinician also using human leukocyte antigen (HLA) typing and iron status.
Table 2.3: Clinical indication to test for coeliac disease in a patient with type one diabetes mellitus

<table>
<thead>
<tr>
<th>Indication</th>
<th>No of respondents (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor growth</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>7</td>
</tr>
<tr>
<td>Erratic blood sugar control</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6</td>
</tr>
<tr>
<td>Family history</td>
<td>5</td>
</tr>
<tr>
<td>Recurrent hypoglycaemia</td>
<td>5</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

(Respondents who don’t screen at diagnosis were asked what features of a case would prompt them to test for CD)

2.3.4 Management after screening positive

After a child was found to have abnormal screening tests, 29/34 participants would refer for a small bowel biopsy. Some qualified the decision to proceed to biopsy with the strength of the positive test, the child’s symptoms, HLA status and discussion with the family. Nine would repeat bloods at the same time as referring for biopsy. Two typically commenced a gluten free diet (GFD) prior to or while awaiting biopsy.

2.3.5 Gluten Free Diet

Thirty-two of the consultants responded that biopsy proven CD was their criteria for commencing a GFD.

2.3.6 Management of symptom free CD

When asked in an open-ended question how they approach subclinical CD, 30/34 consultants said they advise a GFD. Three qualified this further by mentioning that “symptom free” patients often feel better when on a GFD. Seven said they discuss “the pros and cons” with parents and patient to allow them to evaluate the decision to commence a GFD. One practitioner reported that they only test symptomatic cases so has no “routine” practice with asymptomatic children.
2.3.7 Management if Gluten Free Diet is declined

In an open-ended question, clinicians were asked what their approach was when a diagnosis of CD had been made but the patient declined starting a GFD. Thirty-two consultants responded. The responses were very varied but were grouped for analysis. Some responses were placed into more than one category. Fourteen will try to educate the family, 7 will accept their patients’ decision, 14 will provide on-going monitoring and 4 had not encountered the situation. Most clinicians will try and provide the family with adequate information to make a choice, but will not force the issue. If a GFD diet is declined they will continue to monitor the situation, allowing room for on-going education and the ability to re-approach the decision when appropriate. Several comment on the lack of certainty as to the benefits of a GFD especially in asymptomatic disease.

2.4 Discussion

Whilst there are common trends, the responses to this survey demonstrate the varied approaches taken when dealing with CD in children with T1DM in NZ. Over half the clinicians surveyed formally screen for CD, but nearly one third do not. This survey represents the majority of clinicians looking after children with T1DM in NZ with a 92% return rate and as such is a good representation of the current approach to CD in the setting of T1DM in the NZ setting.

The complications of untreated symptomatic CD are well documented and include growth failure, increased fracture risk, and gastrointestinal malignancy (158). Children with T1DM have further potential complications such as impaired growth, hypoglycaemia and osteopenia as well as renal, cardiovascular and eye problems (149). How these complications manifest when CD and T1DM coexist has not been well established. One study looking at cohorts of children with CD and CD & T1DM has suggested that the clinical picture in dual diagnosis is in fact milder than in children with CD alone (161), although this has not been repeated (162).

Many of the clinicians in the current study who don’t have a regular screening programme use poor growth or poor diabetic control as indicators to commence screening for CD. The available evidence, however, is not conclusive as to the impact of CD upon growth or glycaemic control. It is even less conclusive as to how starting a GFD will improve these clinical markers. Many studies are limited by small numbers, unclear
definition of symptomatic versus screening detected CD and a lack of adequate consideration of bias from variables such as compliance and pubertal status.

Gluten free food is often less palatable than gluten containing food and often contains less complex carbohydrates, which can lead to rapid peaks and troughs in blood glucose control. This could mean that blood glucose control is more challenging for families, although evidence is limited that demonstrates that this translates into poor control, as measured by HbA1c (163-169).

Two small studies found statistically significant differences in the rate of hypoglycaemia in screening detected children prior to discovery of CD that resolved after diagnosis (165, 166). However, several other studies including a large observational study (411 T1DM with biopsy-proven CD) found no difference in reported severe hypoglycaemia at diagnosis (163, 167, 168). A population-based study in Sweden examined the hospital records of all children diagnosed with CD&T1DM, and found no difference in the rate of hypoglycaemia admissions, diabetic ketoacidosis or death (170). Untreated CD may increase the risk of potentially serious hypoglycaemia and the response to foods aimed to correct it but this has not been well studied.

HbA1c is often used as a measure of overall control in T1DM. Many studies have tried in various ways to elucidate the impact of CD upon HbA1c in T1DM, both prior to diagnosis and after initiation of a GFD. The majority of reports have found no difference in HbA1c either at diagnosis between cases and controls or after starting a GFD (Table 2.4). Two studies found lower HbA1c in cases than controls, which increased to that of controls after GFD was commenced (164, 169). However, when one of the groups repeated the study some years later, this difference was no longer evident (163). The inclusion and exclusion criteria of these seven studies varied, making comparison of the results difficult.
Table 2.4: Summary of glycosylated haemoglobin (HbA1c) results in recent papers evaluating glycaemic control in children with coeliac disease (CD) and type one diabetes mellitus (T1DM)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N=cases</th>
<th>N=controls</th>
<th>HbA1c at CD diagnosis</th>
<th>HbA1c control</th>
<th>p</th>
<th>HBA1c cases on GFD (yrs of follow up)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artz (171)(2008)</td>
<td>30 †</td>
<td>34</td>
<td>8.04 ± 0.2</td>
<td>8.05±0.1</td>
<td>0.89</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Frohlich-Reiterer (163) (2010)</td>
<td>411 ‡</td>
<td>17661</td>
<td>8.2 ±0.3</td>
<td>8.05±0.2</td>
<td>0.99</td>
<td>7.6 v 7.8 (cases v controls) (5yrs)</td>
<td>ns</td>
</tr>
<tr>
<td>Kaspers (164) (2004)</td>
<td>127 ‡</td>
<td>18470</td>
<td>8.1±1.8</td>
<td>8.8 ±2.4</td>
<td>&lt;0.05</td>
<td></td>
<td>¶</td>
</tr>
<tr>
<td>Rami (168) (2005)</td>
<td>98 ‡</td>
<td>195</td>
<td>8.8 ±2.2</td>
<td>9.3 ±2.5</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saadah (172) (2004)</td>
<td>21 ‡</td>
<td>42</td>
<td>8.03 ± 0.9</td>
<td>8.21 ±1.2</td>
<td>ns</td>
<td>8.04 ±0.98 (1yr)</td>
<td>ns</td>
</tr>
<tr>
<td>Simmons (167)(2011)</td>
<td>79 §</td>
<td>56</td>
<td>8.3 ±0.2</td>
<td>8.1 ± 0.1</td>
<td>0.29</td>
<td>8.1 ± 0.2 (2 yrs)</td>
<td>0.32</td>
</tr>
<tr>
<td>Sun (169) (2009)</td>
<td>49 ‡</td>
<td>49</td>
<td>8.4 ±1.3</td>
<td>8.7 ±0.9</td>
<td>&lt;0.001</td>
<td>8.9 ± 1.5 v 8.8 ± 1.5 (cases v controls) (1yr)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Key:
† seropositive to either TTG or anti-endomysial antibodies
‡ Biopsy proven coeliac disease
§ anti-tissue transglutaminase positive (TTG)
¶ The follow up data is reported in the Frohlich Reiterer data
Poor growth has been identified by the respondents to this survey as a prompt to screen for CD. It is not clear if growth is commonly affected in subclinical CD or that starting a GFD improves growth parameters. Three studies have shown impaired growth parameters in subclinical CD discovered in screening programmes. The largest study found lower height and weight scores in biopsy proven CD, which was persistent despite commencing a GFD, although no attempt was made to identify if compliance altered the result (163). One of the other studies found lower height and weight at diagnosis, of which weight improved but not height unless the children were younger than 14 years (165). The third study found a reduced body mass index (BMI) at diagnosis, which if the children were compliant then increased to match controls after 2 years (167). Four other case control studies found no difference in growth parameters at diagnosis (162, 168, 169, 173). This persisted in three of the studies (162, 169, 173) whilst the other found that after diagnosis weight gain was slightly poorer in those with CD (168).

Reduced bone mineral density has been found in children with both T1DM (174) and CD (175) independently. Studies have shown that children with T1DM and CD also have reduced bone mineral density (BMD) (176, 177). A cross sectional study of 122 children with T1DM and positive CD serology, matched with 129 children with only T1DM, showed that 12% of the children with positive serology had low BMD, compared to 3% without TTG antibodies (p<0.0076) (178). GFD has been shown to be associated with better BMD in CD (177, 179, 180) and the dual diagnosis (171, 176). Recognising CD early and establishing treatment to avoid future fractures could be a convincing argument for screening, but here also, evidence conflicts. One study using Swedish population data did not find an increased fracture risk in young people with dual diagnosis, but the follow up of a median of 13 years, does not seem long enough to be able to ascertain the impact of osteoporotic fractures and as a purely retrospective, observational study it cannot give information on how treating the disease with a GFD will impact on outcomes (181).

Epidemiological studies have shown that there is increased risk of death in both CD and T1DM. This is thought to relate to both cancer risk and increased atherosclerotic complications. A large retrospective population based Swedish study found that 15 years after CD diagnosis the adjusted hazard ratio for mortality in patients with T1DM was 2.8 (95% CI 1.28-6.12) (182). Both cancer risk and increased atherosclerotic complications have independently been found to be significant causes of death when
each illness is diagnosed alone (183, 184). Observational studies regarding microvascular complications in large cohorts of young people with T1DM, also suggests that there is an increased risk of eye, renal and neurological complications in T1DM and CD (185-187). Because such studies are necessarily retrospective and there are many confounding factors, it is difficult to make comment on how recognising and treating CD would change this risk.

Several clinicians who do not screen for CD stated that they use symptoms to trigger testing. Some studies in children with T1DM and CD have found a low rate of reported symptoms although some of these studies rely on retrospectively collected data or chart review (157, 167). Other studies demonstrate that by the time the CD diagnosis is made the majority of patients will report symptoms prior to starting a GFD (165, 188). Some NZ clinicians note asymptomatic cases often report feeling better once a GFD has been started. This could be due to lack of direct questioning, patients simply putting up with vague symptoms that they only recognise once resolved or that there is a certain placebo effect of being on a GFD. A recent report from the TEDDY birth cohort study group showed that symptoms of abdominal discomfort and GI upset were more commonly reported when caregivers were aware of CD immunity than before they were aware (189).

Given the difficulty of identifying CD in a clinical setting, the high incidence and the evidence pointing towards negative consequences of untreated CD, the weight of expert opinion suggests that screening is prudent. Most NZ clinicians do screen for CD in their T1DM populations. The most commonly used tests are TTG and EMA. TTG is a more objective assay than EMA but has more false positives as it can be raised in other clinical situations, including at diagnosis of T1DM, after which it has been demonstrated to normalise (151, 190, 191). Antigliadin antibodies (AGA) are limited in their sensitivity and specificity and are not now recommended for screening (158). The most recent European guidelines suggest that HLA subtyping be done in at risk groups and if negative for DQ2/DQ8 then no further testing be done (50, 158). Work in clinical populations has suggested however this strategy may not be as useful in children with T1DM as there is a high rate of the HLA subtype DQ2/DQ8 – 95% in one Scottish group (192), and 86% in a Dutch group (193). Very few NZ clinicians test for HLA, perhaps reflecting difficulty and expense of accessing the test as well as its limited usefulness for discriminating children at risk.
NZ clinicians screen yearly or biannually with some modifying this with age or years since T1DM diagnosis. Most children are diagnosed with CD within 2 years of diabetes diagnosis but cases continue to be identified over at least the next 10 years (9, 155, 194). International recommendations vary from yearly screening to once initially at diagnosis and then once in the next 5 years (50, 149, 195). It has been shown that there is a higher prevalence of CD in children with a younger age at T1DM diagnosis (163, 191, 194, 196), suggesting that screening should be extended in children younger than 5 years at the onset of diabetes.

The only current treatment for CD once discovered is a life-long GFD. This can be a burdensome and expensive cure. Some studies report compliance rates as low as 25% in patients with both CD and T1DM (172). A major concern for clinicians and patients is the effect of GFD on quality of life (QOL).

In symptomatic CD, QOL and perceived wellness generally improves after commencement of a GFD (197). When subclinical cases of CD are evaluated there seems to be very little change in QOL with GFD (198). Two questionnaire studies in T1DM children found no difference in QOL score in children with or without CD (199, 200). This work suggests that the impact of a CD diagnosis may not be as significant as feared.

