Screening for Celiac Disease in Children With Type 1 Diabetes

Two views of the controversy

Celiac sprue is a chronic intestinal disorder caused by hypersensitivity to prolamins, the glutamine- and proline-rich gluten proteins contained in wheat, rye, and barley. Genetically predisposed subjects who ingest cereal proteins develop an inflammatory enteropathy characterized by proliferation of intraepithelial lymphocytes, crypt hyperplasia, and partial or complete atrophy of small intestinal villi. The inflammatory response is induced by cross-linking and transamidation of gluten peptides by tissue transglutaminase, an enzyme localized to the connective tissue (lamina propria or endomysium) underlying the epithelial cells of the small intestine. Post-translational modification of gluten enhances its uptake by dendritic cells and its binding to HLA-DQ2 and DQ-8, which induce T-cell activation and cytokine release (1,2). The resulting inflammation is accompanied by development of circulating antibodies to transglutaminase and to the endomysium.

Inflammatory denudation of the villous surface gives rise to malabsorption of foodstuffs, folate, fat-soluble vitamins, and iron. Young children with classical symptomatic celiac disease may present with diarrhea and growth failure, muscle wasting, hypotonia, pallor, edema, anemia, and in some cases, rickets. Older children and adults with classical celiac disease may have episodic diarrhea, steatorrhea, weight loss, and osteoporosis, and the risk of gastrointestinal malignancy is increased (3–7). However, many children and adults with celiac disease have nonclassical forms of the illness. So-called silent celiac disease refers to partial or complete villous atrophy in a seropositive patient who has no gastrointestinal or extra-intestinal complications. Subclinical celiac disease refers to villous atrophy in a seropositive patient who has extra-intestinal complications but few or no gastrointestinal complaints. Extra-intestinal maladies associated with celiac disease may include anovulation, infertility and miscarriage, neurologic disorders and epilepsy, and hepatocellular dysfunction.

Studies in Western Europe, North America, and Australia indicate that the prevalence of celiac disease among children and adults with type 1 diabetes (mean 4.1%, range 0–10.4) greatly exceeds the prevalence of the condition in the general population (0.3–0.5%) (7,8 and citations within). This fact has led a number of investigators to propose that all children with type 1 diabetes be screened for celiac disease and that those found to have the condition be treated. However, the potential benefits and risks of screening diabetic children for celiac disease have not been assessed in a systematic, critical manner. The purpose of this review is to assess critically the issue of celiac screening in type 1 diabetes and to present opposing views regarding identification and treatment of the condition.

THE CASE FOR SCREENING—MICHAEL FREEMARK

Most diabetic children with celiac disease have silent or subclinical forms of the illness (3–8), and only a small minority (48 of 400 in a recent meta-review) are identified by clinical symptomatology (7). Most patients have no gastrointestinal complaints or history of food intolerance or food avoidance; some have mild abdominal discomfort, but this is often ascribed to glycemic instability, diabetic gastropathy, or gastroesophageal reflux. Thus, the diagnosis may not be evident to the patient or the treating physician. Screening for celiac disease would be justified if: *1*) asymptomatic patients develop serious gastrointestinal or extra-intestinal complications; *2*) early in their course, these complications cannot be identified readily by history or physical examination; and *3*) treatment reverses or prevents these complications. A review of available evidence suggests that these criteria are fulfilled in children with type 1 diabetes, providing the rationale for celiac screening.

Children with subclinical celiac disease may develop growth failure and osteopenia

Symptomatic celiac disease in children is often accompanied by growth failure and delayed puberty (3–7). Subclinical celiac disease, like symptomatic illness, may also cause growth failure and decreased weight gain (9,10), at least in some patients. A cross-sectional Australian study showed small reductions in height and weight *Z* score in 20 diabetic children with subclinical celiac disease compared with 40 diabetic control subjects matched for age, sex, and duration of diabetes (11), while an English study (12) reported decreased BMI *Z* scores but normal height in 11 diabetic children with celiac disease (10 subclinical and 1 classic) at the time of diagnosis (age 2.6–17.3 years). Nevertheless, studies by Cacciari et al. (13) and Bode et al. (14) found that patients with subclinical celiac disease reach normal adult height even if untreated during childhood or adolescence. However, these studies did not compare childhood or adult heights to parental or target heights. Thus, it remains unclear whether these children reached true height potential.

