Abstract

Celiac disease (CD) and Type 1 diabetes (T1D) are common autoimmune disorders in youth with higher prevalence of CD in those with T1D compared to the general population. T1D and CD research provides evidence of shared genetic susceptibility as well as potential shared environmental risk factors including those associated with early dietary exposures and gut permeability. The inflammatory state of CD and T1D, which is heightened when not appropriately managed, is central to understanding the manifestations and clinical complications of CD in those with T1D. Management of T1D and CD requires a gluten free diet (GFD) and maintaining glycemic control for a lifetime; optimizing medical nutrition therapy to address glycemic control, growth, bone mass density, and cardiovascular health in youth with CD and T1D can address both short-term and long-term risk of disease-related complications. The interdisciplinary team has an important role in providing ongoing support, reinforcement of positive health behaviors, and skills development to overcome new barriers to adherence as parents and youth work daily to manage T1D and CD. Gaps in knowledge exist regarding the co-occurrence of T1D and CD. Very little evidence exists on the level of adherence required over the course of life to prevent disease-related complications and little is known about the natural history of untreated asymptomatic CD. Novel research is investigating prevention efforts, early screening methods, and measures of dietary adherence to better understand the complex etiologies, complications, and management of T1D and CD.

Type 1 Diabetes (T1D), Celiac Disease (CD), Gluten-Free Diet (GFD), Bone Mass Density (BMD), Tissue Transglutaminase (tTG)
Introduction

Celiac disease (CD) and Type 1 diabetes (T1D) are two pediatric autoimmune disorders that are increasingly common in the general population, singularly (CD: Murray 2003, Catassi 2010; T1D: Berhan 2011, Vehik 2007, Onkamo 1999) and concurrently (Fröhlich-Reiterer 2011, Salardi 2008). T1D and CD research provides evidence of shared genetic susceptibility as well as potential shared environmental risk and protective factors. Given the epidemiological evidence of CD and T1D co-occurrence, guidelines suggest screening for CD in those with T1D. At this time, the only available treatment of CD is strict adherence to a gluten-free diet (GFD). It is important to recognize that in addition to eliminating gluten from the diet, children with CD and T1D must also adhere to medical nutrition therapy designed to optimize glycemic control and reduce risk for chronic complications. Those with uncontrolled CD and/or T1D have increased risk of multiple deleterious health outcomes in the short-term and long-term, thus coordinating dietary management of both CD and T1D in the pediatric population, though challenging, is a necessity. This review will focus on CD in the context of T1D including the epidemiology of co-occurrence, shared risk factors, potential short-term and long-term complications, and clinical management.

T1D Pathophysiology and Epidemiology

T1D and CD share common etiologies based in immune-mediated processes. T1D involves aberrant immune function leading to the progressive deterioration of pancreatic beta-cells by anti-islet autoantibodies as well as autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA/GAA) and protein tyrosine phosphatase IA2. The process proceeds at varying rates, depending on genetic susceptibility and environmental exposures, until endogenous insulin production by B-cells ceases (Daneman 2006). There is limited concordance of T1D in monozygotic twin (Hyttinen 2003) and some individuals preserve B-cell function longer than others (Greenbaum 2009) even into adulthood suggesting environmental factors contribute to causation.

Prevalence estimates of T1D is approximately 2 per 1000 non-Hispanic white youth 0-19 years of age (Bell 2009) with incidence highest among the 10-14 year age group (Writing Group for SEARCH 2007). However, current trends in the progression from appearance of autoantibodies to overt diabetes has accelerated in young children (Ziegler 2011) and the incidence of T1D is increasing at roughly 2–5% per year worldwide (Daneman 2006).
CD Pathophysiology and Epidemiology