A repeated observation when trying to determine if screening is worthwhile in populations with CD and T1DM is the benefit of treating with a GFD. Any work that has tried to look at the impact of the dual diagnosis can only really comment on the parameters at diagnosis, and the benefit of GFD is muddied by questions over compliance with a GFD. A study is currently under way that will help determine if making the diagnosis when a child is asymptomatic is important as it aims to evaluate the benefits of GFD in asymptomatic CD in T1DM by randomising participants to GFD or usual diet (201).

### 2.5 Conclusion

In conclusion, this work demonstrates that screening for CD is undertaken by nearly all clinicians but that there are in variations in practise. Clinicians caring for patients are sensitive to the burden of T1DM and the extra burden another diagnosis may place upon the family. If there is symptomatic CD the path is clear, and a GFD will help alleviate symptoms and avoid malabsorption. In subclinical disease the case is less clear, but there are possibly benefits to bone, growth and diabetic control with minimal impact on
quality of life. A nationwide consensus on screening, would help avoid confusion, particularly when patients move from one clinic to another. Further research with large multicentre prospective cohorts of children with agreed definitions of CD, GFD and growth parameters will help provide definitive answers as to the benefit to be derived from identifying subclinical disease.
Chapter Three: Gastric Emptying in Children with T1DM and healthy controls

3.1 Introduction

T1DM is a multisystem disease of glucose homeostasis (202). Good blood glucose control has been shown to improve long-term outcomes (78). Gastric emptying has an impact on post-prandial glycaemia. Rapid gastric emptying may be responsible for elevated postprandial blood glucose, therefore impacting on overall glycaemia (93, 103, 106). Synthetic agents such as pramlintide are available which alter gastric emptying and by inference regulate postprandial hyperglycaemia, an important determinant of overall control (110, 203). Without knowledge of the physiology of gastric emptying in T1DM children the utility of these adjuncts is limited (204, 205).

Several studies using varied methodologies have examined gastric emptying in children and adolescents with T1DM. Although most studies demonstrated altered emptying, two with the most robust methodologies did not show any change (88, 90-94, 206).

With the underlying hypothesis that children with T1DM would have delayed gastric emptying compared to healthy controls, the current study evaluated gastric emptying using a safe non-invasive method. The primary objective of this prospective pilot study was to compare emptying in children with T1DM with that in healthy controls. Further objectives were to elucidate the impact of Body Mass Index (BMI), glucose control, age, gender and duration of disease upon emptying in children with T1DM.

3.2 Subjects and Methods

3.2.1 Cases and Controls

Children with T1DM (defined by standard clinical criteria) (202) were recruited from the paediatric diabetes clinic at Christchurch Hospital, Christchurch, NZ. Inclusion criteria was broad to encourage recruitment. All children aged between 7 and 15 years old with diagnosis of T1DM for longer than six months were approached by a single researcher. Cases were excluded if they had known underlying GI or other medical illness (other than T1DM), or poor diabetic control as defined by recurrent severe hypoglycaemia, recent diabetic ketoacidosis, or HbaA1c >14% (130mmol/mol). Cases
were asked to recruit a control, either a peer or siblings of the case without T1DM or any known underlying GI or serious medical illness.

Demographic data was collected on participants. All caregivers filled in a questionnaire regarding GI symptoms in the children (see Chapter 4 for description of questionnaire). Responses were marked on a 5-point likert scale. The response to each question was added together to give an overall symptom score.

**3.2.2 Breath Testing Protocol**

The Carbon 13 (C\textsubscript{13}) oral breath test methodology as developed by collaborators in Adelaide was followed (Zacharias & Butler, University of Adelaide personal communication). This method is a safe, easily reproducible measure of gastric emptying that compares favourably to the gold standard scintography for measuring gastric emptying in children\textsuperscript{(128)}. The method follows that developed and validated by Ghoos where samples of exhaled carbon dioxide is collected at various time points, then analysed to give measures of the rate of gastric emptying, \textsuperscript{(116)}. Each subject’s Gastric Emptying Coefficient (GEC), gastric half emptying time (GET\textsubscript{$\frac{1}{2}$}) and maximum gastric emptying time (GET\textsubscript{max}) were calculated using linear regression, in a method developed by Ghoos\textsuperscript{(116)}.

Subjects fasted overnight and then consumed a standardised pancake meal for breakfast. The meal consisted of 70g of pancake mix (Edmonds, Auckland, New Zealand) mixed with 100ml of filtered water and 100mcg of sodium octanoate enriched with Carbon 13 (C\textsubscript{13}) (Cambridge Isotope Laboratories, Andover, Mass, USA). The pancake was cooked in 5g of butter, and served with the option of 5g of glucose free jam. The meal was eaten within 10 minutes. No other food was consumed for the duration of the test but subjects were allowed to sip small amounts of water.

Cases administered their usual insulin regime, with an adjustment in the dose if necessary to allow for a smaller carbohydrate meal than their usual breakfast after measuring a baseline blood glucose and in consultation with their caregiver.

Breath samples were collected into a test tube via a drinking straw at baseline, then every 15 minutes from the start of the meal until 120 minutes, then every 30 minutes until 240 minutes. Cases measured their capillary blood glucose (BSL) on their own glucometer at baseline and then every hour or if symptomatic. Low BSL (<3.5 mmol/L) were corrected with 10g of dextrose and a small mixed meal. High BSL (>20 mmol/L)
were corrected with rapid acting insulin. Cases developing hypoglycaemia were excluded from final analysis.

### 3.2.3 Statistical Analysis

This study was intended as a pilot study. The number of children recruited was a convenience sample.

Samples were analysed on an (Sercon) ABCA isotope ratio mass spectrometer (Crewe, UK), at the University of South Australia.

Results were analysed using Stata/IC 12.1 for Windows. Data are presented as mean and 95% confidence intervals as appropriate. Mean values were compared using two sample t-tests. P<0.05 was considered statistically significant. Correlation was examined using Pearson correlation. Ethical approval was granted to the study by the Upper South A Regional Ethics Committee, Christchurch New Zealand (Appendix B). Informed consent was attained from the guardian and children prior to entry into the study.

### 3.3 Results

#### 3.3.1 Demographics

Breath testing was performed on 20 cases and 15 controls. Six cases were excluded from primary analysis as they had hypoglycaemia requiring treatment during their study, leaving a final group of 14 children with T1DM. In post-hoc analysis, the children were divided into two groups that reflected the duration of T1DM: eight of the children had longstanding (defined as greater than 5 years since diagnosis) T1DM (mean 8 years, range 6 – 10 years) and 6 children had early T1DM (defined as less than 5 years since diagnosis) (mean 2 years, range 0 – 4 years). Demographic data comparing the children are presented in Table 3.1. All but one of the cases was on multiple daily dose regime of insulin, with a mixture of long, intermediate and short acting insulin. The remaining child was on an insulin pump.
### Table 3.1: Demographic data of participants

<table>
<thead>
<tr>
<th></th>
<th>(n)</th>
<th>Age in years (SD)</th>
<th>Sex (F)</th>
<th>Duration in years (SD)</th>
<th>HbA1c (%/mmol/mol) (SD)</th>
<th>BMI Z score (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15</td>
<td>11.2 (2.6)</td>
<td>9</td>
<td></td>
<td></td>
<td>0.37 (0.10)</td>
</tr>
<tr>
<td>Cases</td>
<td>14</td>
<td>11.3 (1.7)</td>
<td>8</td>
<td>5.4 (3.4)</td>
<td>9.2/77 (1.1/12.5)</td>
<td>0.56 (0.62)</td>
</tr>
<tr>
<td>Early T1DM</td>
<td>6</td>
<td>11.6 (2.1)</td>
<td>5</td>
<td>2 (1.4)</td>
<td>9.6/81 (0.5/5.2)</td>
<td>0.44 (0.46)</td>
</tr>
<tr>
<td>Longstanding T1DM</td>
<td>8</td>
<td>11.1 (1.3)</td>
<td>3</td>
<td>8 (1.5)</td>
<td>8.9/74 (0.4/4.3)</td>
<td>0.65 (0.73)</td>
</tr>
<tr>
<td>Hypoglycaemic Cases*</td>
<td>6</td>
<td>11.4 (2.5)</td>
<td>4</td>
<td>4 (3.1)</td>
<td>8.4/68 (0.6/6.6)</td>
<td>0.13 (0.69)</td>
</tr>
</tbody>
</table>

Data reported as median values (Standard Deviation). P > 0.05 in all comparisons.
*Cases who developed hypoglycaemia during test and who were excluded from primary analysis.

### 3.3.2 Gastric emptying rates

The mean GEC in cases was higher than in controls, indicating a shorter gastric emptying time (3.19 (2.97 – 3.41) vs 2.90 (2.74 - 3.10), p = 0.03) (Figure 3.1).

Mean GET½ was not statistically different between the two groups (cases 99 (68 - 128) mins vs 103 (88-118) mins, p = 0.8), but did tend to a shorter half time in cases (Figure 3.2). GETmax values were similar in the two groups (cases 106 (88-128) mins vs 105 (94 – 115) mins, p>0.9) (Figure 3.3).
Figure 3.1: Gastric emptying coefficient (GEC) in cases and controls

Figure 3.2: Gastric emptying $T_{1/2}$ in cases and controls
3.3.3 Gastric emptying in longstanding compared to recently diagnosed T1DM

None of the gastric emptying parameters were different between those with early and longstanding diabetes, although the children with a longstanding diagnosis tended to a shorter GET½ and higher GEC (Table 3.2 and Figure 3.4–3.6). When the outlier with an extremely long emptying time was removed, the GET½ approached statistical significance. There was a weak positive correlation between duration of T1DM and GEC, $r = 0.4$ (Figure 3.7). There was no relationship between duration and other parameters (Figures 3.8 and 3.9).

Table 3.2: Comparison of gastric emptying parameters in children with Longstanding compared to Early T1DM

<table>
<thead>
<tr>
<th></th>
<th>Early T1DM</th>
<th>Longstanding T1DM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>3.32 (2.83-3.19)</td>
<td>3.01 (2.94-3.67)</td>
<td>0.13</td>
</tr>
<tr>
<td>GET_{max} (Mins)</td>
<td>101 (81-120)</td>
<td>110 (71-150)</td>
<td>0.66</td>
</tr>
<tr>
<td>GET½ (Mins)</td>
<td>104 (68-139)</td>
<td>95 (41-149)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Mean value (95% confidence interval)
Figure 3.4: Gastric Emptying Coefficient (GEC) in cases with Early or Longstanding T1DM compared to controls

Figure 3.5: Gastric Emptying $T_{1/2}$ in cases with Early or Longstanding T1DM compared to controls
Figure 3.6: Gastric emptying $T_{\text{max}}$ in cases with longstanding or early T1DM compared to controls

Figure 3.7: Gastric Emptying Coefficient (GEC) correlated with duration of T1DM
Figure 3.8: Gastric emptying $T_{1/2}$ correlated with duration of T1DM, $r = 0$

Figure 3.9: Gastric emptying $T_{\text{max}}$ correlated with duration of T1DM, $r = 0.3$
3.3.4 The impact of other factors upon gastric emptying

Amongst children with TIDM there was no correlation with any of the measured gastric emptying parameters and Glycosylated haemoglobin (HbA1c) (Table 3.3).

Table 3.3: Gastric emptying parameters correlated with Glycosylated haemoglobin (HbA1c), r values

<table>
<thead>
<tr>
<th></th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>0.0</td>
</tr>
<tr>
<td>GET_{max}(Mins)</td>
<td>0.4</td>
</tr>
<tr>
<td>GET_{50}(Mins)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

GEC, GET_{max} and GET_{50} did not correlate with BMI z-score, symptom score or age (Table 3.4).

Table 3.4: Gastric emptying parameters correlated with hypothesised modifiers of gastric emptying, r values

<table>
<thead>
<tr>
<th></th>
<th>Symptom score</th>
<th>BMI Z-score</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>GET_{max}(Mins)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>GET_{50}(Mins)</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

There was no difference in the mean emptying parameters between genders (Table 3.5).

Table 3.5: Comparison of gastric emptying parameters by gender, mean value (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>3.12 (2.88-3.37)</td>
<td>3.04 (2.85 – 3.23)</td>
<td>0.6</td>
</tr>
<tr>
<td>GET_{max}(Mins)</td>
<td>105 (94-115)</td>
<td>103 (88-118)</td>
<td>0.9</td>
</tr>
<tr>
<td>GET_{50}(Mins)</td>
<td>103 (74-133)</td>
<td>93 (79-107)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

3.3.5 Gastric emptying in cases initially excluded due to hypoglycaemia.

BSL levels did not remain within physiological limits during the test (Figure 3.10).
GEC, GET½ and GET_max were also calculated for the six cases who became hypoglycaemic, using the breath samples taken up until symptomatic hypoglycaemia. The addition of these values to the original data set did not alter the overall results: the GEC was still statistically significantly higher (p= 0.03) whilst the other parameters were not different (Tables 3.6 and 3.7).

