Review Article

Celiac disease, short stature and growth hormone deficiency

Margaret C. S. Boguszewski, Adriane Cardoso-Demartini, Milene C. Geiger Frey, Adriane Celli

Department of Pediatrics, Hospital de Clínicas, Federal University of Parana, Curitiba, Brazil

Correspondence to: Margaret C. S. Boguszewski. Department of Pediatrics, Federal University of Paraná, Rua General Carneiro, 181, 14° andar, Curitiba 80060-900, Brazil. Email: margabogus@uol.com.br.

Abstract: Celiac disease (CD) is the most common genetically-based diseased associated with food intolerance. In children, the classical form of CD, presenting with gastrointestinal symptoms, starts before 2 years of age, after the introduction of gluten in the diet. Oligosymptomatic CD and atypical presentations are common, including short stature as the only clinical manifestation. Impaired growth in children with CD results mainly from nutritional deficits, and withdrawal of gluten from the diet is associated with a marked improvement of linear growth. Rarely, when catch-up growth does not occur after the initiation of a gluten-free diet (GFD), growth hormone (GH) deficiency must be investigated. One of the possible causes for the GH deficiency is an autoimmune form of hypophysitis. In view of the inflammatory and nutritional aspects of CD, with elevated cytokines and low body weight, some aspects of the physiological system that regulate body weight, fat stores, energy intake and energy expenditure should be discussed. Leptin, the anorexigenic peptide hormone produced by the *ob* gene and secreted mainly by adipocytes, belongs to the long-chain helical cytokine family and is involved in immune regulation. Leptin secretion is reduced during periods of fasting and leptin levels are low in children with CD. Ghrelin, the orexigenic hormone isolated from stomach that stimulates GH secretion, induces a positive energy balance and can override the anorectic action of leptin. Ghrelin levels are increased in children with CD. In this review, we will focus some aspects of the complex network involving nutrition, GH secretion and the energy metabolism regulation in children with CD.

Keywords: Celiac disease (CD); short stature; growth hormone (GH) deficiency; leptin; ghrelin

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Introduction

Celiac disease (CD) is more than a gastrointestinal disease. After the original description in 1888 by Gee, and its association with gluten from the diet in the 1940s by Dicke [review in (1)], the clinical presentation of the most common genetically-based disease associated with food intolerance goes beyond intestinal manifestations. Up to 4% of children seeking medical care due to short stature might have CD, many without gastrointestinal symptoms (2). Improvement in growth velocity and normalization of height is observed with a strict adherence to a gluten-free diet (GFD). However, few children do not show catch-up growth after an extended period of diet. For these children, the possibility of growth hormone (GH) deficiency should be considered. In this review, we discuss the interactions between GH secretion and the gastrointestinal tract in children with CD.

Celiac disease

CD is defined as an immune-mediated enteropathy, with characteristic changes in the intestinal histology. It is characterized as a permanent sensitivity to gluten, and it occurs in genetically susceptible individuals (HLA class II haplotype DQ2 or DQ8). The classic form of CD in children consists of gastrointestinal symptoms starting between 6 and 24 months of age, after the introduction of gluten in the diet. Patients present with malabsorption syndrome that includes chronic diarrhea, poor weight gain or weight loss, vomiting, abdominal distension, abdominal pain, anorexia (3).

Table 1 Nongastrointestinal manifestations of celiac disease (CD) and asymptomatic children and adolescents with increased risk for the disease

Nongastrointestinal manifestations of CD
Short stature
Delayed puberty
Osteopenia and osteoporosis
Dental enamel defects
Arthritis
Unexplained iron deficiency anemia
Dermatitis herpetiformis
Epilepsy with occipital calcification
Elevated levels of transaminases
Patients with increased risk of CD
Type 1 diabetes melllitus
Down syndrome
Autoimmune thyroid disease
Turner syndrome
Williams syndrome
Selective immunoglobulin A deficiency
Autoimmune liver disease
First-degree relatives of patients with CD

The clinical manifestation of patients with CD has changed dramatically over the recent decades, with diarrheal or classic presentations becoming less common. The main presentation seen nowadays in children include recurrent abdominal pain and growth issues (4). Gastrointestinal symptoms in older children include recurrent diarrhea or more nonspecific symptoms like constipation, nausea and vomiting, abdominal pain, bloating, weight loss or even obesity (5,6). Many patients present initially with nongastrointestinal manifestations of CD (*Table 1*). These manifestations include osteopenia and osteoporosis, which increase the risk of bone fractures (triggered even by mild traumatic injuries). In these patients, fracture risk can be reversed by GFD (7,8). Unexplained iron deficiency anemia resistant to oral iron supplementation is the most common nongastrointestinal manifestation in adults, and has been reported in children. Dermatitis herpetiformis is a skin manifestation of CD. Dental enamel defects of permanent teeth, epilepsy with occipital calcification and arthritis were also described. Elevated levels of transaminases of unclear etiology can be seen (5).