Physicians commonly fail to identify celiac disease as a cause of growth failure in diabetic children. More often, they ascribe reductions in weight gain and growth velocity to poor glycemic control. Coexisting thyroid or adrenal disease may confound the clinical assessment. Consequently, an investigation for celiac disease may be deferred until the child reaches adolescence; in such cases, there may be loss of ultimate height potential (15).

Reductions in weight gain and growth velocity in children are often associated with delayed bone maturation. In severe symptomatic celiac disease, chronic malabsorption of vitamin D and calcium may also lead to bone demineralization, osteo-

porosis, and rickets (3–7). The osteopenia may be exacerbated by reductions in plasma IGF-1 concentrations (10) and by sex steroid deficiencies in children with delayed puberty.

Studies in adults (7,16–19) show that subclinical celiac disease, like symptomatic celiac disease, may be accompanied by vitamin D deficiency, mild hypocalcemia, secondary hyperparathyroidism, and a 1.0- to 1.9-SD decline in lumbar spine (LS) bone mineral density (BMD). Whether this is true in children with subclinical disease is currently unclear. A cross-sectional Italian study (20) showed a 6% reduction in LS BMD in celiac children and adolescents (age 2.6–20.4 years, $n = 44$) compared with healthy control subjects ($n = 177$). However, the authors did not characterize the symptoms of their patients, and the celiac and control groups were not matched for age, sex, or pubertal status. A follow-up study (21) by the same investigative group found a 19% decrease in total body bone mineral content (assessed by dual-energy X-ray absorptiometry) in a heterogeneous group of celiac children and adolescents that included patients with symptomatic disease.

To determine whether bone mineralization is reduced in diabetic children with subclinical celiac disease, we measured LS BMD in 7 diabetic children with subclinical illness with BMD in 11 seronegative diabetic children matched for age, sex, duration of diabetes, and mean HbA_{1c} during the previous 12 months (22). BMD *Z* scores were reduced significantly in diabetic patients with untreated celiac disease (-1.5 ± 0.4 SD, $P < 0.01$) relative to seronegative diabetic control subjects (-0.5 ± 0.2). Our findings suggest that subclinical celiac disease may compound the effects of diabetes and impede bone mineralization.

The biochemical and radiologic findings in patients with subclinical disease are less severe than in those with classical symptomatic celiac disease. Accordingly, BMD is restored more quickly in patients with subclinical than with classical symptomatic disease: 1 year of gluten restriction normalized LS BMD in adults with subclinical disease but had little effect in patients with severe symptomatic disease (16). Likewise, BMD increased significantly after 1–4.3 years of gluten restriction in heterogeneous groups of children with symptomatic as well as subclinical celiac disease (20,23). Thus, osteopenia in patients with subclinical disease can be reversed if detected at an early stage. On the other hand, bone mineralization may be more difficult to restore in patients with severe osteopenia due to symptomatic disease.

The reduction in BMD in celiac patients may predispose to fractures (24). A cross-sectional, case control study (25) of 165 Argentinian adults with malabsorption detected fractures in 25% of patients with symptomatic celiac disease but only 8% of those with functional gastrointestinal disorders. Radial and vertebral fractures were most common; three-fourths of the fractures in celiac patients occurred before the age of 50.

Given that bone mass accrual during adolescence and adulthood is critical for long-term bone health, the failure to identify celiac disease and osteopenia in childhood may predispose to osteoporosis and fractures in later life. The deleterious effects of celiac disease may be compounded by poor or inadequate glycemic control. Early institution of a gluten-free diet (GFD) in a diabetic child with subclinical celiac disease should in theory minimize or reverse osteopenia in childhood and reduce the risk of long-term complications.

Menstrual/reproductive disorders and neurologic dysfunction in celiac disease

Delays in bone maturation and growth in symptomatic celiac disease are often accompanied by delays in pubertal development. Reproductive disorders also occur commonly in women with symptomatic illness; these include anovulation, infertility, and habitual miscarriage (3–7). The frequency of reproductive disorders in women with subclinical celiac disease is currently unknown. However, studies in Finland (26) and Sardinia (27) detected celiac disease in 4–8% of women with unexplained infertility. At least some of the women conceived within the first year after initiation of a GFD.