Celiac disease occurs in genetically susceptible individuals with HLA-DQ2 or HLA-DQ8. Ingested gluten is deamidated by transglutaminase into negatively charged gliadin peptides. These deamidated gliadin peptides have an affinity for HLA-DQ2 or DQ8 molecules of antigen presenting cells and when bound, enhance T cell response to gliadin (Briani 2008, Mereiles 2011). The gluten triggered immune-mediated response results in proliferation of antibodies to tissue transglutaminase and endomysium (a connective tissue that surrounds muscle and underlies small bowel epithelial cells). The subsequent inflammatory response leads to the systemic autoimmune injury to epithelial cells including those in the gut, skin, liver, uterus, brain, heart, and other organs. When these tissues are damaged, more transglutaminase is released and leads to the perpetuation of an aberrant immune response to ingested gluten and epithelial cells (Briani 2008, Mereiles 2011). Villous atrophy and intestinal inflammation are primary presentations of symptomatic CD; however CD can be seemingly asymptomatic with villous atrophy present or latent with low grade inflammation and no villous atrophy (Rewers 2005, Alaedini 2005). The autoimmune process is directly linked to gluten intake, thus damaged intestine can heal and return to normal histology by eliminating gluten.

In European and American youth 2 to 15 years of age, prevalence of CD is estimated at 3 to 13 per 1000 children (Hill 2000). Prevalence of CD has increased approximately 5-fold the past three decades, occurring in about 1% of the Western population (Catassi 2010). Incidence of CD is also on the rise, although partly related to late diagnosis of untreated CD and use of serological screening leading to diagnosis of milder cases (Murray 2003). The prevalence of CD among the general population is not reflected similarly in the subpopulation of those with T1D.

Epidemiology: Co-occurrence of T1D and CD

It is well known that the prevalence of CD is greater among individuals with T1D than among the general population (Savilahti 1986, Maki 1984, Walker-Smith 1969). Average prevalence of CD confirmed by biopsy among children with diabetes mellitus in 26 reports was 4.5% (0.97–16.4%) (Holmes 2002). In children and adults, prevalence of CD in those with T1D was estimated at 3%–6% in North American and Western European populations based on systematic review (Dubé 2005). However, prevalence of T1D varies by geographic region as does CD. Thus, when determining prevalence of co-occurrence of T1D and CD, it is difficult to generalize to a “world-wide” estimate based on specific regional population data (see Table 1).
Table 1: Prevalence of the co-occurrence of T1D and CD in various geographic locations

Incidence of CD in those with T1D appears to be increasing, especially among younger age cohorts. Cerutti et al described a 3-fold increase in risk for children <4 years of age at onset of diabetes compared to those >9 years of age based on a cohort of 4,322 Italian youth (2004). In an 18 year longitudinal study, the prevalence of CD among newly diagnosed type 1 diabetes was significantly higher among the 1995-2004 cohort (10.6%) compared to the 1987 to 1994 cohort (3.3%) (Salardi 2008). Increasing prevalence of CD was also found based on a sample of 41,951 patients with T1DM from Germany and Austria where biopsy proven celiac disease increased from 0.6% in 1995 to 1.3% in 2008 (Frohlich-Reiterer 2011). Estimates vary but the trend is clear that incidence of CD is increasing; possibly in part due to increased awareness of CD, screening criteria used for diagnosis, improvements in screening methods, as well as shifts in natural disease course that have led to increased risk of CD diagnosis among those with T1D.
Genetic and Environmental Risk Factors

Genetic susceptibility and environmental exposures are implicated in the risk of developing CD and T1D. Where these risk factors overlap provides insight into understanding why celiac disease occurs approximately six times more often among those with T1D compared to the general population (Fasano 2003).

Genetics of T1D and CD Co-occurrence

Increased prevalence of CD in those with T1D and the role of family history in developing one or both diseases has long been recognized (Maki 1984, Walker-Smith 1969). Genetic susceptibility of developing CD in those with T1D is associated with HLA alleles, specifically HLA DQ2 and HLA DQ8 genotypes, which confer a heightened immune system response to the presence of gliadin by T-cells (Mereiles 2011, Hansen 2006, Bao 1999). Hansen et al observed that of 33 youth with T1D diagnosed with CD, 85% has the HLA DQ2 genotype, 36% has the HLA DQ8 genotype, and 24% had both the HLA DQ2 and HLA DQ8 genotype (2006). Bao et al found similar genotype associations among those with T1D; observing that those with positive tTG autoantibodies had higher prevalence of HLA DQ2 or DQ8 and that one-third of those with homozygous HLA DQ2 had positive tTG autoantibodies compared to less than 2% youth with T1D lacking HLA DQ2 or DQ8 (1999). Although genetic risk is strongly linked to CD in youth with T1D, several genotypes confer protection (Smyth 2008) and much research is investigating how environmental factors can trigger or protect those at risk from developing CD.