Delayed puberty or short stature can be the initial presenting manifestation. The risk of CD in patients with isolated stunted growth or short stature has been calculated as 10-40% (9,10). Impaired growth in children with CD results mainly from nutritional deficits, and withdrawal of gluten from the diet is frequently associated with a marked improvement of linear growth within two years (11). In our unit hospital, from a group of 40 children with the diagnosis of CD, 20% presented with classical CD, 60% had oligosymptomatic CD, 17.5% had atypical CD (15% with short stature), and 2.5% had asymptomatic CD. Some centers still describe a high prevalence of classical CD. This probably relates to referral bias. Our hospital is a referral center for growth disorders, one of the main complaints in children with CD. Most of these children undergo screening evaluation through serological markers. Asymptomatic children and adolescents with increased risk of CD are first-degree relatives with CD, children with type 1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective immunoglobulin A deficiency, and autoimmune liver disease (12).

CD is characterized by the presence of autoantibodies generated in response to gluten exposition in genetically susceptible individuals. Present guidelines are in agreement regarding which test is the best for initial serological screening. Measurement of antibodies against tissue transglutaminase (tTG) is the most reliable and cost-effective test for CD. Measurement of antibodies against endomysium (EMA) is as accurate as tTG, but it is an immunofluorescence test, and is therefore observer-dependent and more subject to interpretation error and added cost (3). A third antibody, produced against the deamidated gliadin peptides may be used as additional test in patients who are negative for other CD-specific antibodies, but in whom clinical symptoms raise a strong suspicion of CD, especially if they are younger than 2 years of age (12).

Serological screening is initially recommended for patients with suspected CD. Those with positive tests should undergo small intestinal biopsy to confirm the diagnosis according to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) (3). Recent guidelines published by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) suggest that biopsies may not be necessary for patients with typical symptoms of CD and antibodies tTG above ten times the upper limit of normal, together with positive antibodies to

Table 2 Possible causes of short stature in children with celiac disease
Malnutrition
Iron deficiency anaemia
Poor adherence to gluten free diet
Growth hormone deficiency (autoimmune hypophysitis? GH insensitivity? low leptin levels?)

GH, Growth hormone.

EMA and an allele for the HLA-DQ2 or DQ8 haplotype. For asymptomatic children at increased risk of CD, the diagnosis is based on positive serology and positive histology findings on biopsies. Both serology and biopsy should be performed while on a gluten-containing diet (12).

The only treatment currently available for CD is strict adherence to a GFD for life, which results in a complete return to health (3,12).

Failure to thrive in children with CD

Failure to thrive and short stature are common findings in children with CD and gastrointestinal symptoms (13,14). Early in the 1970s, the finding of short stature as the only manifestation of CD became more frequently recognized (15,16). Philip *et al*. found short estature in 25%, delayed puberty in 11% and both in 20% of 36 patients as the initial complaint. After complete evaluation, 58% had short stature and 31% had delayed puberty (17). Adherence to a GFD generally leads to catch-up growth (14,18,19). Usually, weight fully catches-up 6 months after the start of a GFD, and height catches-up 2 years later (20,21). However, some children with growth failure do not improve growth after starting a GFD, despite reversion to seronegativity for antibodies. It has been reported that a GFD will be successful if at diagnosis there is a delay of bone age, and in the first year of diet there is an evident catch-up growth (22). When catch-up growth does not occur, it may be due to an associated GH deficiency (23).

In the group studied by Bosio *et al*. (24), patients showed an increased height velocity during the first 3 years while on a GFD, with maximum growth velocity occurring during the first year, but the catch-up growth was incomplete over 3 years. The 12 patients who completed pubertal development reached their target height, independent of the duration of the GFD. The final height seemed influenced mainly by familial characteristics; height was below the third percentile in 31% of parents examined.

Recently, Bozzola *et al*. (25) described the case of a girl presenting with stunted growth and malnourishment, without any signs of gastrointestinal, renal or endocrine disorders. She was evaluated for CD, but resulted negative for anti-tTG antibodies. At the age of 4.1 years, she exhibited iron deficiency anaemia despite repeated iron supplementation, with persistent reduced height, body mass index (BMI), growth velocity and delayed bone age. The CD screening was repeated; very high anti-tTG-IgA and -IgG values were found, and a duodenal biopsy was positive. After only four months of GFD, her growth velocity increased from 4.83 cm/year (–1.79 SDS) to 6.53 cm/year (–0.15 SDS).