A variety of neurological complications may occur in patients in symptomatic celiac disease. Recorded primarily in adults but also in some teenagers, these have included epilepsy with cerebral (particularly occipital) calcifications, cerebral atrophy with dementia, cerebellar ataxia, and cerebral vasculitis (3–7,28–31). Subtle abnormalities in neurological function may occur more commonly: among a group of 75 children and adolescents with classic symptomatic celiac disease, 10 had nonspecific "neurologic findings" including a history of seizures, mild ataxia, or muscular hypotonia, and 20% had unilateral or bilateral T2 hyperintense white matter lesions on magnetic resonance imaging (32).

Whether such problems occur in patients with subclinical celiac disease is unknown. More importantly, the neurological disorders respond to gluten restriction in only a minority of patients (29–32). This finding suggests that the neurological disorders may be associated with, rather than caused by, the gluten intolerance. Interestingly, however, those symptomatic patients who responded to a GFD were younger and had a shorter duration of epilepsy (33). Currently, we do not know whether early detection and treatment of celiac disease might prevent neurological damage in a subset of patients.

Diabetic children with subclinical celiac disease are prone to hypoglycemia

Recurrent or severe hypoglycemia may compromise neurologic function in diabetic children. Erratic absorption of nutrients in symptomatic celiac disease may increase the risk of severe hypoglycemia in diabetic patients; the effects on glycemic control and HbA_{1c} are more variable (7,8,12 and citations within).

The effect of subclinical celiac disease on the frequency of hypoglycemic events was assessed in an Italian study of 18 affected children and 26 control subjects matched for age, sex, duration of diabetes, and height and weight SD score (34). During the period from 6 to 18 months before diagnosis of celiac disease, the number of episodes of hypoglycemia were similar among the celiac and control groups. However, there was a twofold increase in the number of hypoglycemic episodes in celiac patients between 6 months before diagnosis and 6 months after initiation of a GFD. Subsequently, the number of hypoglycemic episodes in the celiac group returned to levels comparable with those in the control group. Thus, untreated subclinical celiac disease in diabetic children may increase the risk of hypoglycemia, while early identification and treatment may reduce hypoglycemic risk.

Celiac disease and other autoimmune disorders

Type 1 diabetes and celiac disease may be associated with other autoimmune disorders including Hashimoto's or Graves' disease, Addison's disease, chronic active hepatitis, pernicious anemia, gonadal failure, collagen vascular diseases, myocarditis, and Sjogren's syndrome. A recent study (35) of 909 celiac patients 12–20 years of age showed that the prevalence of various conditions, including type 1 diabetes, dermatitis herpetiformis, epilepsy with cerebral calcifications, Hashimoto's disease, alopecia, Addison's disease, and gastritis, was considerably higher in those diagnosed with celiac disease after 10 years of age than in those diagnosed before age 10 years. The authors speculate (35,36) that continuing exposure to gluten may facilitate development or progression of autoimmune diseases other than celiac disease. However, anecdotal reports (37,38) notwithstanding, there is no conclusive evidence that gluten restriction alters the clinical course or outcome of other established autoimmune diseases (39–41).

The risk of gastrointestinal malignancy in patients with classical celiac disease raises concerns

Of greatest concern to physicians and patients is the possible risk of malignancy imposed by celiac disease. Adults with symptomatic celiac disease are at increased risk for gastrointestinal carcinoma in general and small bowel non-Hodgkin's lymphoma (NHL) in particular. Estimates of cancer risk in celiac disease were first reported by Geoffrey Holmes (42), who followed prospectively 226 adults with symptomatic celiac disease between the years 1972 and 1996. Among these patients, five developed small bowel lymphoma and an additional seven had cancers of the gastrointestinal tract. In a separate study (43) of 210 subjects, he calculated that celiac patients on a normal or reduced-gluten diet had a 36- to 40-fold increased risk for cancers of the mouth, pharynx, esophagus, and small bowel, while patients on a strict GFD had only a 6.5-fold increased risk.

Consistent with these results, a multicenter, case-control study (44) of 653 Italian adults with NHL found six with celiac disease. In this population, the risk of NHL in patients with celiac disease was increased 3.1-fold, and the risk of small bowel lymphoma was increased 16.9-fold. Two of the six patients with celiac disease appeared to have a subclinical form of the illness. In agreement with these findings, a study (45) of 119 patients with primary small bowel lymphoma found 13 (10.9%) with symptomatic celiac disease and an additional 4 with subclinical illness detected at the time of, or subsequent to, the diagnosis of lymphoma.