**Table 3.6: Reanalysis of gastric emptying parameters including cases initially excluded due to hypoglycaemia. Mean value (95% confidence interval)**

<table>
<thead>
<tr>
<th></th>
<th>Cases including hypoglycaemia</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>3.21 (3.00 - 3.42)</td>
<td>2.90 (2.74 - 3.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>GET_max (Mins)</td>
<td>103 (88-118)</td>
<td>105 (88-118)</td>
<td>0.9</td>
</tr>
<tr>
<td>GET½ (Mins)</td>
<td>92 (70-115)</td>
<td>103 (88-118)</td>
<td>0.5</td>
</tr>
</tbody>
</table>
### Table 3.7: Comparison of gastric emptying parameters between cases who became hypoglycaemic and those who did not, Mean value (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Cases as initially analysed</th>
<th>Cases including hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>3.19 (2.97-3.41)</td>
<td>3.21 (3.00-3.42)</td>
</tr>
<tr>
<td>( \text{GET}_{\text{max}} ) (Mins)</td>
<td>106 (88-128)</td>
<td>103 (88-118)</td>
</tr>
<tr>
<td>( \text{GET}_{\frac{1}{2}} ) (Mins)</td>
<td>99 (88-128)</td>
<td>92 (70-115)</td>
</tr>
</tbody>
</table>

### 3.4 Discussion

The initial hypothesis of this work was that gastric emptying would be delayed in children with T1DM. The results arising however, demonstrated that gastric emptying was faster in children with T1DM, when measured by the GEC. This finding was supported by a shorter \( \text{GET}_{\frac{1}{2}} \) in cases.

The GEC is an index of gastric emptying: it describes the entire shape of the gastric emptying curve and is derived from measured CO\(_2\) excretion. The original paper that established the efficacy of \( ^{13} \text{C} \) breath tests as a method for measuring gastric emptying found the GEC had the best correlation with scintigraphically derived gastric emptying curves (correlation coefficient: 0.94) and was sensitive and specific when looking for delayed gastric emptying (116). GEC could be thought of as a more precise measure than \( \text{GET}_{\frac{1}{2}} \), which had a correlation with scintigraphy of 0.79 (116).

A limited number of studies have investigated gastric emptying in children with T1DM. Although methodological differences make direct comparison difficult, the reported studies show conflicting results. Two studies (88, 206) used electrogastrography (EGG), a proxy measure of gastric emptying with limited clinical usefulness (207). Another study combined EGG with ultrasound to ascertain delay in emptying (90). All the EGG studies reported differences in gastric activity between children with T1DM and healthy controls. Four other studies used more direct measures of gastric emptying: scintography and \( ^{13} \text{C} \) breath testing. Two scintigraphy studies found no difference in gastric emptying (91, 92), whilst one study using \( ^{13} \text{C} \) breath testing demonstrated significantly delayed gastric emptying (93), the other significantly faster gastric emptying in the adolescents they evaluated (95). Another study that included adolescents and young adults used a further technique, electrical impedance tomography, to measure gastric emptying and found a longer \( \text{GET}_{\frac{1}{2}} \) in cases (94).
Only one of the published paediatric studies demonstrated gastric emptying to be accelerated in children with T1DM. Acceleration of emptying has also been shown in studies of adult patients with both T1DM and T2DM (85, 86).

Gastric emptying is a complex process controlled by hormonal and neurological mechanisms, which interact to produce a smooth supply of substrate to the rest of the digestive system (8). Glycaemic, neuronal and hormonal pathophysiology can be examined to find hypotheses to explain the current results.

It has been established that gastric emptying is accelerated when blood glucose is low (208) and decelerates when it is high (102). The children in this study were not on an insulin clamp. The blood glucose of the cases did not remain in the physiological range as demonstrated by the children who became hypoglycaemic or had initial hyperglycaemia (Figure 3.6). However the expected effects of these blood glucose changes were not seen. Gastric emptying was still faster when children with hypoglycaemia were initially excluded. As a number of children were hyperglycaemic it could have been expected that this would result in overall slower gastric emptying in cases, which was not seen. The $^{13}$C breath testing study that demonstrated faster gastric emptying in adolescents noted that faster gastric emptying correlated with a bigger post prandial rise in blood glucose (95). These findings and those of the current study suggest that other mechanisms than direct glycaemic changes are implicated.

The autonomic and enteric nervous systems are both involved in gastric emptying (8) and changes secondary to T1DM could have a bearing on the results seen. Autonomic neuropathy (AN) is believed to be very important in the pathophysiology of gastroparesis in adults (8). However the role AN plays in altered gastric emptying in children with T1DM is less well studied. AN is rare at the onset of diabetes, rising to about 12.2% after the diagnosis of T1DM has been established for more than 9 years (113). AN was an exclusion criteria in most of the studies that examined gastric emptying in children but few children met the criteria to be excluded. Three studies tried to look for a relationship between AN and gastric emptying, however no relationship was found (92, 94, 95). The current study did not look specifically at measures of autonomic dysfunction, as it was assumed these would be subtle and not manifest in this population group, therefore no comment can be made about the impact it has made on the current results.
An interesting theory to explain the observed acceleration in gastric emptying is that rather than there being a mechanism causing accelerated gastric emptying, the cases in fact lacked a mechanism to slow their gastric emptying in response to the hyperglycaemia (209). Amylin (Islet amyloid polypeptide) is co-secreted from pancreatic beta cells with insulin and children with T1DM have reduced levels of this hormone (104). Amylin has been shown to inhibit gastric emptying in healthy controls in response to hyperglycaemia (85, 102). Administering synthetic pramlintide, an amylin analogue, to adults with T1DM resulted in gastric emptying rates slowing to equal to those of controls (85). It may be that the faster GEC observed in the cases in the current study was due to an inability to slow gastric emptying in response to the meal.

Grehelin, another gut hormone, has been shown to accelerate gastric emptying (107) and is elevated in children with early T1DM (104, 108). In an animal study, antagonising grehlin resulted in gastric emptying rates slowing to that of controls (210).

The limited size of the study means that it is inadequately powered to be confident the result is not due to type two error. As it was a pilot study, power calculations were not initially performed, but subsequent analysis suggest that a group of 21 in each group would be powered to 80%. Children with very poor control were excluded from the study for practical reasons. This is a potential limitation as it may have been expected that children receiving inadequate insulin may have even more disordered gastric emptying.

Cases with longstanding T1DM tended to a more pronounced acceleration of gastric emptying and a shorter GET$_{1/2}$. This suggests that there may be a process that occurs as the disease progresses that causes gastric emptying to accelerate. This accelerated gastric emptying may in turn contribute to post-prandial hyperglycaemia, which is difficult to control even with intensive insulin regimens (103). An awareness of the contribution of accelerated gastric emptying to hyperglycaemia may give clinicians alternative pathways to pursue to avoid unwanted post-prandial peaks in blood glucose.

The current study did not include any measures of psychological distress. A clear relationship between the mind and gut has been established (142). It has been shown that psychological distress can influence the rate of gastric emptying (144). It would therefore be interesting when repeating this work in larger groups to include a self-administered measure of psychological distress such as the Pediatric Quality of Life
Inventory (211) or the Problem Areas in Diabetes Survey(212) to examine any potential effect psychological factors may have had on gastric emptying.

The significant fluctuations in blood sugar of the participants was a limitation of this study. As stated an insulin clamp was not practical within the resources of the current study, however in future studies altering the methodology to include tighter blood glucose parameters, perhaps by ensuring stable capillary glucose levels of between 4-10mmol for a time period before the test may reduce the impact of hyper- and hypo-glycaemia on gastric emptying.

It is also important to note that there is significant inter-individual and intra-individual variation in gastric emptying, reflecting the many factors that can influence emptying(213). Repeating this study in the same individuals would strengthen the conclusions that can be drawn from the results.

3.5 Conclusion

The current study showed that in this group of children with T1DM, gastric emptying was faster than in cases than controls when eating a standardised pancake meal. This finding conflicts with most other research but all studies have been small and few have directly measured gastric emptying.

Further research is needed to establish the physiology of gastric emptying in children with T1DM. Examining breath testing in larger groups and repeating the test in the same individuals over time may give a clearer picture of the effect that disease progression has on gastric emptying. Studying children in euglycaemia and measuring amylin and grehlin may illuminate the hormonal mechanisms involved and give better weight to pharmacological methods aimed at augmenting blood glucose control. When repeating this study in a larger group cases with longstanding and short standing T1DM could be recruited to try to further examine the relationship between duration and gastric emptying.
Chapter Four: Gastrointestinal symptoms in children with T1DM

4.1 Introduction

Children commonly report gastrointestinal (GI) symptoms, such as abdominal pain (134, 214). These GI symptoms can impact adversely on the quality of life of a child and their family (133). Anecdotally children with T1DM are reported to complain more frequently of GI symptoms than their healthy peers. Potential explanations for this could include factors such as higher rates of coeliac disease (CD) in T1DM (9), the physiological effects of T1DM (215) and that living with a chronic illness may lead to altered perception of and increased complaints of pain (216).

Two reports have assessed GI complaints in children with T1DM compared to healthy peers (131, 132). One study evaluating symptoms in adolescents found a high prevalence of at least one symptom in cases (75%) and controls (77%): however the intensity of symptoms was not ascertained (132). The other report examined the prevalence of symptoms in children, but its control group was limited to children of hospital staff (131). They found lower rates of symptoms (36.8% cases, 44.9% controls) with no statistical difference between the groups. To date there are no published data about GI symptoms in New Zealand children with or without diabetes. Consequently, the current study aimed to establish the rate and intensity of GI symptoms in a clinic population of New Zealand children with T1DM compared to an aged-matched group of healthy children.

4.2 Methods

4.2.1 Subjects

Cases were children with T1DM aged 15 years and younger attending the diabetes clinic at Christchurch Hospital (the tertiary referral centre for the mid-South Island of New Zealand). To establish control data, each case was invited to also give the questionnaire to an age matched healthy peer or sibling. Other controls were healthy siblings of children admitted to the paediatric wards at Christchurch Hospital and children of staff at the Paediatric Department at Christchurch Hospital.

Children were excluded if they were unable to communicate complaints. They were not excluded if they had a pre-existing medical condition.
4.2.2 Questionnaire

Caregivers completed a questionnaire regarding GI symptoms (Appendix C). This 10-question tool was designed to establish the presence and intensity of common gastrointestinal symptoms in the preceding 6 months. The questionnaire was adapted to suit a New Zealand audience from a questionnaire designed by Saps et al. (139) to study GI symptoms in a community based group of school aged children. This device uses questions taken from the Children’s Somatisation Inventory, an extensive well validated questionnaire covering many symptom complexes (140). The caregiver was asked to include the child when completing the questionnaire.

Symptoms assessed were: abdominal pain, nausea, vomiting (either an episode or persistently), diarrhoea, (either an episode or persistently), constipation, (either an episode or persistently), bloating and reflux. “Persistently” was defined as more than once in 24 hours for vomiting and greater than a week for constipation and diarrhoea. Respondents were asked to choose an answer from a 5-point likert scale (0=not at all, 1 = a little, 2 = somewhat, 3 = a lot, 4 = a whole lot). A symptom was recorded as “present” if the respondent had complained of or experienced the symptom on at least one day in the past 6-months. A response of “Severe” was created for each symptom if the response on the likert scale was 3 or above. The presence of any of the upper GI symptoms (nausea, bloating, vomiting or reflux) was recorded as “Upper GI” present/absent, as was the presence of “Lower GI” symptoms (constipation, diarrhoea, persistent constipation or persistent diarrhoea). A composite GI symptom score for each individual was recorded by summing the likert scale score for each question.

The questionnaire included questions about demographics, past medical history (PMH) of GI disorder, pre-existing medical conditions and family history (FH). In cases the result of glycosylated haemoglobin (HbA1c) testing within 3 months of completing the questionnaire was obtained from each child’s hospital records, to serve as a proxy measure of blood glucose control.

4.2.3 Statistical analysis

Results were analysed using Stata/IC 12.1 for Windows (Statacorp, Texas, USA). Data were presented as means or proportions as appropriate. Mean values were compared using two sample t-tests. Odds ratios (OR), Pearson’s chi2 or Fisher’s exact test were used to compare dichotomous responses. Regression analysis was performed to
evaluate the impact of background factors on the results, logistic for discrete variables, linear for continuous. P<0.05 was considered statistically significant. 95% confidence intervals were reported where appropriate.

