Use of Growth Hormone Therapy in Patients with Celiac Disease, An Overview

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Abstract: Celiac disease (CD) is a genetically based enteropathy that is associated with lifelong sensitivity to gluten. In individuals with genetic susceptibility for CD, gluten ingestion effects an inflammatory reaction to the small intestine, ultimately resulting selective or generalized malnutrition and subsequently growth retardation. The classical symptoms of CD are becoming less common nowadays. In children with CD, short stature as the sole manifestation of the disease has become more and more frequent. Restriction of gluten from the diet usually leads to prompt growth recovery within 12 months. In fact, within 2 years of initiation a gluten free diet (GFD), CD children return to their normal growth curve for weight and height. However, in some CD patients, catch up growth remains absent after a GFD period, despite showing negative serology for specific autoantibodies. A careful endocrinological investigation is necessary for those subjects, as they may have a coexisting growth hormone (GH) deficiency and thus could benefit from substitutive therapy with GH. This review will discussthe association between CD and GH deficiency. We will also discuss the importance of GH therapy in CD patients with GH deficiency.
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Introduction

Celiac disease (CD) is an inherited enteropathy that is associated with permanent intolerance to gluten. Ingestion of gluten, in those who are genetically susceptible to CD (HLA-DQ2 and DQ8 genotypes), results in immune-mediated inflammatory reaction to the small intestinal mucosa, causing nutrient malabsorption with a number of extraintestinal and gastrointestinal complications [1-3]. In children, the classic gastrointestinal symptoms of CD appear before age 2, specifically when gluten is introduced into the diet [4].

Common gastrointestinal manifestations of CD include chronic diarrhea, abdominal distension, nausea, vomiting, and recurrent abdominal pain [4-6]. CD can manifest with extraintestinal symptoms, such as short stature, iron-deficiency anemia (IDA), pubertal delay, rickets, and dental enamel defect, as well [4, 7]. In fact, the classic presentations are becoming less common nowadays. Over the last decades, short stature and IDA have been identified as the most dominant features of CD [3, 5].

The standard treatment for patients with CD is lifelong adherence to a gluten-free diet (GFD) [3]. Exclusion of gluten-containing foods from the diet usually leads to improvement in growth velocity. Although an apparent growth hormone (GH) deficiency is often seen in CD patients, it generally normalizes when they start adhering to GFD. In fact, weight reaches the expected catch-up within 6 months after initiating a GFD and height reaches the normal percentile within 2 years [8-10]. However, some patients with CD show no catch-up growth despite adhering to a GFD for an extended period [11]. These subjects should be investigated for GH deficiency, as they could benefit from GH replacement therapy. In this review, we discuss the problem of GH deficiency and the importance of GH therapy in those CD patients who do not show catch-up growth after a certain period on a GFD.

Materials and Methods

For this review, we conducted a computerized, electronic search of articles on GH deficiency and GH therapy in patients with celiac disease. We searched PubMed, Cochrane Library, and Science Direct, with no language restrictions, using the search strings *human growth hormone, growth hormone, growth hormonedeficiency*, and*somatotropin* combined with the term *celiac disease* and *coeliac disease*. The strings were combined with additional search terms to find best, current available information in our particular areas of interest. We used filters to exclude certain publication types such as letters, commentaries, and dual publications.

All articles that were relevant to the topic were included in the review. The reference lists of the selected articles were reviewed and scrutinized for pertinent articles. The most relevant articles were retrieved in full. Based on the level of evidence, key data were analyzed to review, discuss the most appropriate information on our areas of interest. This

review also cites a number of classic literatures to illustrate certain earlier findings and developments.