Finally, a retrospective study (46) of 12,000 Swedish subjects with a history of celiac disease diagnosed in adulthood revealed significantly increased risks for a number of malignancies, including oropharyngeal and esophageal carcinomas (relative risks increased 2.3-fold and 4.2-fold, respectively), small bowel carcinoma (10-fold), hepatocellular carcinoma (2.7-fold), and lymphoma (5.9-fold). Those hospitalized with celiac disease as children or adolescents had no apparent increase in cancer risk. The authors speculate that the failure to detect an increase in cancer rates among those hospitalized with celiac disease as children may reflect insufficient follow-up time. One other possibility, not addressed in this study, is that early institution of gluten restriction prevents subsequent development of one or more malignancies.

Thus, the risk of gastrointestinal malignancy is increased in patients with symptomatic celiac disease. Whether patients with silent or subclinical celiac disease are at increased risk for gastrointestinal malignancies is currently unclear. The actual risk of malignancy in silent or subclinical disease may depend in part on the rate of progression from subclinical to symptomatic illness. We do not yet know this rate, because many subclinical patients are never biopsied, some are self-treated, and there are no long-term studies of the natural history of subclinical illness.

CONCLUSIONS — *1*) Asymptomatic patients with subclinical celiac disease may develop short-term growth failure, delayed puberty, osteopenia, anemia, menstrual irregularity, and mild hepatocellular dysfunction. Some of these complications cannot be detected readily by history or physical examination. Others (growth failure, delayed puberty, and menstrual irregularity) may be ascribed to poor glycemic control rather than subclinical celiac disease.

2) Many of the complications of subclinical celiac disease can be reversed with gluten restriction. Thus, early detection and treatment of such complications may prevent irreversible consequences.

3) Classical symptomatic celiac disease predisposes to small bowel lymphoma and certain other malignancies. However, the risk of malignancy in silent or subclinical disease is unknown.

Recommendations

Rationale for screening. The high prevalence of celiac disease in children with type 1 diabetes and occurrence of preventable and treatable complications provide a strong rationale for screening. Treatment of celiac disease can reverse growth failure, osteopenia, anemia, and hepatic dysfunction; may limit or prevent the chronic gluten-induced inflammation that may predispose growth failure, osteopenia, anemia, and hepatic dysfunction; and may limit or prevent the chronic gluten-induced inflammation that may predispose to gastrointestinal malignancy. Screening will also identify patients needing careful monitoring because they have the potential for developing complications. Finally, screening may identify collateral illness in family members, who are at significantly increased risk for the disease (47,48).

When to screen. A study by Barera et al. (49) is instructive. In a prospective evaluation of 273 diabetic children, celiac disease was detected in 3.3% at diagnosis and in an additional 2.9% thereafter. But no patients were found to have celiac disease >4 years after diabetes onset. This finding suggests that screening for celiac disease would be most effective if applied to new-onset patients or to those who developed diabetes within the previous 4 years. Screening should be conducted at any time if a diabetic child or adolescent develops intestinal or extra-intestinal symptoms consistent with celiac disease.

Who should be treated. Gluten restriction should be considered only for those with histologic evidence of celiac disease. Seropositive, asymptomatic children with normal biopsies or with minimal or equivocal histologic changes (scattered intraepithelial lymphocytes without villous atrophy) may require repeat endos-

copy and biopsy, with treatment considered if villous atrophy is detected.

Dietary intervention is recommended strongly for children with classical symptomatic illness as well as subclinical patients with osteopenia, growth failure, hepatic dysfunction, menstrual irregularity, unexplained epilepsy, or ataxia. In the case of silent celiac disease with no apparent complications, the physician should openly discuss the uncertainties regarding the course and prognosis of the condition, and the family should make the final decision regarding treatment. If future studies of silent or subclinical disease reveal an increased risk of malignancy, then gluten restriction should be recommended for all patients with biopsy-proven celiac disease.