Dietary Exposures and Risk of T1D and CD

Evidence suggests that there is a relationship between infant feeding practices, early immune response and development of T1D and/or CD. Gluten exposure is noted as a possible trigger in the development of T1D. In NOD mice, a gluten free diet prevented onset of T1D (Funda 1999). In infants, feeding practices and timing of introduction of gluten influenced risk of developing autoantibodies and later T1D and/or CD diagnosis (Ziegler 2003, Norris 2003, Hogen Esch 2010). However, others have not associated gluten exposure to risk of developing positive islet autoantibodies in infants (Virtanen 2006). Introduction of gluten containing cereals prior to 3 months of age was associated with significant increases in islet autoantibodies compared to infant solely breastfeed until 3 months and to infants introduced gluten between 3 and 6 months of age (Ziegler 2003). There may be a window of time, noted by Norris et al to be 4-6 months of age, in which introduction of gluten confers the least risk of
developing islet autoantibodies (2003). Furthermore, decreased risk of islet as well as CD autoantibodies was associated with the introduction of gluten while the infant is still breastfeeding (Norris 2003, Hogen Esch 2010).

The possible link of early infant feeding practices and development of CD is strongly evident in population observations coined “the Swedish CD epidemic.” During the mid-1980s CD rose dramatically. After review of possible causes, infant feeding practices were implicated. During this time gluten within commercial infant cereals increased, most mothers stopped breastfeeding around 4-6 months, and national recommendations suggested infant cereals be introduced after 6 months of age. When recommendations were adjusted to encourage introduction of gluten between 4-6 months while the infant is still breastfeeding and gluten was reduced in commercial infant foods, incidence of CD decreased (Hogen Esch 2010). Given these risks of T1D and CD related to dietary exposures, several studies are investigating how to prevent T1D or CD by adjusting these early dietary exposures.

**The Gut Immune System and Risk of T1D and CD**

The concept of gut permeability is being explored to understand how various dietary and environment exposures may be associated with development of T1D and/or CD. Visser et al described the role gut microflora, enterocyte tight junctions, and exposure to gluten in autoimmune response (2009). With gluten intake, colonization of gut microflora is altered and favors the *Bacteroides* species that can activate zonulin. Additionally through a different pathway, gliadin can up-regulate activation of zonulin. When zonulin is activated, it causes the intestinal epithelium to disassemble tight junctions and leads to increased gut permeability, greater activity of antigen-presenting cells to T-cell, and overall enhanced immune response that can lead to autoimmune diseases including CD and T1D (Visser 2009).

Interestingly, in children born by elective caesarean section, risk of T1D (OR 1.23) and CD (AOR 1.15) is increased which indicates that early exposure/lack of exposure to maternal bacteria influences infant gut microflora which has a role in susceptibility to T1D and CD (Cardwell 2008, Marild 2011). Infection may also play a role in the gut immune system and subsequent development of T1D and CD, noting that those born by caesarean section are at increased risk for infection (Cardwell 2008, Tiittanen 2008). However, the role of infection in T1D and CD is conflicting as others have not found association with childhood viral diseases and early islet or CD autoimmunity (Hummel 2000, Welander 2010). A study of infection at time of gluten introduction showed that 41% of children with CD had an infection at time of gluten introduction however, after adjusting for age at gluten introduction and breastfeeding duration, there was no association of infection and future development of CD (Welander 2010).
The relationship of breastfeeding, dietary intake of gluten, gut microflora, and infection as it relates to the gut immune system and overall risk for T1D and CD autoimmune diseases is not fully understood. However, it is important to note that risk for T1D and CD is not solely determined by genetic susceptibility; there is a role, of yet to be determine significance, for adjusting environmental exposures as a way to reduce the risk of future T1D and CD.