The pathogenesis of CD-associated short stature is still unclear. The damages to the small intestinal mucosa, with consequent nutritional deficits, are responsible for impaired growth. These children usually present with reduction of insulin-like growth factor 1 (IGF1), IGF2 and insulin-like growth factor binding protein 3 (IGFBP-3), increase of IGFBP-2 and IGFBP-1 levels, and a blunted GH response to pharmacological stimuli. A significant inverse association was found between the duration of gluten exposure and IGF1 levels, and a significant reduction in IGF1 levels was observed after prolonged gluten exposure, before growth failure (21). These findings correspond with those observed in chronically malnourished children (21,26). Reevaluation of IGF1 levels while on a GFD showed rapid reversal, with an increase in GH binding protein (GHBP), IGF1, IGF2 and IGFBP-3 levels, and a decrease in IGFBP-1. These changes suggest an improvement in the sensitivity to GH, reflecting the recovery towards a normally functioning somatotrophic axis (21,27).

A summary with possible causes of short stature in CD patients are presented in *Table 2*.

GH deficiency in children with CD

Rarely, it has been shown that poor catch-up growth response to GFD is due to a coexistence of GH deficiency (11,22,23,28). Out of 7066 children with short stature, Giovenale *et al*. (2) found 16 (0.23%) subjects with both GH deficiency and CD, and two of them with probable congenital GH deficiency (23). CD is an autoimmune disease often associated with other endocrine and non-endocrine autoimmune diseases (12). In fact, CD is actually seen as an immune-mediated systemic disorder. Iughetti *et al*. (28) have demonstrated the presence of high titers

of antipituitary antibodies in CD children without catch-up growth after GFD, suggesting an autoimmune form of hypophysitis in these patients. The Italian Autoimmune Hypophysitis Network Study also reported high titers of antipituitary antibodies associated with height impairment in newly diagnosis celiac patients (29). However, Ferrante *et al.* (30) could not confirm the presence of antipituitary antibodies in adult patients with CD and pituitary dysfunction. More recently, Aguado *et al.* (31) showed that antipituitary autoantibodies can also be detected in patients with gastroenteropathies other than CD, but without a direct relationship with growth development nor with IGF1 levels, suggesting that another feature could be responsible for different clinical manifestations between CD and nongluten-related enteropathies.

The pathophysiological mechanisms leading to the absence of catch-up growth after GFD in some children with CD are not totally understood yet. Presumably, these mechanisms can be explained by blunted GH and IGF1 secretion, and these children might benefit from GH treatment (32). GH-treated patients with CD and GH deficiency can reach final adult height close to their genetic potential (33).

Interactions between the endocrine system and the gastrointestinal tract

CD is an immune-mediated disease that occurs in individuals intolerant to gluten. It is generally accepted that it is a T-cell-mediated disease, in which gliadin-derived peptides are deaminated by tTG and presented by antigen presenting cells to lamina propria T helper (Th) lymphocytes. Pro-inflammatory cytokines are released with activation of intraepithelial lymphocytes and consequent histologic alterations. Cytokines are elevated and correlated with disease activity, characterizing the inflammatory aspect of this disease (34). In view of the inflammatory and nutritional aspects of CD, some aspects of the physiological system that regulates body weight, fat stores, energy intake and energy expenditure should be taken in consideration. This regulatory system is formed by multiple interactions between the gastrointestinal tract, adipose tissue, the endocrine and the central nervous systems.

Leptin in CD

Leptin is a peptide hormone produced by the *ob* gene and secreted mainly by adipocytes. A number of other cell types also produce leptin, including gastric and colonic epithelial cells, and T-cells, especially during acute inflammation. The production of leptin is higher in subcutaneous fat than in visceral fat, and in the blood, leptin levels correlate directly with the amount of body fat. The secretion of leptin is reduced during periods of fasting and increased after meals. Leptin stimulates anorexigenic neurons and inhibits orexigenic neurons that express neuropeptide Y and Agouti-related peptide. Leptin is the main catabolic adiposity signal, which actions result in reduced food intake, increased energy expenditure and weight loss (35,36). Leptin receptor belongs to the type I cytokine receptor family and intestinal mucosa contains leptin receptors. It was postulated that direct leptin signaling in the intestine might be involved in the regulation of nutrient absorption and intestinal motility. Furthermore, leptin is involved in immune regulation (37).