Costs and benefits. Given recent increases in the incidence of type 1 diabetes in children, the total costs of screening are high. Transglutaminase IgA antibody assays can be performed at a cost approximating $10 (U.S.) per sample; it may also be necessary to measure total serum IgA in seronegative patients who have symptoms or a clinical course suggesting the possibility of celiac disease (48). But these costs must be balanced against the potential costs of failing to screen; these include the evaluation and treatment of potential complications, any resulting pain and suffering, and even the failure to identify collateral illness in family members.

Current treatment of celiac disease requires life-long changes in diet. This is an onus to the child or adolescent already burdened with responsibilities for care of his or her diabetes. But the future holds great promise. Recent studies have identified a 33–amino acid gluten peptide that is transamidated by tissue transglutaminase, triggering the immunological response that leads to villous atrophy in patients predisposed to celiac disease (1,2). This peptide is resistant to stomach acid, pancreatic proteases, and small intestinal brush border membrane enzymes but is cleaved by a bacterial prolyl endopeptidase, which destroys its antigenicity and binding to HLA-DQ2. These findings raise the possibility that dietary supplementation with the bacterial protease might permit gluten ingestion in children and adults with celiac disease. Identification of celiac disease through screening of diabetic children may prevent irreversible complications before such proteases or other novel therapeutic agents become available.

THE CASE AGAINST SCREENING—LYNNE LEVITSKY

Clinical screening programs can be difficult to implement and problematic to maintain. Therefore, any mandate for additional screening in a disorder like diabetes must be backed by excellent data demonstrating the necessity for screening, the effectiveness of screening, and the outcome of such a program. Screening should not substitute for clinical judgment but should rather be an additional tool in good clinical care. When the data are reviewed, it becomes clear that these criteria have not yet been met for celiac disease screening in type 1 diabetes.

The rationale for the institution of a screening program should be that: *1*) the disorder is difficult to diagnose clinically; *2*) the outcome of failure to diagnose is profound; *3*) the risk-to-benefit ratio of screening is acceptable; and *4*) screening is economically feasible and/or results in cost saving.

Celiac disease is usually suspected clinically

Classical celiac disease is easy to diagnose. The symptoms of weight loss, malnutrition, and poor growth should be obvious to the careful physician. Mild celiac disease may present with hard-to-elicit symptoms and signs including iron- or folate- deficiency anemia, nonspecific abdominal pain, dental anomalies, fatigue, or depression. In one large study of 485 children with celiac disease, 35% were iron deficient, 30% had short stature, 13% had anorexia, 3.5% had constipation, 1.8% were thin, and 2.5% had dermatitis herpetiformis, and neuropsychiatric complaints were reported in 3.7% with seizures or cerebral calcifications in 2.7% (50). There was no control group, and no definitions were offered for "short stature" or "thinness." Nevertheless, if the clinician managing children with diabetes is astute, clinical criteria will reveal the diagnosis of celiac disease even in mildly symptomatic cases.

Diagnostic criteria for celiac disease may vary

It is now recognized that tissue transglutaminase is the offending endogenous antigen in celiac disease (1,2,52). Presently, many would suggest that the presence of endomyseal and tissue transglutaminase antibodies is enough to make the diagnosis and that small intestinal biopsy is simply confirmatory. Nonetheless, biopsy remains the gold standard of diagnosis (53–55).

Celiac disease may be entirely silent except for the presence of the diagnostic antibodies and an abnormal biopsy. In addition, some patients may present with "potential celiac disease," i.e., positive antibodies with a normal biopsy and no symptoms. In some centers the presence of a few inflammatory cells in an otherwise normal epithelium is sufficient to make the diagnosis in a seropositive patient. In these centers the prevalence of biopsy-positive celiac disease in individuals with humoral antibodies is higher than in others with more stringent criteria. The variations in diagnostic criteria may create confusion in establishing the frequency of the disease and in selecting patients for treatment.

The long-term outcome of subclinical celiac disease in diabetic children is unknown

Celiac disease is more common in children with type 1 diabetes than in the general population. A review of seven published studies from Europe and North America (49,56–61) demonstrates that 7.4% of children with this diagnosis have positive anti-endomyseal or tissue transglutaminase antibodies (Table 1). However, the presence of positive anti-endomyseal or tissue transglutaminase antibodies is not fully congruent with the presence of symptoms or of positive small intestinal villous biopsies. In these studies, only 32.5% of these children were symptomatic; of the children biopsied, 80% were positive, and of the 11 children placed on GFDs in this group, only 9 felt that the diet improved their well-being (Table 1).