### 4.2.4 Ethical approval

Ethical approval was granted to the study by the Upper South A Regional Ethics Committee, Christchurch, New Zealand. Informed consent was attained from the guardian and children prior to entry into the study (Appendix B).

### 4.3 Results

#### 4.3.1 Subjects and demographics

One hundred and fifty cases (88% of eligible population) and 94 controls (38% of distributed questionnaires returned) completed the questionnaire. Although cases were older than controls, p = 0.01), the two groups were similar for gender and ethnicity (Table 4.1).

Only two cases were excluded due to inability to communicate complaints due to developmental delay.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (mean (95% confidence interval))</td>
<td>10.5 (9.9-11.0)</td>
<td>9.3 (8.7-10.0) (p=0.01)</td>
</tr>
<tr>
<td>Gender</td>
<td>47% – male</td>
<td>47% – male</td>
</tr>
<tr>
<td>HbA1c (%/mmol/mol) (mean (95% confidence interval))</td>
<td>8.9/74 (8.7-9.1/72-76)</td>
<td>-</td>
</tr>
<tr>
<td>Ethnicity - euro</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>Ethnicity - nz maori</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Ethnicity - other</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

#### 4.3.2 Overall GI symptom score

Children with diabetes were more likely to have a higher mean GI symptom score than controls, 4.9(CI 4.0-5.8) v 3.4(CI 2.6-4.2), p = 0.02.

Eighty percent of controls and 85% of cases reported at least one GI symptom in the preceding 6 months, OR 1.5 (CI 0.7 – 3.1) p = 0.3. Adjusting for age, sex, FH or PMH of GI condition did not impact on the result (p^adj^ = 0.3).
### 4.3.3 Specific GI Symptoms

The most common symptom reported by children was abdominal pain. Most children (73% of cases and 66% of controls) reported at least “a little” abdominal pain in the preceding 6 months. (OR 1.4, 95% CI 0.8 – 2.5) (Table 4.2). For each question the mean response on the likert scale was higher for cases. Mean likert scores for abdominal pain 1.3v 1.0 (p= 0.02) and reflux 0.4 v 0.2 (p= 0.01) were the most significantly different responses (Table 4.2). Children with T1DM were more likely to complain of the presence of any reflux symptoms: OR 2.2 (CI 1.1 – 4.6) (Table 4.2).

**Table 4.2: Gastrointestinal symptoms in children with T1DM and healthy controls**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presence of symptom</th>
<th>Likelihood of symptom in case</th>
<th>Mean response on Likert scale (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Case (n=150) 73%</td>
<td>Control (n=94) 66%</td>
<td>OR (95% CI) 1.4 (0.8-2.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43%</td>
<td>36%</td>
<td>0.9 (0.7-2.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19%</td>
<td>16%</td>
<td>1.2 (0.6- 2.6)</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>9%</td>
<td>6%</td>
<td>1.4 (0.5-4.6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>53%</td>
<td>43%</td>
<td>1.5 (0.9- 2.7)</td>
</tr>
<tr>
<td>Persistent diarrhoea</td>
<td>12%</td>
<td>6%</td>
<td>2.0 (0.7-6.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>31%</td>
<td>26%</td>
<td>1.3 (0.7- 2.5)</td>
</tr>
<tr>
<td>Persistent constipation</td>
<td>10%</td>
<td>5%</td>
<td>2.0 (0.7-7.1)</td>
</tr>
<tr>
<td>Bloating</td>
<td>30%</td>
<td>22%</td>
<td>1.5 (0.8-2.8)</td>
</tr>
<tr>
<td>Reflux</td>
<td>27%</td>
<td>15%</td>
<td>2.2 (1.1- 4.)*</td>
</tr>
</tbody>
</table>

(OR adjusted for gender, PMH of GI disorder and positive family history of GI disease). * indicates p<0.05.

There was an increased proportion of complaints of “severe” abdominal pain in cases, 17% v 5% of controls; (fisher’s exact p < 0.01), OR 3.6 (1.3 – 12.3). Very few respondents answered 3 or above on the Likert scale for other symptoms; consequently none of the other comparisons reached statistical significance (Table 4.3).
### Table 4.3: Severe gastrointestinal symptoms in cases and controls

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Likelihood of mean response &lt;3 in case, OR (95% CI)</th>
<th>p</th>
<th>Case (n)</th>
<th>Control (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3.6 (1.3 - 12.3)</td>
<td>P= 0.01</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2 (0.5-12.5)</td>
<td>n/s</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>-</td>
<td>n/a</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>n/a</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2.2 (0.5-12.5)</td>
<td>n/s</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Persistent diarrhoea</td>
<td>2.2 (0.5-12.5)</td>
<td>n/s</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.9 (0.1-11.4)</td>
<td>n/a</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Persistent constipation</td>
<td>-</td>
<td>n/a</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bloating</td>
<td>-</td>
<td>n/a</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Reflux</td>
<td>2.6 (0.5-25.5)</td>
<td>n/s</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

When examined as symptom complexes, there was no difference in the prevalence of upper GI symptoms between cases and controls (61% cases v 49% controls, OR 1.6 (0.9-2.8)). Similarly there was no difference in the percentage of children who complained of lower GI symptoms (56% v 62% OR 1.3 (0.7-2.2)).

#### 4.3.4 Pre-existing GI conditions

Children were not excluded if they had a pre-existing GI issue. Pre-existing conditions included: constipation, coeliac disease and abdominal migraine (Table 4.4). Cases were more likely to have any pre-existing GI condition, OR 3.0 (95% CI 1.2-8.4, p =0.01). Coeliac disease was the most frequently diagnosed condition.

### Table 4.4: Pre-diagnosed gastrointestinal conditions in cases and controls (other was not specified by respondent)

<table>
<thead>
<tr>
<th></th>
<th>Case (n=150)</th>
<th>Control (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>80% (120)</td>
<td>93% (87)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5% (7)</td>
<td>4% (4)</td>
</tr>
<tr>
<td>Functional Abdominal Pain</td>
<td>2% (3)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>7% (10)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease</td>
<td>5% (8)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1% (2)</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>
4.3.5 Other Pre-existing medical conditions

Most had no other medical problems (93% of cases and 90% of controls). Seven cases (5%) and 9 controls (10%) listed a diagnosis of asthma, 3 cases (2%) and 1 control (1%) listed attention deficit hyperactivity disorder as a pre-existing medical condition.

4.3.6 Family History of GI condition

Twenty-three controls and 34 cases had a family history of GI issues (no difference between the groups, chi2 0.746). Complaints listed included: gastroesophageal reflux, irritable bowel syndrome, non-specific abdominal pain, coeliac disease and inflammatory bowel disease.

4.3.7 Factors predictive of gastrointestinal symptoms.

The presence of T1DM was predictive of a higher GI symptom score (adjusted effect size 1.60, p 0.01). Higher HbA1c and female gender were both predictive of a higher symptom score, whereas ethnicity and age were not. When the model was adjusted for gender, the relationship remained significant (Table 4.5).

Table 4.5: Predictors of gastrointestinal symptom score in NZ children, * indicates p<0.05, **adjusted for gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (95% CI of coefficient)</th>
<th>Adjusted Coefficient** (95% CI of coefficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.48 (0.24-2.74)*</td>
<td>1.50 (0.27-2.73)*</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.66 (0.02 – 1.30)*</td>
<td>0.66 (0.02 – 1.30)*</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ Euro</td>
<td>-1.24 (-4.46 – 1.97)</td>
<td></td>
</tr>
<tr>
<td>NZ Maori</td>
<td>-0.14 (-3.39 – 3.09)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>-1.85 (-3.06 - -0.65)*</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.32 (-2.09-0.15)</td>
<td></td>
</tr>
</tbody>
</table>

4.4 Discussion

This study confirms that complaints of GI symptoms are common in childhood. Overall, 83% of the total group reported symptoms. The children with T1DM complained of GI symptoms as frequently as their peers. However, the intensity of their complaints overall was more severe than their peers. In particular, they complained of more severe
abdominal pain and reflux symptoms. Factors associated with a higher GI symptom score in cases included higher HbA1c and female gender.

The overall prevalence of GI symptoms in the current report was higher than reported in most studies, however no other studies have examined six-month prevalence. A community based study found weekly prevalence rates of 45% for any GI complaint (133). Most (90%) children complained of abdominal pain during the study period, with a weekly prevalence rate of 38%. Weekly rates for other symptoms (nausea 23%, diarrhoea 9%, constipation 8% and vomiting 7%) (133) were all lower than the six-month prevalence reported by the current control group. Higher intensity on a likert scale correlated with more absenteeism and increased likelihood of depression and anxiety. Further work by the same group found six weekly prevalence rates for the same group of symptoms of about 20%, and reported an average intensity of approximately 1.7 for each of the symptoms, which for the most part is higher than the current study (217).

Other work has focused on complaints of abdominal pain only, with most prevalence rates reported at around 50%, again lower than the 73% of cases and 66% of controls in the present study. A prospective prevalence study in Australian children presenting to a GP practice found 44% had complained of abdominal pain in the last 12 months (218). A large World Health Organisation study of the prevalence of somatic pain in adolescents (mean age 13.6yrs +/-1.7) found that 49.8% complained of stomach-ache monthly or more often (134). Girls (59.5%) had a higher prevalence than boys (39.4%) and older adolescents (53.4% at 15yrs) complained more than younger children (45.1% at 11yrs). Age was not found to be related to symptoms in the current study, however female gender was predictive of a higher symptom score.

Reflux symptoms were not commonly reported overall in the current study. However, these symptoms were more common and complaints were more severe in children with T1DM than in controls. Although the prevalence of reflux symptoms vary between countries and in different age groups, estimates of symptoms in children and adolescents range from 2% - 10% (219, 220). Lodefalk et al. (132) found no difference in the proportion of young people complaining of reflux symptoms in health or T1DM, but that higher rates were associated with certain socio economic factors, such as an unemployed father.
Most of the studies investigating the prevalence of pain and other GI disorders in childhood have been population-based case finding studies. These studies have used the Rome criteria, which were designed as diagnostic criteria for functional gastrointestinal disorders (FGID) (221). The current tool was not designed to make a diagnosis of FGID, but four children reported a pre-existing GI pain condition. This is much lower than the 12.5 – 25% previously published for pain predominant conditions (137, 216, 222). It is likely there are children in the current study with functional abdominal pain syndromes who have not had a formal diagnosis.

Two studies have investigated complaints of abdominal pain in children with T1DM. A Greek study investigated the prevalence of GI symptoms in a consecutive sample of children and adolescents attending a diabetes clinic and a well-matched control group of siblings of hospitalized children and offspring of hospital staff (131). As in the current study, they found no difference between cases and controls (36.8% v 44.9% in controls; p 0.17). The overall prevalence rate of any GI symptom complaint was much lower than in the current study. The symptoms were assessed by a single researcher administering a standard (unidentified, unreferenced) questionnaire. Cases with symptoms did not differ significantly from those without. Their results suggest that T1DM had no impact on symptom prevalence. However, they did not report the intensity of the symptoms or details of the specific symptoms.

A Swedish study used a postal questionnaire to determine the presence of 13 GI symptoms in a population-based group of adolescent cases and controls (132). Their findings are similar to the present study with a high prevalence of any GI symptom in cases and controls (75% vs 77%; p=ns). They did not find any difference in prevalence for any of the individual symptoms, but subgroups were affected by environmental and disease specific factors, such as gender and HbA1c, as in the current study.

The current study has shown that children with T1DM complain of more intense symptoms than their peers. The reasons for this may be due to comorbidity, direct metabolic effects of hyperglycaemia and psychological reasons.

Altered gastric emptying is one putative explanation for the increased prevalence of GI symptoms in cases. Whilst adult studies (84) have consistently found alterations in gastric emptying in diabetes, in children and adolescents the findings have been less convincing, with some studies finding delayed gastric emptying (90, 106), others no
difference (91, 92) and our own research showing it to be accelerated (Chapter three). When present, altered gastric emptying has not consistently been linked to symptoms (91, 92). Although altered gastric emptying is a possible explanation for the increased complaints of reflux in cases, evidence to support this hypothesis is not convincing.

In older patients autonomic neuropathy (AN) has been proposed as an explanation for more intense and frequent GI complaints (84, 223, 224). In children however, autonomic neuropathy is very rare at the onset of diabetes (113) and therefore unlikely to impact upon the rate of GI symptoms.

Coeliac disease is more prevalent in T1DM, with rates somewhere between 2.4%-16.4% (225). However, there is a low rate of reported symptoms in undiagnosed children (157, 167). The standard local practice is to screen at least biannually, so the prevalence of undiagnosed CD can be assumed to be low and is unlikely to explain the difference in symptom score.