Clinical significance

Screening and CD Diagnosis

Position statements by the American Diabetes Association (Silverstein 2005) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (Hill 2005) state that those with T1D should undergo screening for CD. The ADA recommends that initial screening should occur at diagnosis of T1D while the NASPGN recommends screening of asymptomatic children in high-risk groups (including T1D) begin around 3 years of age. Initial screening is based on serological evidence of CD, namely IgA antibody to tissue transglutaminase (tTG). Testing for IgA antibody to endomysium (EMA) is an alternative option reported to be more specific compared to tTG but less sensitive for detection of CD and subject to interpretation error (Hill 2005, Silverstein 2005). If screening results indicate elevated levels of autoantibodies, a small bowel biopsy (SBB) is required to confirm diagnosis of CD. It is recommended that multiple biopsy specimens be obtained in various locations within the small bowel. Even with SBB, diagnosis of CD can be missed due to patchy villous atrophy in the duodenum (Bonamico 2004, Rewers 2005) and variable pathologist interobserver reproducibility (Corazza 2007). Reversal of positive serological tests after GFD is also supportive of a positive CD diagnosis (Hill 2005) and therefore, it is important that initial testing occur prior to initiating a GFD (Ventura 2000).

However, the benefits of a GFD in asymptomatic patients, the consequences of elevated autoantibodies in the setting of a negative SBB, and the level of gluten that those with CD can tolerate are unclear and under debate (Sud 2010). Parakkal et al surveyed 169 practicing gastroenterologists and 22 experts and found that there was significant disagreement between these two groups’ responses regarding CD screening, diagnosis, and management (2011). The majority of doctors will not recommend a GFD to those who do not have CD confirmed by SSB (Sud 2010) however there is evidence that the elevated autoantibodies are secondary to an aberrant immune response which can lead to low grade inflammation. Overtime, in untreated individuals with positive CD serology, this can progress to bowel inflammation and villous atrophy as well as increased prevalence of autoantibodies to other organs like the thyroid and pancreas (Cerutti 2004, Glastras 2005, Ventura 2000). This link to increased
occurrence of various autoantibodies as well as shared genetic susceptibility has led some researchers to question whether CD-associated or T1D-associated autoantibodies occur first among those with both T1D and CD and whether disease progression is independent or correlated with presence of one or more autoantibodies (Ludvigsson 2006, Visser 2009, Galicka-Latała 2009); especially since several studies have shown that those diagnosed with CD had significantly earlier onset of T1D (Hansen 2006, Frohlich-Reiterer 2011).

**Clinical Course of CD in those with T1D**

Classical manifestations of CD are predominantly GI related and include diarrhea, abdominal distension, failure to thrive, and malnutrition related to malabsorption. Other manifestations include dermatitis herpetiformis, short stature, osteopenia, chronic fatigue, and anemia. Many children with T1D have asymptomatic CD (positive CD serology and villous atrophy but no typical symptoms) or latent CD (normal intestinal mucosa but positive CD serology) (Mereiles 2011, Peretti 2004, Sud 2010), noting the importance of screening recommendations in this population. A study of children with newly diagnosed asymptomatic CD found that the level of inflammatory severity based on bowel biopsy did not predict clinical symptoms upon presentation (Goh 2010). With few noticeable symptoms of CD among those with T1D, decisions regarding the plan of care, namely initiation of a GFD, can be complicated. CD has both short-term and long-term consequences, particularly if the pro-inflammatory immune-response continues unidentified and uncontrolled; multiple health complications overlap and in some cases these are compounded further among those with both T1D and CD.

**Short-term Complications of CD in those with T1D**

During childhood and adolescence, evidence implicates CD in poor glycemic control, impaired growth, and inadequate bone mass density; however, the evidence is inconsistent.

The DCCT confirmed that hypoglycemia is a barrier to achieving good metabolic control in those with T1D (DCCT 1993) and multiple studies show that hypoglycemia occurs more often in those with CD (Mohn 2001, Abid 2011). Ludvigsson et al observed that individuals with CD and T1D had elevated risk of ketoacidosis or diabetic coma before 20 years of age (2006). It appears that HbA1C varies study to study (Amin 2002, Abid 2011, Goh 2010), but there is some evidence of improved glycemic control as evidence by fewer episodes hypoglycemia (Abid 2011, Mohn 2001). Specifically, Mohn et al and Abid et al observed that insulin dosing after the introduction of a GFD resulted in an increasing trend (2001, 2011). The insulin dosing measure provides evidence of changes in blood glucose and the need to adjust
insulin accordingly, possibly related to improved absorption and/or fewer episodes of diarrhea. It is important to note that no studies measured the effect of a GFD on total dietary carbohydrate intake or the possible influence of the GFD intervention on overall diet quality and diabetes management compared to those who do not receive a dietary intervention.