Children with CD usually present with weight loss and malnutrition, which can be severe or mild. Maggio *et al.* (38) reported low leptin levels in 14 children with CD, 71% of them with values below –2 SD score for gender and age. A direct correlation with weight and BMI was found, but the physiological association of leptin with age described in healthy individuals was lost. Leptin levels were lower in patients with severe mucosal atrophy and rose after 6-12 months of GFD. The association with the histopathologic findings was not confirmed by Ertekin *et al.* (39), despite similar findings of low leptin levels in CD children. In contrast, in children with CD and satisfactory nutritional status at the diagnosis, comparable with the general population, leptin levels were also comparable with that from controls, reflecting the similarity of fat mass in both groups (40).

Few data is available on leptin and inflammatory activity in children with CD. When analyzing both leptin and the pro-inflammatory cytokine tumour necrosis factor (TNF) in children with CD, the low leptin levels were confirmed in active CD, but without correlation with BMI. This correlation was present only for those patients in remission. TNF receptor (TNFr-1) levels were higher in patients with active CD. The authors suggested that leptin does not contribute to anorexia and failure to thrive in patients with CD; in contrast, the TNF system could be involved (41). It is well know that leptin induces growth by regulating the energy levels of the organism and by stimulating the production and secretion of GH (42). However, the effect of low leptin levels on GH secretion in children with CD is not known.

Ghrelin

Ghrelin is a peptide hormone that has been isolated from

stomach. It is found mostly in endocrine cells in the oxyntic mucosa, but small amounts are also found in the small intestine and arcuated nucleus of the hypothalamus (43,44). Ghrelin receptors are expressed in all parts of the gastrointestinal tract (45). Ghrelin has several functions. Besides its GH-releasing effect in the pituitary, it stimulates appetite, reduces fat utilization, affects body composition, induces hyperglycemia and can override the anoretic action of leptin (43,46).

In healthy children, ghrelin levels decrease with age and puberty, correlate negatively to IGF1 and IGFBP-3 and positively with IGFBP-1, effects that lower tissue availability of IGF1 (47). The authors suggested that the reduction of ghrelin with age and during puberty with higher IGF1 levels contribute to growth spurt during puberty. During starvation, ghrelin levels increase as a response of the neuronal circuits to induce a positive energy balance. Ghrelin reduces energy expenditure through action on the hypothalamic-pituitary-thyroid axis, decreasing TSH levels and stimulating the hypothalamic-pituitary-adrenal axis. GH secretion also increases (48). Since ghrelin is an endogenous agonist at the GH secretagogue receptor, this could be one explanation for the high GH levels in anorexic patients and for the decreased GH secretion in the obese ones (49).

Ghrelin also has a role in immune and inflammatory responses and gastrointestinal motility. Since gastrointestinal diseases exhibit gastrointestinal dysmotility and/or inflammation, ghrelin might have clinical implications in these diseases (50). Serum ghrelin levels are higher in adults with CD at the diagnosis compared with controls, decreasing with GFD; an inverse association between ghrelin and BMI is observed only after appropriate diet (51,52). In children with CD, biopsies taken from distal duodenum showed higher number of ghrelin-positive cells compared with controls. The density of ghrelin-positive cells did not correlate with age, BMI or clinical presentation (53). In a study involving 36 children with CD, serum ghrelin levels were higher in children with CD compared with controls, and negatively correlated with BMI (50). No significant difference was found between children with classic CD (chronic diarrhea, abdominal distention and malnutrition) and children with short stature only. After 6 months of GFD, ghrelin levels decreased, but remained higher than those controls (46). Mean serum ghrelin levels were not different in prepubertal and pubertal children (46,54), boys and girls (46,47).

Taken together, these results show an overproduction of ghrelin in children with CD and suggest that the mucosal inflammation is not a major factor affecting the level of circulating ghrelin. The impaired nutritional status increases ghrelin levels, which return to normal after GFD and weight recovery. The growth failure in CD children despite high ghrelin levels probably occurs because the increased ghrelin level does not act as a direct growth-promoting hormone, but suggest a complex network regulating appetite and energy metabolism regulation.

Conclusions

CD is more than a gastrointestinal disease. CD is a common immunological disorder that can present at any age with classical or atypical symptoms. Nutritional status can vary from undernourished to obesity or only micronutrient deficiencies. Inadequate intake of some micronutrients can continue after a strict adherence to a GFD. Although we have come a long way to understand the mechanisms of nutrition, energy regulation and hormone secretion in children with CD, more studies are still necessary to come to a full understanding.

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