Short Stature in Patients with CD

CD is not just a disease involving the gastrointestinal tract; in fact, its clinical presentation goes beyond intestinal manifestations [4]. Many patients with CD are reported to be asymptomatic and oligosymptomatic [12]. Although the earlier authors have primarily defined CD as a gluten-sensitive enteropathy [13-15], it is now described as a multisystem autoimmune disorder that could even manifest with extraintestinal symptoms (Table 1) [1-4, 16]. Among these extraintestinal manifestations, short stature has been a dominant feature of CD, and sometimes it can be the principal or only manifestation of CD, even without the gastrointestinal manifestations [17-19]. The estimated prevalence of short stature in patients with CD varies between 2.9% and 8.3% [20, 21].

Pathogenesis

The pathogenetic processes of CD-associated short stature are yet not fully explored [22]. It has been suggested that the CD pathogenesis involves the interplay of multiple factors, including genetic, immunological, and environmental. However, despite the influence of genetic and autoimmune factors, ingestion of gluten is known to be the single most important factor to develop CD [1]. Gluten is a heterogeneous molecule that contains storage proteins known as prolamins, which are high in proline content and thus make gluten hard to digest. In genetically predisposed individuals, prolamins in gluten help it to cross the intestinal epithelium and effect an inflammatory reaction to the small intestine [7]. These events ultimately cause an imbalance in the intestinal mucosa, with flattening of the villi and elongation of the crypts (i.e. crypt hyperplasia) [1, 6]. It has long been hypothesized that this damage to the small bowel mucosa results in selective or generalized malnutrition, which subsequently leads to nutritional deficiencies and finally growth retardation [4, 23].

Furthermore, in CD children of both sexes, a persistently low insulin-like growth factor 1 (IGF1) level has been evidenced after prolonged gluten exposure [24-28]. This decrease in IGF1 level is found to correlate with the nutritional status (i.e. the duration of gluten exposure) [18]. In addition, multiple changes in the circulating IGF system have been reported in celiac patients at diagnosis. These include a reduction in IGF2 and IGF binding protein (IGFBP)-3, and an increase in IGFBP-1 and IGFBP-2 [27, 28]. However, in a recent study, serum IGFBP-1 was found similar compared with the healthy subjects at diagnosis, though the value was marginally lower in CD patients (54·35 ± 7·74 vs. 61·06 ± 6·7 ng/ml) [29]. Gluten restriction has shown to normalize the changes and make rapid reversal, with an increase in IGF1, IGF2 and IGFBP-3 levels, and a decrease in IGFBP-1 and IGFBP-2 [27, 29]. Taken together, it can be suggested that because the IGF system plays a major role to integrate growth and metabolism in the body, the imbalance in the system can possibly have a correlation with the CD-associated short stature.

Apart from the involvement of the IGF system, a role for ghrelin in CD-associated growth retardation has recently been proposed [3, 4]. Ghrelin is a novel gastrointestinal hormone that is isolated from the stomach. It plays several major functions in the body, including release of growth hormone from the pituitary, stimulation of appetite, regulation of core body temperature, and reduction of fat utilization [30]. In CD patients, increased serum ghrelin levels were found compared to control subjects at diagnosis, which decreased after the initiation of GFD for at least 6 months [31-33]. In addition, the serum ghrelin level was shown to have an inverse correlation with the BMI in both children and adults with CD. However, it has been highly debated whether the change in serum ghrelin levels is caused by mucosal inflammation or related to nutritional deficiency [3]. Recently, Boguszewski *et al.* [4] suggested that because ghrelin levels return to normal after the introduction of GFD, impaired nutritional status is a more viable cause for the alteration in ghrelin concentration than inflammatory changes in the mucosal morphology.

Serological Test

In genetically predisposed individuals, gluten exposition is also known to generate celiac-specific autoantibodies as a result of its immunological response [1, 4]. Measurement of specific antibodies, therefore, needs to be carried out in undiagnosed children with short stature to exclude the possibility of CD, even if the subjects show no symptoms of gastrointestinal problems [22-23, 34]. This is because clinically CD is often underdiagnosed, and these days only a few cases come up with the classic gastrointestinal presentations [23]. Fortunately, with the availability of new accurate serological tests in the past few years, screening of atypical forms of CD, for example those in which short stature may be the sole manifestation, has become relatively common nowadays [3, 35]. As a result, in recent years, the number of diagnosed cases of the disease has dramatically increased worldwide [36]. Two of the most widely used serological tests for CD are antibodies against endomysium (EMA) and tissue transglutaminase (tTG). However, tTG is considered more reliable and cost effective than EMA, because EMA is an observer dependent test and is therefore subjected to interpretation error and additional cost [4].