Several studies have found significantly lower height z-score (Hansen 2006, Frohlich-Reiterer 2011), weight z-score (Hansen 2006, Amin 2002, Frohlich-Reiterer 2011), and BMI z-score (Amin 2002) among those with T1D and CD compared to children with T1D alone. Simmons et al also found that children with T1D and elevated tTG autoantibodies had lower weight, BMI, and midarm circumference z-scores (2007). This study provides evidence for potential negative health consequences that are directly related to tTG levels, not biopsy confirmed CD, which is supportive of a GFD even in those without GI symptoms or villous atrophy to ensure growth potential can be reached. Conversely, several studies have shown no differences in height, weight or BMI z-scores comparing those with CD and T1D and those with T1D alone (Diniz-Santos 2007, Mohn 2001, Goh 2010).

IGF (insulin-like growth factor) decreases with increased concentration of inflammatory makers leading to endocrine dysfunction and impaired growth (Troncone 2010, Van Sickle 2009, Simmons 2007). Specifically related to CD, Troncone et al discusses the role of increased inflammation in those with uncontrolled CD and its relation to growth retardation (2010). Those with poorly controlled T1D also have dysfunction of the GH/IGF-1 axis related to the interaction of inflammatory markers (Van Sickle 2009, Simmons 2007). Simmons et al investigated this interaction of CD and T1D and found that IGF-1 was lowest among those with both CD and T1D compared to those with T1D alone and controls (2007). Evidence suggests that when the dysfunctional GH/IGF-1 axis is corrected, catch up growth can take place (Troncone 2010).

In addition to growth, there are also concerns regarding optimization of bone mass density (BMD) in youth and early adulthood and possible implications on bone health later in life. Several studies have investigated various bone measures to determine the combined role of seropositive CD (tTG antibodies) and T1D. In a small case-control study, those with T1D and presence of seropositive CD (N=8) was associated with reduced BMD (g/cm3 and z-scores) and bone mineral content (Diniz-Santos 2007). In a larger study, although HbA1c and episodes of severe hypoglycemia were similar, those with T1D and positive tTG (N=79) had signs of higher bone turnover (urine cross-linked N-telopeptides of type I collagen (NTX)) and specifically those with consistently positive tTG throughout the two year follow-up, had lower BMD z-scores (Simmons 2007). Related to children with untreated and treated CD, those with untreated CD had significantly higher parathyroid hormone (PTH) and lower BMD, bone mineral
content, and serum calcium than those children treated with a GFD for 1 year. Additionally, in those children treated with a GFD for 1 year, BMD and bone mineral content was similar to healthy control subjects (Kavak 2003).

Cardiovascular health is also a concern and although primarily focused on in adulthood, cardiovascular disease (CVD) begins early in life. Risk factors for CVD include family history, HbA1c above target level, high LDL, low HDL, high BP, BMI >95th percentile, persistent microalbuminuria, and smoking. Based on these CVD risk factors, Norwegian youth with T1D had high prevalence of cardiovascular risk factors with 86% having at least one, 45% having at least two, and 15% having at least three (Margeirsdottir 2008). The SEARCH for Diabetes in Youth study observed at least two of the following risk factors in 14% of those with T1D - high blood pressure, high triglyceride levels, low HDL cholesterol, and high waist circumference (Rodriguez 2006). Although not as dramatically elevated as the study with Norwegian youth, each study used a different set of defined CVD risk factors. Urbina et al observed that youth with T1D have increased arterial stiffness, with peripheral stiffness more common than central stiffness, compared to healthy controls (2010). Given the risks for further adverse health outcomes related to heart disease in the future, management of these risk factors early on would be beneficial.

The inflammatory state of CD and T1D, which is heightened when not appropriately managed, is central to understanding the growth, skeletal, and other complications in youth with both CD and T1D.