Perception of sensation from the GI system has been shown to change in both hyperglycaemia and hypoglycaemia (102, 208, 215). In the current study higher HbA1c was predictive of increased symptom score suggesting on-going persistent hyperglycaemia may contribute to symptom prevalence. However, poor control has been associated (226, 227), with symptoms of anxiety and depression, and it may be that higher HbA1c is a marker of psychological distress rather than the cause of the increased symptom complaints.

The complaints of pain in cases may be associated with the child's reaction to and interpretation of pain. T1DM in children has been shown in a recent meta-analysis to be associated with small to moderate levels of psychological distress (226). Functional abdominal pain is often worse in children with psychological distress (216). There was no measure of psychological upset in the current questionnaire, but it is likely cases did have distress, which may affect their interpretation of pain.

The way parents react to their child’s pain can alter the impairment that results from that pain (143). In two large population studies of health related quality of life (HRQL) in children with T1DM, children and their parents reported different rates of psychological distress (227, 228): the children rated their HRQL higher than their parents reported the child’s HRQL. Parent and child were asked to answer the current questionnaire together, but as the completion of the questionnaires was not supervised, it is not possible to
know how consistently this was done, so the current results may not reflect the true symptom intensity experienced by the child.

A limitation of the current study is the selection of control group children. Siblings of children with T1DM are not necessarily a true representation of the normal population. The initial intention was to use peers, but recruitment was difficult. Using this group does however control for parenting practices and family history. Children recruited from the ward were from the same community and geographical area as the cases.

The current study did not include any measure of psychosocial factors. The participants’ addresses were not included in data collection, so there was no means to examine how socio economic status may have impacted on children’s reports of GI symptoms. No caregivers reported psychological diagnoses, which is surprising given reports of rates of up to around 30% for both depression and anxiety in children with T1DM.(229, 230). This is also surprising given the questionnaire was administered after the major earthquakes in the Canterbury region in 2010 and 2011 which were associated with an increase in anxiety and significant psychological distress(231). Given the strong association between psychological distress and GI symptoms including a measure of psychological distress such as the Pediatric Quality of Life Inventory(211), or perhaps designing the demographic portion of the questionnaire to be more specific about psychological co-diagnoses would be useful when repeating the study, to evaluate whether there is a link between psychological factors and higher reported rates and intensity of symptoms.

This was a clinic population study, there was an excellent response rate and it was representative of the diabetes clinic. A greater number of subjects would have improved the power; it is currently powered to detect a difference of 0.7. The size of the study also means that the significance of subgroup analysis is limited. Although this questionnaire did have multiple questions, the likelihood of each response is not independent as the symptoms occur in complexes and therefore a Bon Ferroni correction would be too conservative in this case. While the questionnaire has not been independently validated, and therefore results do need to be interpreted with caution, it has been adapted from an independently validated questionnaire (139) and the language adapted to the New Zealand population.
4.5 Conclusion

Gastrointestinal complaints were common in this group of children. The children with diabetes complained of more intense symptoms than their peers without diabetes. The reason for this difference in symptom severity may be related to the pathophysiology of T1DM or a psychological response to chronic illness. Further work examining GI function and dysfunction in children with T1DM and the psychological and family reaction to their illness may be useful to examine and elucidate the reasons for this difference.
Chapter Five: Summary and future directions

5.1 Coeliac disease screening and management benchmark

There is an increased rate of CD in children with T1DM, with rates of at least 5% compared to 1% for CD alone in the NZ population. The two diseases share genetic markers and the pathophysiology is almost certainly linked, whether causal or perhaps sharing a common pathway.

There is no clear guidance about who and when to screen for CD in children with T1DM, although as time has progressed, it is becoming more accepted that screening is appropriate. Evidence is not clear that the combination of the two conditions in asymptomatic children does lead to worse outcomes in terms of both growth and poor control. The best evidence for the benefit of adopting a GFD is for improving bone health and there is emerging evidence that the dual diagnosis is linked to atherosclerotic outcomes that may be improved with a GFD. It can also be argued that many children report recognise feeling better after commencing the diet, suggesting that they were not actually truly asymptomatic.

This research set out to establish a benchmark of what clinicians in NZ were doing to screen and manage children.

It was well supported and gives a good picture of what 92% of the clinicians caring for children with T1DM were doing at that point in time.

Although the majority of respondents did screen at diagnosis, approximately a third did not. Those that did not screen used symptoms, poor growth and poor control as triggers, as well as the recognition that family history put children at risk. This approach has the potential risk of missing children as much of the body of evidence suggests that these presenting features are not commonly found in children with CD. All but two respondents suggested that they would recommend to commence a GFD once CD was diagnosed. Commencement of GFD in this setting, regardless of the presence of symptoms, is currently the standard of care. However, clearly, as acknowledged by the responding physicians, this does place an additional burden upon these children and their families. Although there is no definitive data at present, there is a very interesting randomised control trial under way that may well provide some guidance to whether or not this is indeed best practice in children with T1DM (201).
5.2 Gastric emptying rates in children with T1DM

Most methods to measure GE are invasive (i.e. scintigraphy) or are only indirectly related to gastric emptying (i.e. electrogastrography). Delayed gastric emptying has repeatedly been shown in adults with T1DM. GE in children with T1DM is far less well documented. Several small studies exist using various methodologies (88-90) but the results are conflicting, some demonstrate delayed gastric emptying (93), no change in two (91, 92) and one study showed faster gastric emptying (95).

This was a pilot study to determine if children with T1DM have slower GE compared to non-diabetic controls. Gastric emptying was measured using Carbon 13 (C\textsubscript{13}) breath testing, a non-invasive, very low risk procedure that accurately correlates with GE time. Nineteen cases and 15 age and sex matched controls underwent testing. In conflict with the original hypothesis the mean GEC in cases was higher than in controls, indicating a shorter gastric emptying time (3.19 (2.97 – 3.41) vs 2.90 (2.74 - 3.10), p = 0.03). Mean GET\textsubscript{1/2} was not different between the two groups (cases 99 (68 - 128) mins vs 103 (88-118) mins, p = 0.8).

Secondary analysis suggested that there was a connection between the duration and a more pronounced increase in the speed of gastric emptying but numbers were small and the result didn't meet statistical significance. There was no correlation with Hba1c, BMI-z score, symptom score or age.

This finding was contrary to the original hypothesis, but there are several mechanisms, which could explain the finding. GE is difficult to measure and many factors influence the rate. One major drawback of the current study is that the children were not clamped and their blood glucose did not remain within the physiological range. However the children with hypoglycaemia which could potentially have caused an acceleration of GE were excluded and many of the children were in fact hyperglycaemic especially initially, which would have been expected to delay gastric emptying, rather than cause the accelerated GE seen.

The literature does offer potential explanations for accelerated gastric emptying such as alterations in gastric hormones such as amylin and ghrelin, which may mean that in T1DM the normal slowing of gastric emptying in response to a meal is disrupted. This acceleration may contribute to the often observed post prandial hyperglycaemia, which
is an important target when looking to modify blood glucose control and achieve better long term outcomes for children with T1DM.

5.3 Gastrointestinal symptoms in children with T1DM

Complaints of gastrointestinal symptoms are common in the paediatric age group. Children with T1DM are reported to have more gastrointestinal symptoms than their healthy peers, however evidence demonstrating this is limited. The evidence that is available suggests that rates of complaints are the same in children with and without T1DM. No attempt had been made to estimate the intensity of symptom complaints in children with T1DM. We aimed to document the rate and intensity of gastrointestinal symptoms reported in a clinic population of children with T1DM compared to an age matched group of healthy children.

A large group of children, 88% of the eligible clinic population, completed the questionnaire. As in previous work both groups had similar rates of any GI symptoms (80% of controls v 85% cases OR 1.5 (0.7-3.1)). The proportion of children complaining was much higher than one study (approximately 40%) (131), but was concordant with a larger group of adolescents (around 70%) (132). Methodological differences and the way symptoms were measured partially explains the differences in symptom rate.

Children with T1DM had higher mean scores for abdominal pain (1.3 v 1.0, p = 0.02) and reflux (0.4 v 0.20, p = 0.02). The overall mean score was also higher in cases (4.9 v 3.4, p = 0.02) indicating the intensity of their complaints was higher than healthy controls.

There are many plausible mechanisms, both physical and psychological that suggest children with T1DM would complain of more intense symptoms than healthy controls. Certain pathologies are found more commonly in children with T1DM, such as gastric emptying differences, higher rates of subclinical CD, or direct effects of hyperglycaemia. A higher HbA1c was associated with a greater symptom score in the current study. Children with T1DM were more likely to have a PMH of a GI condition, such as CD, although adjusting for this did not alter the significance of the result.

It is also likely that children with T1DM and their parents react differently to pain than children without a chronic illness. The gastrointestinal system and central nervous system are closely related; psychological stress exacerbates and magnifies the bodies’ response to stimuli that may otherwise be interpreted as innocuous. T1DM is associated
with higher levels of psychological distress; a chronic disease such as T1DM is a burden and will impact on how children interpret messages from their body.

5.4 Future Directions

5.4.1 Coeliac Disease in T1DM

The prospective randomised controlled trial currently underway will be very welcome as it will hopefully give better information as to what to do in the vexing situation of an asymptomatic child with T1DM (201). It aims to document bone density, hypoglycaemia and HbA1c as well as quality of life, with a proposed follow up of one year. This is a short time period as many of the potential drawbacks of the combination diagnosis will take many years to be apparent, particularly when considering bone health and microvascular complications of T1DM. A study to follow a cohort of children randomised to GFD/non GFD would be ideal, although given there is potential harm of not adopting a GFD, ethical and design strategies would need to be carefully thought out.

There is potential for such a study to shed light on causal mechanisms of CD. The children could have their bowel flora measured and this could be contrasted and compared with a group of non-sero positive children. Prospectively changes to the microbiota on the GFD could be examined.

One way to gather data about potential mechanisms would be to retrospectively examine the clinic population in Christchurch over the last 10 years, when it has been customary to measure coeliac serology at least once, but more typically every other year in the diabetes clinic population. This could give good prevalence data and can add to the information regarding growth and HbA1c. Children and adolescents could be recruited for further study, bone density could be measured and information gathered regarding T1DM complications, much of this data would be pre-existing. Quality of life and a measure of GI symptoms could also be included.

5.4.2 Gastric emptying

As the current work was a pilot it will be important to repeat the study in a larger group of cases and controls. In order to demonstrate more clearly the physiology of gastric emptying in T1DM intra-individual variation is perhaps more important than inter-individual variation, so to further explore the finding that duration may be linked to rapid gastric emptying repeating the study in the same individual over a series of years
would be very interesting. This could be coupled with prospective evaluation of symptoms, growth parameters and blood glucose control.

To add further weight to the robustness of the measurement of gastric emptying, EEG could be used as another supplementary measure and the results correlated.

If funding and ethics could be obtained then studying the children on an insulin clamp and with measurement of gastric hormones would give information about potential hormonal causal mechanisms. Collecting data on coeliac sero-positivity and subsequent development of the disease may be interesting, but numbers would have to be very large to gather meaningful data.

5.4.3 GI symptoms in children with T1DM

This novel finding of more intense symptoms in children with T1DM poses many questions that could be explored in future work. As this study was purely observational it does not offer explanations as to what drives the increase in intensity of symptoms.

Future investigation could look to examine the pathophysiological differences in the gut in T1DM, hormonal changes and of course gastric emptying.

Studies may be able to focus on some of the physical causes such as correlating gastric emptying parameters in a much larger group of children with intensity of symptoms. Similarly measurement of gastric or systemic hormones postulated to be involved may be illustrative.

Other areas of focus could be the psychological impact of T1DM and how this impacts on children and their quality of life. Work could focus on better measurement of psychological parameters; perhaps it could correlate measures of quality of life or psychological distress with symptoms.

In addition it could be useful to explore more information about the cases, particularly age, although it was not obviously associated with intensity in this study a larger group of adolescents may be worth studying, and including data about duration of T1DM to see if this too impacts on results.

A very interesting field that is becoming the focus of more work is that of the gut flora. Stool samples could be analysed between cases and controls to see if there is a particular
flora that is linked with symptoms. This could lead to interventional studies, such as investigating whether treatment with a probiotic changes the intensity of symptoms.

5.5 Final Thoughts

This thesis examines three relatively diverse aspects of gastrointestinal manifestations of T1DM. However all three aspects, CD, gastric emptying and the experience of GI symptoms are related.

Coeliac disease can cause significant disease and symptoms. Living with two chronic illnesses can be burdensome and increase a child and their family’s level of psychological distress, especially if their clinicians cannot offer them good advice on the best way to proceed with management of the dual diagnosis.