Treatment

The most effective treatment for CD patients with short stature is strict adherence to a GFD for life. Withdrawal of gluten is generally followed by a prompt growth recovery, normally during the first 6 months on a GFD [3]. The catch-up growth during rehabilitation is frequently associated with a remarkable improvement in linear growth, and this often occurs at a rate well over the usual ranges per age group. Within 2 years of gluten restriction, the children with CD usually return to their normal growth curve for weight and height, though height catches up lately compared to weight [37, 38]. However, in some cases, children with CD show incomplete catch-up growth despite on a GFD [11]. These cases could be due to the persistent nutritional deficits, marked acceleration in bone maturation or impaired GH secretion [22, 38-40]. Therefore, a careful endocrinological evaluation is necessary for those who do not reach the expected catch-up growth even with a GFD, as GH deficiency is one of the major causes of short stature [23].

There are not much data about the final height of CD children with short stature, especially when they become adult. So far, a few studies have investigated on this; however, the findings have been to some extent inconsistent. While some authors suggested 1.5 standard deviation score for the final height despite strict adherence to a GFD and careful follow-up [41], others reported absolute success in reaching the target height in their subjects [42, 43]. However, a majority of reports up to now indicated that the final adult height of CD patients could be equivalent to the height of the general population [44-46], though some studies reported a height deficit only in men [47, 48]. Based on the findings of these studies, it seems that the incomplete catch-up growth has an inverse relationship with the age at which CD is diagnosed. Therefore, considering the facts discussed above, it can be suggested that the difference in study findings may be due to a delayed diagnosis of CD.

GH Deficiency and CD

The pathogenesis of GH deficiency in patients with CD is still unclear [34]. A majority of earlier studies on the somatotropic axis of the celiac patients has indicated that GH secretory response to both pharmacological-stimuli and hypoglycemia may be blunted [49-51], though some authors have reported normal levels of basal GH during the active phase of the disease [52]. The classic studies done by Wolter *et al.*[49] and Cacciari *et al.*[51] actually observed an apparently transient GH deficiency. In untreated CD patients, a temporary decrease of GH secretion generally normalizes after the strict restriction of gluten from the diet [52]. However, except the study conducted by Verkasalo et al. [50], for decades there was no report of a GH deficiency in CD patients with short stature that persisted after the introduction of a GFD. Therefore, in the past, the possibility of a correlation between CD and persistent GH deficiency was not considered as a matter of significant clinical importance.

Interestingly, in 2005, Bozzola *et al.*[34] first demonstrated a coexistence of GH deficiency in three pre-pubertal CD children who showed no catch-up growth despite adhering to a GFD for at least 12 months. These patients were found seronegative for celiac antibodies as well. In addition, endocrinological investigation revealed the presence of both isolated and multiple GH deficiency. In the same year, another study reported persistent isolated GH deficiency in 12 CD children with short stature [54]. Moving forward, in 2009, Nemet *et al.*[55] presented two CD children with a coexisting GH deficiency, with one patient having a likelihood of developing congenital hypopituitarism.

Furthermore, in a population of 7,066 short children, Giovenale *et al.*[23] found that 0.23% (16) subjects had GH deficiency in addition to CD, and these children did not grow after 1 year of GFD. Among these patients, two subjects were found with genetic disorders: one with Down's syndrome and another with Turner's syndrome. This observation further emphasized the association of CD and GH deficiency with other genetic syndromes.