**Long-term Complications of CD in those with T1D**

Susceptibility to additional health risks in adulthood stresses the importance of early identification and management of these autoimmune diseases with concurrent and consistent adherence to disease management strategies. Do note that few studies investigate the combined health risks of T1D and CD, however based on separate studies of CD and T1D, there are many overlapping health risks, including increased risk for various disease-related complications, osteoporosis, malignancy, lymphomas, and heart disease related death. Leeds et al provides evidence that in adults with T1D and previously undetected CD there is higher prevalence of retinopathy, nephropathy, and peripheral neuropathy and observed that those with both T1D and CD had worse glycemic control when compared to adults with T1D alone (2011).

Regarding bone health, multiple studies share the observation that osteoporosis risk increased with T1D and CD. In those with T1D, a meta-analysis of 5 studies showed that hip fracture risk was almost seven times greater in those with T1D compared to subjects without diabetes (Vestergaard 2007). BMD
Z-score was decreased in those with T1D which may be explained by BMI, a major determinant for BMD in both the spine and hip. Although HbA1C was not linked to BMD, those with complications of diabetes had lower BMD and greater risk of fracture (Vestergaard 2007). Additional evidence from the Women’s Health study showed that compared to women without T1D, women with T1D were over 12 times more likely to report an incident hip fracture (Nicodemus 2001). Kemppainen et al observed that adults with CD had higher prevalence of osteoporosis compared to matched-controls, and that low BMD was associated with age (men), low serum vitamin D, low body weight, and post-menopausal status (women), and CD particularly in those with poorly controlled CD (1999). Fracture risk and lower BMD has roots in adolescence and early adulthood when bone mineralization accrues and reaches its peak; long-term bone health appears to be linked to maintaining metabolic control as well as control of CD from diagnosis in youth through adulthood.

Both T1D and CD are associated separately with increased risk of malignancies. Zendehdel et al observed a 20% increase in overall cancer incidence (SIR = 1.2) in a cohort of 29187 patients hospitalized for T1D from 1965 to 1999 compared to the reference population of all Swedish citizens; observing elevated risk for stomach, cervix, and endometrium cancers (2003). In those with CD, Askling et al observed a 30% increase in overall cancer incidence (SIR = 1.3) in adults with CD; noting increased risks for malignant lymphomas, small-intestinal, oropharyngeal, esophageal, large intestinal, hepatobiliary, and pancreatic carcinomas (2002). Additionally, a meta-analysis found an overall fourfold increased risk of Non-Hodgkin lymphoma (Kane 2011). Taking into account these estimated cancer risks, the associated risk for cancer in those with both CD and T1D is likely elevated as well but it is unclear if having CD and T1D may compound the overall cancer risk; further investigation is needed.

As discussed earlier, youth with T1D have increased CVD risk factors which support the evidence of increased rates of CVD in those with both CD and T1D in adulthood. Pitocco et al demonstrated that those with both T1D and CD have greater carotid intima-media thickness (c-IMT) and more severe subclinical atherosclerosis compared to those with only T1D or CD (2011). Additionally, those with T1D and CD in combination or alone have significantly elevated C-reactive protein levels, a sign of inflammation, compared to healthy controls (Pitocco 2011). Ludvigsson et al observed an increased risk of ischemic heart disease (myocardial infarction or angina pectoris) of 19% in those with CD, 28% in those with small intestinal inflammation but no villous atrophy (Marsh stage 1 to 2) and 14% increase in individuals with positive CD serology but normal mucosa (latent CD, Marsh stage 0) (2011). Based on a Swedish cohort study, patients hospitalized for CD from 1964 to 1993, all-cause mortality risk was 2-fold higher in those with CD compared to the general population; noting that a majority of the deaths were
related to immune dysfunction (Peters 2003). It appears that those with both T1D and CD have greater morbidity than those with only T1D or CD; however evidence is very limited on the combined risk of long-term complications associated with both T1D and CD.

**Concurrent Management of T1D and CD**

With the information regarding short- and long-term health complications associated with T1D and CD, there is evidence supporting early and continued screening for incidence cases of CD in youth with T1D. Health care providers, parents and patients should be aware of the above mentioned potential health risks/comorbidities and should assess for signs and symptoms during regular check-ups (Atkinson 2001).