Gastric emptying has important implications for the control of T1DM. Alterations in gastric emptying may cause symptoms such as nausea and reflux. Recognition of altered gastric emptying may give the clinician and families another way to improve control of T1DM.

Although all children complain of symptoms, those complaints are more intense in children with T1DM. Whilst it is likely there are disease-related pathologies, such as CD and altered gastric emptying contributing to this, the child and their family’s level of stress and how they perceive their quality of life may well modify the level of distress caused by GI symptoms. Perceiving GI symptoms and dealing with these complaints is likely to increase the burden they perceive from their illness.

Poor control of T1DM is linked with increased GI symptoms and alterations in gastric emptying. CD and altered gastric emptying both potentially contribute to hyperglycaemia. The current study emphasises the fact that T1DM affects all body systems. Research and clinicians should ensure their focus is not only on blood glucose control. By recognising and managing the important GI manifestations, the burden for a child and their family can be eased and hopefully allow for optimal disease management.
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Appendix A – Coeliac Survey

Page One

Thank you for taking part in the survey. There are 3 pages with 24 questions. It should take about 5 minutes to answer.

If the answer is multi-choice please place a y beside the most appropriate answer.

The first two pages are designed to discover current practices in New Zealand regarding Coeliac disease in T1DM.

1.) Please enter your contact details, responses will be confidential
   First Name: ___________________________________________
   Last Name: ____________________________________________
   City: ________________________________
   Email Address: ____________________________________________
   At which DHB(s) do you currently care for children with type one diabetes?:
   ______________________________________________

2.) Which best describes you?
   [ ] Paediatric endocrinologist
   [ ] General paediatrician
   [ ] Adult physician
   [ ] Other

3.) In your diabetes clinics how many children (15 and under) have T1DM?
   ______________________________________________

4.) In your diabetes clinics how many children with T1DM have been diagnosed with coeliac disease?
5.) In your diabetes clinics do you have a formal protocol for screening and managing coeliac disease? (If you work at more than one hospital, please answer for the main hospital you work at)

( ) Yes
( ) No

6.) If you answered yes to question 5 please briefly detail that protocol below:

7.) Do you screen children for coeliac disease at diagnosis of T1DM?

( ) Yes, please go to question 8
( ) No, please go to question 11

8.) If you do screen for coeliac disease at diagnosis of T1DM, what do you use? (you may mark more than one answer)

[ ] Tissue transglutaminase (TTG)
[ ] Endomysial autoantibodies (EMA)
[ ] Antigliadin antibodies
[ ] Deaminated gliadin
[ ] HLA typing
[ ] Iron levels
[ ] Serum IgA
[ ] Other, please specify
9.) If you answered yes to question 7, how often do you subsequently screen for coeliac disease? (assuming the tests were negative at diagnosis)

____________________________________________

10.) If you answered yes to question 7, what do you use to screen for coeliac disease in T1DM subsequently? (you may mark more than one answer) After you answer this please go straight to question 13

[ ] Tissue transglutaminase (TTG)
[ ] Endomysial autoantibody (EMA)
[ ] Antigliadin antibody
[ ] HLA typing
[ ] Deaminated gliadin
[ ] Iron levels
[ ] Serum IgA
[ ] Other, please specify

11.) If you answered no to question 7, what is your trigger if any, for screening for coeliac disease? (you may mark more than one answer)

[ ] Diarrhoea
[ ] Anaemia
[ ] Poor growth
[ ] Erratic blood sugar control
[ ] Recurrent hypoglycaemia
[ ] Family history
[ ] Other, please specify:
[ ] Abdominal pain
12.) If you answered no to question 7, but you do screen for coeliac disease in T1DM, what do you use? (you may mark more than one answer) After you answer this please go straight to question 13

[ ] Tissue transglutaminase (TTG)
[ ] Endomysial autoantibody (EMA)
[ ] Antigliadin antibody
[ ] HLA typing
[ ] Deaminated gliadin
[ ] Iron levels
[ ] Serum IgA
[ ] Other, please specify

13.) If screening suggests possible coeliac disease, what is your next step? (you may mark more than one answer)

[ ] Refer for endoscopy
[ ] Commence a gluten free diet without endoscopy
[ ] Repeat bloods
[ ] Other, please specify
14.) With reference to screening for coeliac disease in T1DM, what is your criteria for requesting endoscopy?

15.) What is the criteria in your population group for commencing a gluten free diet? (please pick one answer)

( ) Biopsy proven coeliac disease
( ) Positive coeliac serology
( ) Symptoms suggestive of coeliac disease
( ) Other, please specify

16.) What is your standard approach with children who have T1DM and symptom free coeliac disease?

17.) What is your standard approach with children who decline to adopt a gluten free diet?
New Page

The next section is designed to assess the level of understanding surrounding coeliac disease in type one diabetes.

18.) What do you understand to be the prevalence of coeliac disease in children with T1DM?

____________________________________________

19.) What do you think is the most common presentation of coeliac disease in T1DM? (please pick one answer)

( ) Asymptomatic - discovered incidentally/on screening
( ) Erratic blood sugar control
( ) Poor growth
( ) Anaemia
( ) Diarrhoea
( ) Abdominal pain
( ) Frequent hypoglycaemia
( ) Other, please specify:

20.) What do you think is the most sensitive test to screen for coeliac disease?

[ ] Tissue transglutaminase (TTG)
[ ] Endomysial autoantibody (EMA)
[ ] Antigliadin antibody
[ ] HLA typing
[ ] Deaminated gliadin
[ ] Iron levels
[ ] Serum IgA
[ ] Other, please specify
21.) What do you think is the most specific test to screen for coeliac disease?

[ ] Tissue transglutaminase (TTG)
[ ] Endomysial autoantibody (EMA)
[ ] Antigliadin antibody
[ ] HLA typing
[ ] Deaminated gliadin
[ ] Iron levels
[ ] Serum IgA
[ ] Other, please specify

22.) What is the best test to diagnose coeliac disease once it is suggested by screening?

____________________________________________

23.) Are you aware of the current APEG (Australian Paediatric Endocrine Group) guidelines regarding coeliac disease in T1DM?

[ ] Yes
[ ] No

24.) Please feel free to add any additional comments regarding coeliac disease in T1DM below:

Thank You!

Thank you very much for taking the time to complete the survey. I will endeavour to send you a copy of the results.
Appendix B – Ethics Approvals

16th June 2010

Dr Jody Porter
Department of Paediatrics
University of Otago, Christchurch

Mā te rangahau hauora e tautoko te whakapiki ake te hauora Māori
All health research in Aotearoa New Zealand benefits the hauora (health and wellbeing)
of tangata whenua

Tena koe, Jody

Thank you for taking the time to meet with me at the University of Otago, Christchurch on
Tuesday 16th June 2010 to discuss your research study titled:

Gastrointestinal manifestations of Type One Diabetes in Children

I note that your research has two parts in the study, with the first part being a questionnaire; the
second part being a child’s breath test. Thank you also for the additional information you sent.

It was apparent in your summary of the research that there could be a small number of Maori
participants and that this research may have impact on Maori health and that is important. I
mentioned your meeting with Toriana Hunt, Maori Health worker for Paediatrics could be
helpful.

Although Maori are less likely to have type one diabetes, the high incidence of diabetes overall
for Maori should not be ignored. This research may have impact on Maori Health, and that is
important.

We also discussed the relevance of the research in regard to improving Maori health status and
referred to the HRC’s Nga Pou Rangahau Hauora Kia Whakapiki Ake Te Hauora Maori 2004-
other reference that is available is Hauora Maori Standards of Health IV: A study of the years
2000-2005 by Bridget Robson and Ricci Harris, Maori Health Research Unit, Wellington School
of Medicine. All provide Maori specific information on a range of health issues.

The recent publication Tatau Kahukura, Ministry of Health, 2008, is an update relating to the
socio economic determinants of health, health status and service utilisation of the Maori
population. Further references are available from the HRC’s Guidelines for Researchers on
Health Research Involving Maori (page 22), www.hrc.govt.nz. All publications make particular
reference to diabetes and Maori.

It is also advisable that researchers review and refer to the District Health Board Annual Plan
and/or the current Health Targets published by the Ministry of Health (1 July 2009).
It was agreed that there is a need to acknowledge the issues pertaining to ethnicity and to consider how ethnicity data will be collected in your study. Through our discussion the Census 2006 ethnicity question was considered to be the preferred tool in recording ethnicity.

Guidelines have been developed by the University of Otago, Christchurch to comply with cultural practices. As discussed, explicit consent must be obtained from the individual (or authorised family/whānau) and information sheets in the project must also be explicit regarding the explanation of samples to be taken and the disposal of samples.

It is a requirement of the ethics approval process that a final report be submitted when the research is complete. A copy of the report should be provided to me at that time as findings from this project may contribute to the development of future research hypotheses or projects. It is therefore important that appropriate Māori organisations, Māori health professionals and Māori researchers are aware of your findings. The Research Office of the University of Otago, Christchurch and in particular myself as the Research Manager of Māori health would be willing to assist in the dissemination of your findings once your project has reached a successful conclusion.

My suggestions do not necessarily relate to ethical issues with the research, including methodology. Other committees may also provide feedback on these areas. I hope this letter will suffice in terms of the application. Please contact me should you need any other information that may not have been included in the letter relevant to our conversation.

I wish you well in your research.  

"Mo tatou a mo ka uri a muri ake nei" Ngai Tahu 2025

Ka nui tonu nga mihi

Elizabeth Cunningham
Research Manager - Māori
28 September 2010

Associate Professor Andrew Day
Department of Paediatrics
University of Otago
PO Box 4345
Christchurch, 8140

Dear Associate Professor Day

Ethics ref: URA/10/07/051 (please quote in all correspondence)
Study title: Gastrointestinal manifestations of type one diabetes in children
Investigators: A/Prof A Day, Dr J Porter

This study was given ethical approval by the Upper South A Regional Ethics Committee on [insert date]. A list of members of the Committee is attached.

Approved Documents

- Protocol version 2 dated 04/08/10
- Information sheet and consent form for children with type one diabetes, Part A, version 2.a dated 03/08/10
- Information sheet and consent form for children with type one diabetes, Part B, version 2.b dated 03/08/10
- Information sheet and consent form for children without diabetes, Part A, version 2a dated 03/08/10
- Information sheet and consent form for children without diabetes, Part B, version 1.b dated 03/08/10
- Information sheet and consent form for young children, Part A Questionnaire, version 1.a dated 03/08/10
- Information sheet and consent form for young children, Part B version 1.b dated 03/08/10
- Information sheet and consent form for young children without diabetes, Part A Questionnaire, version 1.a dated 03/08/10
- Information sheet and consent form for young children without diabetes, Part B version 1.b dated 03/08/10

This approval is valid until 30 September 2011.

Amendments and Protocol Deviations

All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
- the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

**Annual Progress Reports and Final Reports**

**Requirements for the Reporting of Serious Adverse Events (SAEs)**
For the purposes of the individual reporting of SAEs occurring in this study, the Committee is satisfied that the study’s monitoring arrangements are appropriate.

SAEs occurring in this study must be individually reported to the Committee within 7-15 days only where they:

— are unexpected because they are not outlined in the investigator’s brochure, and
— are not defined study end-points (e.g. death or hospitalisation), and
— occur in patients located in New Zealand, and
— if the study involves blinding, result in a decision to break the study code.

There is no requirement for the individual reporting to ethics committees of SAEs that do not meet all of these criteria. However, if your study is overseen by a data monitoring committee, copies of its letters of recommendation to the Principal Investigator should be forwarded to the Committee as soon as possible.

Please see [www.ethicscommittees.health.govt.nz](http://www.ethicscommittees.health.govt.nz) for more information on the reporting of SAEs, and to download the SAE Report Form.

We wish you all the best with your study.

Yours sincerely

[Signature]

_Alieke Dierckx_
Administrator
Upper South A Regional Ethics Committee
Email: alieke_dierckx@moh.govt.nz
## List of members of the Upper Region A Ethics Committee, July 2010

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Role</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liz Richards</td>
<td>Consumer Representative Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>(Chair)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carolyn Bull</td>
<td>Legal representative, Maori representative Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>Murray Cameron</td>
<td>Health Researcher Health Professional Member</td>
<td>Male</td>
</tr>
<tr>
<td>Angelika Frank-Alexander</td>
<td>Community Representative Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>Allison Franklin</td>
<td>Consumer representative Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>John Horwood</td>
<td>Biostatistician Lay member</td>
<td>Male</td>
</tr>
<tr>
<td>Ellen McCrae</td>
<td>Pharmacist Health Professional member</td>
<td>Female</td>
</tr>
<tr>
<td>Edie Moke</td>
<td>Maori representative Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>Barbara Nicholas</td>
<td>Ethicist Lay member</td>
<td>Female</td>
</tr>
<tr>
<td>Christine Robertson</td>
<td>Health Practitioner Health Professional member</td>
<td>Female</td>
</tr>
<tr>
<td>Russell Scott</td>
<td>Health Practitioner Health Professional member</td>
<td>Male</td>
</tr>
<tr>
<td>Jane Ward</td>
<td>Researcher Health Professional Member</td>
<td>Female</td>
</tr>
</tbody>
</table>

John Horwood was not present at the meeting of 19 July 2010.