It is therefore important to examine the potential for untoward outcome in the children with symptomatic disease and those with silent or occult disease. Symptomatic undiagnosed individuals can develop profound growth attenuation, failure of pubertal maturation, gastrointestinal illness (3,52), neurologic dysfunction (32), non-Hodgkin's lymphoma (44), osteopenia (23), infertility in females (62), and anemia (51). In addition, it has been suggested that unexpected hy-

Table 1—*Summary of published studies of children with type 1 diabetes screened for celiac disease with endomysial or tissue transglutaminase antibodies*

Source	Positive screen	Positive biopsy	Symptoms	Diet improved
Denmark (56)	10/104 (9.6%)	9/9	6/9	5/6 (4 refused)
British Columbia (57)	18/232 (7.7%)	14/18	10/18	NI
Wisconsin (58)	17/218 (7.8%)	10/14	3/10	2/3
Germany (59)	13/205 (6.3%)	7/8	3/8	NI
Italy (49)	27/273 (9.9%)	16/20	2/16	2/2
New York (60)	10/211 (4.7%)	3/3	NI	NI
North Carolina/ Maryland (61)	3/81 (3.7%)	1/3	0/3	NI
Total	98/1324 (7.4%)	60/75 (80%)	24/64 (37.5%)	9/11 (81.8%)

NI, no information given.

poglycemia is a common finding in patients with type 1 diabetes and untreated celiac disease (63). The data supporting screening and treatment to protect from these disorders should be considered.

This author does not consider growth attenuation, failure of pubertal maturation, gastrointestinal illness, or anemia to be valid arguments for screening because these problems should be identified in the course of good medical care and not require a screening program. Problems of infertility usually fall within the purview of physicians who care for adults, and laboratory testing for celiac disease in infertile women may well be recommended. Earlier diagnosis by the pediatrician is not required in this situation. Neurologic dysfunction is a rare concern in celiac disease. A report of increased white matter lesions in the brains of children with celiac disease is of interest, but because lesions did not seem to be related to dietary adherence, screening would not likely reduce risk of this rare finding (32).

Increased risk of hypoglycemia, non-Hodgkin's lymphoma, and osteopenia must be addressed because these are potentially serious complications that might be ameliorated by screening.

Hypoglycemia

Hypoglycemia has been anecdotally described as a warning sign for celiac disease in diabetes. Children with increased episodes of hypoglycemia are often screened for celiac disease in clinical practice. Several studies attempt to address the frequency of hypoglycemia. In one small case-control study of well-controlled children and adolescents with diabetes with (18 patients) and without celiac disease (26 patients), the individuals with celiac disease had significantly more hypoglycemic episodes in the 6 months before and after diagnosis than the control subjects (4.5 ± 4 vs. 2.0 ± 2.2 episodes/month) (34,63). There was no difference in HbA_{1c} between the groups, but the celiac disease group had a slightly decreased need for insulin. Four of the hypoglycemic episodes were severe, requiring assistance in the children with concomitant celiac disease compared with only two severe episodes in the control children. A similar study of adults with celiac disease did not show such differences, but the adults were much more poorly controlled as assessed by HbA_{1c} (64). It is likely that hypoglycemia is more common in well-controlled children with early celiac disease. However, if hypoglycemia is considered a warning of potential celiac disease, then it might be perfectly appropriate to screen at the presentation of increased hypoglycemia rather than to screen whole populations of children with diabetes.

Gastrointestinal malignancy

Non-Hodgkin lymphoma is a relatively rare disorder with an incidence of ~10–30/100,000 person-years (65–67). However, in adults with non-Hodgkin lymphoma, the risk of finding concomitant celiac disease is much greater than in the general population. The development of non-Hodgkin lymphoma in adults with untreated celiac disease is at least twice (CI 1.5–2.7) that in the general population (44). In one study, mortality risk was decreased after 5 years on a GFD (43). In patients with malabsorption, mortality risk was 2.5 times that of the general population (1.8–3.40). But in individuals with minor symptoms, or those diagnosed by antibody screening, the risk was 1.1 (0.5–2.2) and 1.2 (0.1–7.0), respectively (68). Therefore, the risk in children who are asymptomatic should not be increased even if they remain on a gluten-containing diet into adulthood. Symptomatic children who are not treated may be at increased risk in adulthood.