**Medical Nutrition Therapy**

Concurrent management of CD and T1D and vigilant monitoring of adherence to a GFD and diabetes medical nutrition therapy can be an effective means of reducing risk of complications associated with these two autoimmune disorders. In general, those with both T1D and CD have earlier age of T1D onset compared to those with T1D alone (Hansen 2006, Frohlich-Reiterer 2011). Therefore this population begins dietary and behavioral interventions at a younger age which must be maintained throughout life to manage T1D, CD, and related complications.

ADA guidelines for management of T1D focus on achieving and maintaining blood glucose levels within normal range as well as promoting an overall healthy dietary pattern to reduce risk for complications like vascular disease. Monitoring carbohydrate intake and providing appropriate insulin coverage is the cornerstone of T1D management (ADA 2008). As for CD, a GFD is the only proven treatment available for those with CD requires all sources of gluten, namely wheat, rye, barley, and oats be avoided, even in trace amounts. However, controversy surrounds the benefits of initiating a GFD in those patients without biopsy confirmed CD and the level of adherence to a GFD required for improvements in symptoms and/or long-term benefits as the child ages.

In the short-term, adherence to a GFD resolves GI symptoms (Narula 2009) and can reverse autoantibody test results from positive to negative (Atkinson 2001, Hansen 2006). A GFD may also improve weight, height, and BMI z-scores (Hansen 2006, Amin 2002) with evidence suggesting that a GFD can correct the dysfunctional GH/IGF-1 axis allowing catch up growth to take place (Troncone 2010). Evidence is conflicting; showing no difference in weight, height and/or BMI z-scores at baseline or no improvements over time with a GFD (Abid 2011, Mohn 2001, Simmons 2011). In particular, a GFD
in those with asymptomatic CD, showed no improvements in BMI z-score, weight z-score or metabolic control (HbA1C) after 1 year (Goh 2010).

Dietary compliance also has shown short-term evidence of improved bone health; after 1 year on a GFD, BMD and bone mineral content in those with CD became comparable to healthy control subjects (Kavak 2003, Mora 2001). In a study of bone quality using phalangeal ultrasounds, those patients with both T1D and CD who reported habitual transgressions from a GFD and had positive CD serology had higher prevalence of osteopenia defined as Ad-SoS (amplitude depended speed of sound) z-score less than two standard deviations compared to those who occasionally transgressed from a GFD but had negative CD serology (Valerio 2008).

Although there is evidence of T1D and CD related complications that occur in adulthood, there is very little evidence of the level of adherence required over the course of life to prevent such complications. There is great variability in dietary adherence in those with T1D and CD and quality of life, economic feasibility, and availability of gluten-free food are often cited as a primary challenges (Sud 2010, Patton 2011). Sud et al observed that those with asymptomatic CD had worse adherence than symptomatic children; parents of children with both CD and T1D reported greater concern about their child's social functioning; children greater than 13 years of age reported significantly more worry in regard to their diabetes than younger children; and those with greater dietary adherence tended to have higher emotional and psychosocial functioning scores (2011).

Implementing this combination of dietary information appropriately entails extensive dietary knowledge and support to ensure dietary needs are met even with dietary restriction of gluten and perceived restrictions when monitoring carbohydrate intake (Patton 2011). In youth with T1D, continued emphasis on carbohydrates and glycemic effects of food may be detrimental to perceptions of healthful eating; for example limiting fruit intake due to risk of postprandial hyperglycemia (Mehta 2009). The vast majority of youth with T1D do not meet dietary recommendations for fat intake <30% of energy, saturated fat <10% of energy, fiber intake of at least 25 grams daily, nor servings of fruit, vegetable, and grain intake (Mayer-Davis 2006, Overby 2007, Margeirsdottir 2008, Rovner 2009, Patton 2011). It is evident that management of T1D is difficult for parents and youth, but with the addition of a GFD for management of CD, further confusion regarding dietary options is likely and may lead to inadequate nutrient intake and worse glycemic control as many gluten-free foods are high in carbohydrates and may be unfamiliar (Silverstein 2005).