_Signed:_ Alike Dierckx (Administrator)  
_Date:_ 28.07.2010
8 August 2011

Associate Professor Andrew Day  
Department of Paediatrics  
University of Otago  
PO Box 4345  
Christchurch, 8140

Dear Associate Professor Day

Ethics ref: URA/10/07/051 (please quote in all correspondence)  
Study title: Gastrointestinal manifestations of type one diabetes in children  
Investigators: A/Prof A Day, Dr J Porter

Thank you for the progress report for the above study, which was considered by the Chairperson of the Upper South A Regional Ethics Committee.

Ethical approval is confirmed for a further 12 months from the report due date. We look forward to receiving another report from you in September 2012.

Yours sincerely

Alieke Dierckx  
Administrator  
Upper South A Regional Ethics Committee  
Uppersoutha_ethicscommittee@moh.govt.nz
21 December 2012

Professor Andrew Day
Paediatric Department
University of Otago, Christchurch
PO Box 4345
Christchurch 8140

Dear Professor Day

Re: Ethics ref: URA/10/07/051/AM01
Study title: Gastrointestinal manifestations of type one diabetes in children

This letter is to confirm receipt of the annual progress report for this study, submitted on 20 December 2012. HDEC approval for the study is re-confirmed for the period 30 September 2012 to 30 September 2013.

The Southern Health and Disability Ethics Committee will be in contact with you within 15 days of this date if it requires further information on any matter relating to this annual progress report, or if it wishes to reconsider its approval for the study. In the absence of such contact you should assume that the annual progress report has been accepted and approved without comment. No separate letter will be sent confirming this.

Please don’t hesitate to contact us for further information.

Yours sincerely,

Kirsten Forrest
Administrator
Health and Disability Ethics Committees
hdecs@moh.govt.nz
Appendix C – Gastrointestinal Symptoms Questionnaire

Questionnaire about gastrointestinal symptoms in children

Please answer each question as truthfully as you can. You are encouraged to talk to your child about the answers

Today's date:

Child's name:

Child's date of birth:

Your relationship to child:

What ethnic group does your child belong to:
(please tick as many as apply)

NZ European [ ]  NZ Maori [ ]
Samoan [ ]  Fijian [ ]
Chinese [ ]  Other European [ ]
Other Pacific Island [ ]  Other Asian [ ]
Other, please specify ____________________________.

Does your child have any ongoing medical problems?
(you can tick as many options as you feel apply)

Diabetes [ ]  No [ ]  Kidney disease [ ]  Yes [ ]
Coeliac disease [ ]  Heart disease [ ]  No [ ]
Reflux [ ]  Asthma [ ]  Irritable bowel disease [ ]
Inflammatory bowel disease [ ] (Crohn's) [ ]
Other (please specify ____________________________

Does your child take any medications: yes [ ]  no [ ]
If yes please list ____________________________

Does your child have any allergies? yes [ ]  no [ ]
Please specify ____________________________

Has your child ever been diagnosed with a stomach problem in the past?
(including reflux, abdominal migraine, constipation)

Yes [ ]  No [ ]
Please specify ____________________________

Does anyone in your child's family have problems with their stomach? yes [ ]  no [ ]
Please specify ____________________________
Please mark the answer you think most applies to your child by circling the appropriate answer. For example:

<table>
<thead>
<tr>
<th>not at all</th>
<th>a little</th>
<th>somewhat</th>
<th>a lot</th>
<th>a whole lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

In the last 6 months has your child complained of a headache?

(This answer means your child has not complained of a headache at all in the last 6 months.)

Questions:

**Q. 1** In the last 6 months has your child complained of tummy pain

**Q. 2** In the last 6 months has your child complained of nausea (like they might vomit) when they don’t have a tummy bug?

**Q. 3** In the last 6 months has your child vomited persistently (more than once in 24 hours) when they didn’t have a tummy bug?

**Q. 4** In the last 6 months has your child vomited when they didn’t have a tummy bug?

**Q. 5** In the last 6 months has your child had diarrhoea (meaning the poo is much runnier (more liquid) than normal or they need to do poos much more often than normal)

**Q. 6** In the last 6 months has your child had persistent diarrhoea (meaning for more than 1 week their poo is runnier (more liquid) than normal or they need to do poos more often than normal)

**Q. 7** In the last 6 months has your child had constipation? (meaning pain, difficulty/problems or a delay doing poos)

**Q. 8** In the last 6 months has your child had persistent constipation? (meaning for more than one week they had pain, difficulty/problems or going longer than normal without doing a poos?)

**Q. 9** In the last 6 months has your child complained of abdominal bloating? (This means a feeling of fullness in their tummy, feeling full when they have only eaten a little or had a noticeably swollen belly)

**Q. 10** In the last 6 months has your child complained of reflux (meaning bringing food back up into the mouth, burping sick or feeling a pain in their chest)

Thank you very much for your participation
Appendix D – Published Paper

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases of childhood. In New Zealand (NZ), the incidence has been observed to be 17.9/100,000, which is one of the highest rates in the world.23 T1DM is strongly associated with certain human leukocyte antigen (HLA) subtypes, although other genes as well as environmental factors have potential causal roles.22 T1DM is associated with increased risk of other autoimmune diseases, including coeliac disease (CD).6

CD is also strongly associated with certain HLA subtypes and is caused by a complex interaction of genetic and environmental factors.27 CD may present in several ways: the 'classical' picture of malabsorption; the 'non-classical' scenario, which includes various symptoms such as chronic abdominal pain, short stature or anaemia; and the increasingly recognised 'subclinical' disease, which is asymptomatic on routine clinical assessment.28

Prevalence studies from around the world have established that CD is more frequent in T1DM.24 Rates vary from 2.6% to 16.4%, illustrating a substantial increase from the 1% rate of CD in the general population.

The two diseases share HLA subtypes. CD is potentially involved in the aetiology of T1DM; it has been postulated that increased intestinal permeability seen in CD could allow environmental aetiogens access to spark the immune processes leading to T1DM33.35

In the last decade, the presentation patterns of CD have changed greatly, with more non-classical or subclinical cases diagnosed and fewer classical presentations.33 This is especially true in children with T1DM where up to 71% are reported to be asymptomatic at presentation.31 This pattern of CD in T1DM reflects in part the introduction of active screening programs in some diabetes clinics. However, the role of screening and the optimal screening system remains undefined.30,37

Most international bodies recommend screening, but how and how often is not clear, as summarised in Table 1. The 2011 Australian Paediatric Endocrine Group diabetes management guideline suggests screening at diagnosis and once in the next 5 years but offers no suggestion as to which antibodies to use,3 whereas the 2012 European Society for Paediatric Gastroenterology, Hepatology and Nutrition Coeliac Disease management
Table 1: International recommendations regarding screening for celiac disease in type 1 diabetes mellitus

<table>
<thead>
<tr>
<th>Specialist group</th>
<th>Publication year</th>
<th>Timing of screening recommended</th>
<th>Recommended screening test</th>
<th>Frequency of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Paediatric Endocrine Group</td>
<td>2011</td>
<td>Screen at diagnosis in children and adolescents</td>
<td>Not specified</td>
<td>If negative, should be re-screened, at least once in the first 5 years after diagnosis</td>
</tr>
<tr>
<td>International Society for Paediatric and Adolescent Diabetes14</td>
<td>2011</td>
<td>At diagnosis</td>
<td>TTG and/or EMA, IgA</td>
<td>Annually for first 5 years, then less frequently, more frequently if first degree relative with CD or suggestive symptoms</td>
</tr>
<tr>
<td>European Society for Paediatric Gastroenterology, Hepatology and Nutrition</td>
<td>2012</td>
<td>Not specified</td>
<td>Start with HLA type, if positive then TTG and IgA, EMA if weak positive</td>
<td>Retest at intervals, no firm evidence but opinion is every 2–3 years</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence</td>
<td>2009</td>
<td>Not specified</td>
<td>TTG initially, check IgA if serology negative</td>
<td>Insufficient evidence to make a recommendation</td>
</tr>
</tbody>
</table>

CD, celiac disease; EMA, anti-endomysial antibody; HLA, human leukocyte antigen; IgA, total immunoglobulin A; TTG, tissue transglutaminase.

guidelines suggest establishing the HLA subtype at diagnosis and proceeding to screen at diagnosis and every 2–3 years only if at risk.1

Due to the conflicting nature of this advice, it is unclear how clinicians actually approach the issue. A recent North American postal survey of health professionals looking after adults found very varied screening practices.17 We aimed to create an accurate picture of current practice for screening and management of CD among clinicians caring for children with T1DM in NZ.

Materials and Methods

Participants and inclusion criteria

Consultant paediatricians and adult physicians who cared for children under 15 years with T1DM in secondary or tertiary hospital clinics around NZ were invited to complete a questionnaire. A comprehensive list of consultant paediatricians caring for children with T1DM was compiled.

Each consultant was sent an email inviting participation in the study. Non-responding consultants were sent an email reminding them of their invitation. Subsequently, the respondents who still had not responded were sent a paper copy of the questionnaire and asked to return it by mail or hand.

Survey design

An online questionnaire was designed using Surveygizmo (www.surveygizmo.com). The questionnaire was designed to establish current practices regarding screening and subsequent management of CD in NZ children with T1DM. Areas covered were departmental screening procedures, the individual’s own screening practices and the management of CD after diagnosis. The questionnaire was a mixture of multiple choice and open-ended questions. Answers to open-ended questions were grouped for interpretation. (The questionnaire is available on request from the authors.)

Results

Respondents

Of the 37 consultants invited, 34 responded (Table 2).

Demographics

The number of children with T1DM cared for by individual participants ranged from 6 to 400. The respondents estimated that between 6% and 30% of children in their T1DM clinic had been diagnosed with CD.

Screening protocols

Twenty-one of the respondents have a formal departmental protocol for screening for CD in their population of children with T1DM. Regardless of the departmental protocol, the respondents were asked about their individual practice. Twenty-five of the consultants screen for CD at diagnosis of T1DM. Of those who do screen, all use anti-endomysial antibodies (EMA) antibodies, some use anti-transglutaminase (TTG) antibodies, some use anti-endomysial antibodies (EMA) in addition and a few use other antibodies.
Twenty-one of the respondents who screen at diagnosis subsequently screen for CD every 1–2 years. The other four use symptoms and/or the patient’s age as a trigger to rescreen.

The nine consultants who don’t regularly screen at diagnosis were asked what if anything did trigger them to screen (Table 3). All use IgT to test for CD when they do screen, with most also using EMA, one adding anti-gliadin antibodies (AGAs) and one clinician also using IHLA typing and iron status.

Management after screening positive

After a child was found to have abnormal screening tests, 29/34 participants would refer for a small bowel biopsy. Some qualified the decision to proceed to biopsy with strength of the positive test, the child’s symptoms, IHLA status and discussion with the family. Nine would repeat bloods at the same time as referring for biopsy. Two commenced a gluten-free diet (GFD) prior to or while awaiting biopsy.

Gluten-free diet

Thirty-two of the consultants responded that biopsy-proven CD was their criteria for commencing a GFD.

Management of symptom-free CD

When asked in an open-ended question how they approach subclinical CD, 30/34 consultants said they advise a GFD. Three qualified this further by mentioning that ‘symptom-free’ patients often feel better when on a GFD. Seven said they discuss ‘the pros and cons’ with parents and patient to allow them to evaluate the decision to commence a GFD. One practitioner reported that they only test symptomatic cases so has no ‘routine’ practice with asymptomatic children.

Management if gluten-free diet is declined

In an open-ended question, clinicians were asked what their approach was when a diagnosis of CD had been made, but the patient declined starting a GFD. Thirty-two consultants responded. The responses were very varied but were grouped for analysis. Some responses were placed into more than one category. Fourteen will try to educate the family, seven will accept their patients’ decision, 14 will provide ongoing monitoring and four had not encountered the situation. Most clinicians will try and provide the family with adequate information to make a choice but will not force the issue. If a GFD diet is declined, they will continue to monitor the situation, allowing room for ongoing education and the ability to re-approach the decision when appropriate. Several comments on the lack of certainty as to the benefits of a GFD especially in asymptomatic disease.