Bone development

There is a risk of osteopenia in children and adults with symptomatic celiac disease. Several studies demonstrate that bone mineral density and bone mineral content is diminished before treatment and improved after adherence to diet in symptomatic children (23,69). Fracture risk and risk of severe osteopenia are increased in noncompliant or newly diagnosed adults with longstanding celiac disease. Several small uncontrolled studies suggest that relatively asymptomatic adults with and without type 1 diabetes may have decreased bone mineral density (16,19,24,70,71). Children and adolescents with diabetes are already at risk for relatively low bone mineral. Because the pubertal years are the times of most active accrual of bone mass, a missed diagnosis of celiac disease during this time period could be quite catastrophic for adult bone mass. However, the risk in an asymptomatic individual is unknown.

Risk-to-benefit ratio of screening

Institution of a GFD is not a trivial undertaking. It adds another level of complexity to nutritional management of diabetes. It is expensive and burdensome to children and adolescents. Fast foods and restaurant foods are almost all impermissible. Asymptomatic children and adolescents are unlikely to adhere to such a regimen. In one study of 22 symptomatic children diagnosed in early childhood, 21 were still reasonably adherent to a GFD after 12–13 years and none were endomyseal antibody positive. Of 27 relatively asymptomatic children identified through a screening program and diagnosed in early adolescence, only 22 were willing to participate in follow-up. Three patients who did not agree to follow-up were said to be healthy on a normal diet and only 12 of the 22 were reasonably adherent to a GFD. Seven were endomyseal antibody positive at the end of 5 years (72).

It is unclear whether the institution of a GFD in asymptomatic children is beneficial. In one study of 11 of 166 children

with diabetes who screened positive for celiac disease, of whom 8 of 9 were biopsy positive and 3 of 8 were asymptomatic, there was no statistically significant change in growth or other parameters after treatment initially (73). However, on evaluation over the years, 11 children with celiac disease had lower HbA_{1c} and a diminished BMI compared with case control subjects. After treatment, HbA_{1c} continued to improve and there was a recovery of BMI (10). In another study of 20 children with diabetes and celiac disease, only 30% adhered to a GFD and there were no differences in energy or nutrient intake, growth parameters, or diabetes control among the groups (9).

A GFD may increase the psychological burden in children with diabetes. Children and adolescents with celiac disease who responded to a survey instrument documented that they had a perceived a lack of friends, uneasiness because they were different, and envy of the independence of their friends (74). These same findings have been demonstrated many times over in the psychological profiles of children with diabetes. It is therefore possible that the addition of another chronic illness requiring careful attention to diet and interfering with participation in many common adolescent activities would enhance the psychological distress already experienced by children with diabetes.

There is no evidence to support cost-saving from screening

Because the screened antibodies are IgA and individuals with celiac disease are at least five times more frequently IgA deficient than healthy control subjects, appropriate screening for celiac disease requires measurement of endomyseal or tissue transglutaminase antibodies and immunoglobulin A (3,48). If every asymptomatic child who is screened as positive has a duodenoscopy and duodenal biopsy and 80% are then placed on an unnecessarily restricted and expensive diet, there is no cost-saving.

Conclusions and proposal

Given the uncertainties regarding diagnosis and complications of subclinical celiac disease and the potential difficulties associated with treatment, I do not think that screening of all diabetic children is justified at this time. Nonetheless, failure to protect bone mineral in vulnerable children and adolescents could have devastating adult consequences. We do not yet have evidence-based guidance for this serious potential deleterious outcome of celiac disease in diabetes.

I therefore propose that rather than immediately instituting screening and treatment programs, a multicenter screening protocol should be developed to identify a group of potentially at risk asymptomatic children. Bone density and bone mineral content should be used as primary end points. Children with positive antibody screens can be compared with a matched group with negative screens and bone mineral density can be measured. After duodenoscopy and biopsy to confirm celiac disease, the antibody-positive children can be followed with and without a GFD for 1–2 years to determine effect of diet on bone mineral and other measures in these asymptomatic children. This would give us the evidence we need to decide whether strict adherence to a GFD in this population improves bone and general health and would be an important aid in decision making.

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