It is recommended that all those with T1D and CD meet with a registered dietitian who has experience in dietary management of both T1D and CD (Silverstein 2005). The registered dietitian can
tailor the nutrition counseling sessions to meet educational and behavioral goals of the patient, family, and interdisciplinary medical team. Understanding barriers to adherence and preferences of parents and patients is vital in determining how best to personalize a dietary plan that is gluten-free, that has appropriate quantity and types of carbohydrates, and that meets both macronutrient and micronutrient recommendations for age. Continued support of an interdisciplinary medical team can reinforce the importance of medical and dietary adherence as the child grows and takes on more responsibility for dietary intake and diabetes management. Behavioral interventions that target improving self-efficacy are very important as these behaviors learned at a young age will be utilized through adulthood.

**Filling in the Knowledge Gaps**

Knowledge deficits about the causes, diagnosis, management, and health consequences of T1D and CD co-occurrence are abundant, however increases in incidence has sparked many researchers to further investigate the complexities of these two autoimmune disorders. For example, the PreventCD Study will investigate primary prevention strategies by analyzing the role of HLA and non-HLA risk alleles, early immunological response to gluten introduction, and the role of infant nutrition with respect to gluten introduction and breastfeeding as well as incorporating a dissemination component to increase awareness of CD and current trends in research (Hogen Esch 2010). Other study groups are looking into the prevention of T1D, including the T1D Prediction and Prevention Project (DIPP), the BABYDIA study, and the TEDDY study (Virtanan 2006, Knip 2010, Ziegler 2011).

Innovations include diagnostic tools like a video capsule endoscopy to better detect villous atrophy (Zawahir 2009) and the role of dentists in monitoring for signs of dental enamel defects often present in youth with celiac disease in youth (Condo 2011). Additionally, novel biomarkers to determine dietary adherence include a breath test to measure adherence to GFD (Tveito 2011) or blood levels of citrulline (Ioannou 2011). Citrulline is an amino acid rarely found in food and not included in body proteins. Circulation is dependent on de novo synthesis by enterocytes in the proximal small bowel mucosa and decreases as enterocyte function decreases (i.e. villous atrophy as a result of gluten-containing diet) (Ioannou 2011). Furthermore, there are additional studies investigating everything from genetically modifying grains to remove gluten producing abilities to creating drugs and enzymes that would allow for dietary intake of gluten-containing foods (Sollid 2009).

Criteria for management of CD and T1D is unclear given the lack of understanding of the natural history of untreated CD, especially differences in those with asymptomatic versus symptomatic CD. Also, when should dietary interventions begin for those with CD and T1D and what level of adherence is
required to minimize complications? Is there a maximum level of gluten in the diet that is safe? Given the inconclusive data relating T1D and CD to deficits in stature in those with CD and T1D; consider that poor glycemic control is associated with reduced IGF-1 and IL8 so controlling blood glucose may be enough to promote attainment of an individual’s maximum stature and appropriate overall growth (Van Sickle 2009). There is also limited evidence that asymptomatic CD and elevated tTG can have negative clinical outcomes regardless of CD diagnosis by biopsy which has implications for possible treatment of asymptomatic youth with a GFD (Diniz-Santos 2007, Simmons 2007, Cellier 2000). As cancer, CVD, and osteoporosis are risks of T1D and CD, should prevention strategies be implemented in youth, besides controlling blood glucose levels and avoiding gluten, to prevent associated complications in adulthood.

**Conclusion**

The plethora of unanswered questions regarding T1D and CD co-occurrence is evidence of the complexities that are associated with genetic and environmentally influenced autoimmune disorders. T1D and CD, common in youth, are diseases that must be managed utilizing medical, behavioral, and dietary interventions for a lifetime. Appropriate dietary management is required to decrease the potential risk of both short-term and long-term deleterious health consequences however adherence is difficult. The potential for long-term benefits does not always trump the environmental and social pressures faced by parents and youth that make straying from a GFD and individualized diabetes management plan easier than it is to comply. The interdisciplinary team has an important role in providing ongoing support, reinforcement of positive health behaviors, and skills development to overcome new barriers to adherence as parents and youth work daily to manage T1D and CD.


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