Discussion

While there are common trends, the response to this survey demonstrates the varied approaches taken when dealing with CD in children with T1DM in NZ. While half the clinicians surveyed formally screen for CD, not one-third do not. This survey represents the majority of clinicians looking after children with T1DM in NZ with a 92% return rate and as such is a good representation of the current approach to CD in the NZ setting.

The complications of untreated symptomatic CD are well documented and include growth failure, increased fracture risk and gastrointestinal malignancy. Children with T1DM have further potential complications such as impaired growth, hypoglycaemia and osteopenia as well as renal, CVS and eye problems.2,3 How these complications manifest when CD and T1DM coexist has not been well established.

Many of the current clinicians who do not have a regular screening programme use poor growth or poor diabetic control as indicators to commence screening for CD. The available evidence however is not conclusive in its impact on CD upon growth or glycaemic control. It is even less conclusive as to how starting a GFD will improve these clinical markers. Many studies are limited by small numbers, unclear definition of symptomatic versus screening-detected CD and a lack of adequate consideration of bias from variables, such as compliance and pubertal status.

Two small studies found statistically significant differences in the rate of hypoglycaemia in screening-detected children prior to discovery of CD that resolved after diagnoses.201,202 However, several other studies including a large observational study (411 T1DM with biopsy-proven CD) found no difference in reported severe hypoglycaemia at diagnosis21,21,24. Untreated CD may increase the risk of potentially serious hypoglycaemia and the response to feeds altered to correct it, but this has not been well studied.

Glycosylated haemoglobin (HbA1c) is often used as a measure of overall control in T1DM. Many studies have tried in various ways to elucidate the impact of diagnosis of CD upon HbA1c in T1DM. The majority of reports have found no difference in HbA1c either at diagnosis between cases and controls or after starting a GFD (Table 2). Two studies found lower HbA1c in cases than controls, which increased to that of controls after GFD was commenced.20,21 However, one Austrian group found, when they repeated the study some years later, this difference was no longer evident.22

Poor growth has been identified by the respondents to this survey as a prompt to screen for CD. It is not clear if growth is commonly affected in subclinical CD or that starting a GFD
Table 4: Summary of HbA1c results in recent papers evaluating glycaemic control in children with CD and T1DM

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>n- cases</th>
<th>n - controls</th>
<th>HbA1c at CD diagnosis</th>
<th>HbA1c control</th>
<th>P</th>
<th>HbA1c in T1D with CD</th>
<th>P</th>
<th>follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arzt et al.</td>
<td>30</td>
<td>24</td>
<td>8.04 (±0.10)</td>
<td>8.05 (±0.13)</td>
<td>0.89</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Frechlich-Reiterer et al.</td>
<td>111</td>
<td>17</td>
<td>8.2 (±0.2)</td>
<td>8.05 (±0.17)</td>
<td>0.09</td>
<td>7.6 vs 7.1</td>
<td>1.7</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Kaspers et al.</td>
<td>127</td>
<td>218</td>
<td>8.1 ± 1.8</td>
<td>8.8 ± 2.4</td>
<td>&lt;0.05</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rams et al.</td>
<td>198</td>
<td>195</td>
<td>8.8 ± 3.2</td>
<td>9.3 ± 2.5</td>
<td>0.35</td>
<td>0.04 ± 0.08 (1 yr)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Szidán et al.</td>
<td>21</td>
<td>42</td>
<td>8.03 ± 0.86</td>
<td>8.21 ± 1.10</td>
<td>0.29</td>
<td>8.1 ± 0.2 (2 yrs)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Simmons et al.</td>
<td>798</td>
<td>56</td>
<td>8.3 ± 0.2</td>
<td>8.7 (±0.9)</td>
<td>&lt;0.001</td>
<td>8.9 ± 1.5 vs 8.8 ± 1.5</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Sun et al.</td>
<td>14</td>
<td>49</td>
<td>8.4 (±1.3)</td>
<td>8.03 ± 0.9</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

†Seropositive to either TGt or anti-endomysial antibodies, ‡Tolypey proven coeliac disease, §Anti-tTG positive, ‡The follow up data are reported in the Frechlich-Reiterer data, CD, coeliac disease; HbA1c, glycated haemoglobin, n.s., not specified, T1DM, type 1 diabetes mellitus, tTG, tissue transglutaminase.

Improves growth parameters. Three studies have shown impaired growth parameters in subclinical CD discovered in screening programmes. The largest study found lower height and weight scores in biopsy-proven CD, which was persistent despite commencing a GFD, although no attempt was made to identify if compliance altered the result. One of the other studies found lower height and weight at diagnosis, of which weight improved but not height unless the children were younger than 14 years. The third study found a reduced body mass index at diagnosis which if the children were compliant then increased to match controls after 2 years. Three other case-control studies found no difference in growth parameters at diagnosis. This difference persisted in two of the studies, while the other found that after diagnosis, weight gain was slightly poorer in those with CD.

Reduced bone mineral density (BMD) has been found in children with both T1DM and CD independently. Studies have shown that children with T1DM and CD also have reduced BMD. GFD has been shown to be associated with better BMD in CD, and the dual diagnosis. Recognizing CD early and establishing treatment to avoid future fractures seems compelling.

Epidemiological studies have shown that there is an increased risk of death in both CD and T1DM. This is thought to relate to both cancer risk and increased atherosclerotic complications. A large retrospective population-based Swedish study found that 15 years after CD diagnosis, the adjusted hazard ratio for mortality in patients with T1DM was 2.8 (95% confidence interval 1.28-6.12). This is thought to relate to both cancer risk and increased atherosclerotic complications which have both independently been found to be significant causes of death when each illness is diagnosed alone. Because such studies are necessarily retrospective, it is difficult to make comment on how recognizing and treating CD would change this risk.

Several clinician’s who do not screen for CD stated that they use symptoms to trigger testing, some studies in children with T1DM and CD have found a low rate of reported symptoms although some of these studies rely on retrospectively collected data or chart review. Other studies demonstrate that by the time the CD diagnosis is made, the majority of patients will report symptoms prior to starting a GFD. Some NZ clinicians note asymptomatic cases often report feeling better once a GFD has been started. This could be due to lack of direct questioning, patients simply putting up with vague symptoms that they only recognize once resolved or that there is a certain placebo effect of being on a GFD.

Given the difficulty of identifying CD in a clinical setting, the high incidence and the evidence pointing towards negative consequences of untreated CD, the weight of expert opinion suggests that screening is prudent. Most NZ clinicians do screen for CD in their T1DM populations. The most commonly used tests are TGt and EMA. TGt is a more objective assay than EMA but has more false positives as it can be raised in other clinical situations, including at diagnosis of T1DM. ACAAs are limited in their sensitivity and specificity and are not now recommended for screening. The most recent European guidelines suggest that HLA subtyping should be done in at-risk groups, and if negative for DQ2/DDQ8, then no further testing should be done. Very few NZ clinicians test for HLA, perhaps reflecting difficulty and expense of accessing the test.

NZ clinicians screen yearly or biannually with some modifying this with age or years since T1DM diagnosis. Most children are diagnosed with CD within 2 years of diabetes diagnosis, but cases continue to be identified over at least the next 10 years. International recommendations vary from yearly screening to once initially at diagnosis and then once in the next 5 years. It has been shown that there is a higher prevalence of CD in children with a younger age at T1DM diagnosis, suggesting that screening should be extended in children younger than 5 years at the onset of diabetes.

The only current treatment for CD once discovered is a lifelong GFD. This can be a burdensome and expensive cure. Some studies report compliance rates as low as 25% in patients with both CD and T1DM. A major concern for clinicians and patients is the effect of GFD on quality of life (QOL). In symptomatic CD, QOL and perceived well-being generally improves after commencement of a GFD. When subclinical cases of CD are evaluated, there seems to be very little change in QOL with GFD. A questionnaire study in T1DM children

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found no difference in QOL score in children with or without CD.  

This work suggests that the impact of a CD diagnosis may not be as significant as feared.  

In conclusion, the study demonstrates that screening for CD is worthwhile, by nearly all clinicians but that there is variations in practice. Clinicians caring for patients are sensitive to the burden of TDID and the extra burden another diagnosis may place upon the family. If there is symptomatic CD, the path is clear, and a GFD will help alleviate symptoms and avoid malabsorption. In subclinical disease, the case is less clear, but there are possibly benefits to bone, growth and diabetic control with minimal impact on QOL. A nationwide consensus on screening would help avoid oxymoron, particularly when patients move from one clinic to another. Further research with large multi-centre prospective cohorts of children with agreed definitions of CD, GFD and growth parameters will help provide definitive answers as to the benefit to be derived from identifying subclinical disease.

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References


Appendix E – Posters

Gastrointestinal Symptoms in Children with Type One Diabetes Mellitus

Jody A Porter MBChB, Karen MacKenzie PhD, FRACP, Brian Darlow MD, FRACP, Andrew E Day MD, FRACP
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Introduction
Complaints of gastrointestinal (GI) symptoms are common in the paediatric age group.
Adults with T1DM have higher rates of GI symptoms than healthy controls.
Children with T1DM are reported to have more GI complaints than healthy peers, but evidence showing this is limited.

Aims
To document the rate and intensity of gastrointestinal symptoms in a clinic population of children with T1DM.
Compare this to an age-matched group of healthy children.

Methods:
Subjects:
Children with T1DM aged 10 years and younger attending the diabetes clinic at Christchurch Hospital and their healthy peers of similar age were included in the study.
Excluded if major communication issues or children too young to voice complaints.

Questionnaire:
A 10-point questionnaire regarding gastrointestinal symptoms in the previous 6 months.
Symptoms were rated on a 5-point Likert scale.

Questions covered:
Abdominal pain, vomiting, nausea, diarrhea, persistent rhinitis, constipation, reflux and bloating.

Demographic information, paediatric history, and family history also obtained.

Results
160 cases (56% of eligible population) 24 controls (20% of eligible questionnaires returned).
Age: cases 10.8 yrs of control 9.3 yrs (p = 0.01)
Sex matched

Figure 1: Total proportion of any children with any gastrointestinal symptom in the previous 6 months.

Figure 2: Gastrointestinal symptom score in children with T1DM compared to healthy controls.
Each individual’s 10 responses were totaled to give a score.

Figure 3: Intensity of abdominal pain in children with T1DM compared to healthy controls.

Mean response (95% CI):
Case: 1.22 (1.09 - 1.36)
Control: 2.35 (2.16 - 2.54)

Mean score (95% CI):
Case: 4.24 (4.04 - 4.45)
Control: 3.46 (3.29 - 3.63)

Conclusions
Children with T1DM report gastrointestinal symptoms more frequently than their peers.
The intensity of their complaints is more severe than their peers.
They complain more frequently of reflux symptoms and this is more intense than their peers.
They complain more of abdominal pain symptoms.

Acknowledgments
Dr. Porter has been the recipient of the Freemasons Fellowship in Paediatrics and Child Health.

Interpretation
The reason for the difference in symptom severity may be related to the pathophysiology of T1DM or a psychological response to chronic illness.
Looking for Coeliac Disease in Children with Type One Diabetes Mellitus; The New Zealand Perspective

Jody A Porter MBChB, Karen MacKenzie PhD, FRACP, Brian Darlow MD, FRCP, FRACP, FRCPCH, Andrew S Day MD, FRACP
Paediatric Department, University of Otago, Christchurch, New Zealand

Introduction
Coeliac disease (CD) is more common in patients with type one diabetes mellitus (T1DM) than in the general population. Prevalence rates vary between 2 – 10%, compared to 1% in the general population.

The diseases are both autoimmune and have human leukocyte antigen subtypes in common.

Most cases of CD in T1DM do not present in a "classical" manner with establishment, but rather in a "subclinical" fashion with no or very minimal symptoms.

This leads to the important clinical question of whether it is advisable to screen for CD in T1DM. Many bodies do advise screening, but what and how frequently varies.

Method
Consultant paediatricians and adult physicians who cared for children under 15 years with T1DM were invited to complete an online survey.

The questionnaire covered departmental screening procedures the individual's own screening practices management after CD diagnosis.

Results
92% (47 of the 51 respondents) of the consultants responded to the questionnaire.

Clinical indication to test for CD
(If clinician does not screen)

Management if CD suggested by serology

Management of symptoms from CD

Sero logical tests used to screen for CD

References

Acknowledgements
Dr Porter has been the recipient of the Foundation's Fellowship in Paediatrics and Child Health. Thanks to clinicians throughout the country who participated in the survey.