The presence of antipituitary autoantibodies (AAPs) is also reported in children with CD and GH deficiency. Iughetti *et al.*[11] found four out of five CD children with GH deficiency that resulted positive at high titers for AAPs. Iughetti and colleagues also detected the presence of both antipituitary and antihypothalamus antibodies in seven CD children who did not show catch up growth after at least 12-months on a GFD, suggesting an autoimmune involvement between the two entities. More recently, Delvecchio *et al.*[56] also demonstrated high APA titers in children and adolescents with CD, which further emphasized the involvement of autoimmune pituitary process in height impairment. However, in adult patients with CD, the presence of APA is not yet confirmed. In a recent study, Ferrante *et al.*[57] reported the absence of APAs in all adult subjects, suggesting uncertain cause of pituitary dysfunction in celiac patients.

Growth Hormone Therapy in Patients with CD

GH replacement therapy has significant clinical importance in the treatment of CD-associated growth retardation. Although GFD is the only standard treatment for patients with CD and typically results in prompt growth recovery [1], GH therapy can be a treatment of choice for those who show incomplete or no catch-up growth after a GFD period due to a

concomitant GH deficiency [23, 34]. In these patients with CD, replacement therapy has been shown to facilitate catch-up growth, significantly improve height and growth velocity, and help reach normal final height [22, 54, 55, 58].

Over the last decade, a number of interesting studies have highlighted the clinical importance of GH treatment in patients with CD and GH deficiency. In 2005, Salardi *et al.*[54] suggested that in CD children in whom catch-up growth is absent after GFD and GH deficiency is confirmed, a short course of substitutive GH therapy along with the diet could be useful to improve their linear growth. The authors reached to this conclusion based on their study findings. They found that 50% (four out of eight) of the CD subjects with short stature and GH deficiency reached target height for their age after a period of GH replacement therapy in association with GFD. The authors started replacement therapy at a dose of 20 IU/m^2/week and continued it for 1-3 years.

In a later study, Giovenale *et al.*[22] also supported the suggestion made by Salardi *et al.* that a period of GH replacement therapy might improve the final height in patients with CD and GH deficiency. Giovenale *et al.* administered substitutive GH therapy to 14 prepubertal CD children with GH deficiency at the weekly dose of 0.25 mg/kg and evaluated these patients in every 6 months during the therapy. After 3 years of substitutive GH therapy, significant improvement in both height and growth velocity was observed in these patients. Based on the results of this study, the authors suggested that in children with CD and GH deficiency, the failure to catch up for linear growth after a GFD period is not solely due to nutritional deficiency, but probably to low GH and IGF-I secretion.

Furthermore, in 2009, a case report, which presented two celiac children with coexisting GH deficiency, also reported significant improvement in linear growth after a period of exogenous GH therapy in combination with GFD [55]. More recently, Meazza *et al.*[58] demonstrated that in patients with CD and GH deficiency, GH replacement therapy could help achieve a final height that could be comparable to their predicted genetic target value. The authors administered substitutive GH therapy to nine prepubertal celiac children with GH deficiency and continued the therapy until they complete puberty. These patients treated with GH therapy ultimately showed complete catch-up growth and a good height gain.

Taken together, in light of the above discussion, it can be suggested that in CD patients with GH deficiency confirmed after ≥ 12 months on a GFD, substitutive GH therapy is essential to allow complete catch-up growth. In addition, it is of critical importance that these patients continue to follow a strict GFD and show negative serology for CD at the same time, because GH replacement therapy cannot restore poor IGF-1 secretion [25] and positive serology indicates poor gluten restriction [3, 7].

Conclusion

CD is a genetically based permanent intolerance to gluten. In fact, CD is an autoimmune disease that frequently manifests with growth retardation. In children with CD and short stature, strict gluten restriction often leads to prompt improvement in their height and growth velocity. Rarely, the problem of GH deficiency persists in patients with CD. When GH deficiency is diagnosed, a period of GH replacement therapy along with a GFD can be beneficial to facilitate catch up growth. However, more research is needed to establish the replacement therapy as a treatment of choice for patients with CD and GH deficiency.

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