Current Trends in Endocrinology

Mini-Review

Growth failure in celiac subjects: an endocrinological or nutritional matter?

Elvira Verduci[1], Alberto Villani[2], Roberta Giacchero[1], Maria Cristina Mancuso[1], Elena Bozzola[2], Pietro Ferrara[3] and Mauro Bozzola[4,5,*]

[1]Department of Paediatrics, San Paolo Hospital, Department of Health Sciences, University of Milan, via Antonio di Rudinì n 8, 20142, Milan; [2]Department of Pediatrics, Pediatric and Infectious Diseases Unit, Bambino Gesù Children Hospital IRCCS, Piazza Sant'Onofrio 4, 00165 Rome;
[3]Institute of Pediatrics, Catholic University, Largo Francesco Vito 1, 00168 Rome;
[4]Department of Internal Medicine and Therapeutics, Unit of Pediatrics and Adolescentology, University of Pavia, Piazzale Camillo Golgi 19, 27100 Pavia; [5]Onlus "Il Bambino e il suo pediatra", Galliate (Novara), Italy.

ABSTRACT

Short stature is the most common extraintestinal feature of celiac disease (CD) and may be the only symptom of the disease. In fact, in evaluating a short child, the first step is usually the exclusion of CD as it may be responsible for growth failure. Once the diagnosis of CD has been made, the introduction of a gluten-free diet (GFD) increases the intestinal absorption of both macro and micronutrients leading to improved height and weight in celiac children with malabsorption. The pathogenesis of the growth failure is yet unclear. The various presentations of CD create a clinical challenge to clinicians in reaching an early diagnosis. Undiagnosed CD can lead to infertility, osteoporosis and malignancy. Adherence to GFD can limit the risk for adverse clinical outcomes but some nutritional imbalances in the diet of celiac children have been noted. In celiac patients treated with GFD, significant catch-up growth is generally observed with a recovery of growth pattern. On the other hand, an endocrinological investigation including an evaluation of growth hormone (GH) secretion should be performed in celiac children who show no catch-up growth after at least one year on a strict GFD when seronegativity for antibodies anti-transglutaminase and anti-endomysium is confirmed. At the same time, it is very important to carry out nutrition education sessions during the follow-up of celiac children because it is necessary, in addition to the elimination of gluten, to evaluate the overall diet and improve the quality of the celiac diet in order to achieve optimal health. The effect of a gluten-free diet on growth should be evaluated mainly in biopsy-proven celiac patients who show a poor response to growth despite strict adherence to dietary restrictions.

KEYWORDS: celiac disease, short stature, growth failure, gluten-free diet, catch-up growth, growth hormone deficiency, malabsorption.

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy triggered by dietary gluten-containing cereals in genetically susceptible individuals and results in a wide-range of intestinal and extraintestinal manifestations [1]. About 1% of the European and North-American population is affected, but the number of undiagnosed patients is estimated to be much greater because of the presence of prevalent forms of CD with nonspecific symptoms. In fact, the epidemiology of CD is represented by an

*Corresponding author: mauro.bozzola@unipv.it

iceberg whose visible tip represents the individuals with clinical manifestations, while its submerged part describes those with minimal or no symptoms. If undiagnosed or diagnosed late, CD can lead to severe conditions in adulthood including dwarfism, infertility, osteoporosis and malignancy [2, 3]. After the introduction of gluten into their diet, children with classical CD present with typical intestinal symptoms including chronic diarrhea and abdominal distension, failure to thrive or weight loss, especially in the first two years of age. Moreover, if the diagnosis is delayed, they may show signs of severe malnutrition. In older subjects, the occurrence of extraintestinal signs such as growth failure, iron deficiency, anemia, enamel hypoplasia and recurrent aphthous stomatitis may be more frequently observed. It has been postulated that the degree of the villous atrophy does not necessarily correlate with the severity of clinical symptoms. Therefore, the various presentations of CD create a clinical challenge to the clinician in reaching an early diagnosis. This narrative review aims to provide some insights into the growth failure in celiac subjects, focusing on major endocrinological and nutritional concerns.

Endocrinological factors

Short stature is the most common extraintestinal feature of CD and may be the only symptom of the disease. In fact, in evaluating a short child, the first step is usually the exclusion of CD as it may be responsible for growth failure. Between 8 and 10% of children with apparent idiopathic short stature have serologic evidence of CD, i.e. positive IgA antibodies against transglutaminase and antiendomisium [4-7]. In the presence of CD, a blunted GH response to pharmacological stimuli does not reflect a real GH secretion. False insufficient GH responses to pharmacological tests have been observed, followed by their normalisation after initiation of a gluten-free diet [8].

The pathogenesis of growth failure is probably due to malabsorption or abnormality in the endocrine growth axis or growth hormone resistance [9]. A lack of adequate nutrient availability seems to inhibit regular hormone generation, like in patients with undernutrition. In short, in children with CD the introduction of a gluten-free diet (GFD) increases the intestinal absorption of both macro and micronutrients leading to an increase in both height and weight in celiac children presenting with malabsorption including weight loss, failure to thrive, and poor weight gain. However, thirty-five percent of celiac children with short stature fail to display catch-up growth despite a strict GFD [10]. The influence of CD as a chronic disease on linear growth has been postulated. In some children growth failure occurs even when their weight-height ratio is normal and in the absence of serious gastrointestinal symptoms. Therefore, growth failure in CD patients is not completely due to undernutrition. This finding is confirmed by reports of overweight or obese children at the time of CD diagnosis [11, 12]. These patients lost weight after the introduction of GFD [13]. On the other hand, 80% of underweight subjects reached normal weight on a GFD, while 20% remained underweight. However, some studies have suggested that GFD may contribute to undesirable weight gain and obesity [14-16]. Therefore, the pathogenesis of growth failure is still unclear.

Nutrition: A key role

Nutritional deficiencies, mainly in iron, zinc, folate, vitamin D, vitamin B12 and B6, are often observed in patients with CD at diagnosis [17]. Currently, a GFD is the only effective therapy for CD. Calcium and phosphorus deficiency may occur as a result of malabsorption or a decreased intake of milk and dairy products due to secondary lactose intolerance. All wheat (gluten), rye (secalin), and barley (hordein) products must be strictly avoided. Therefore, the GFD is based on the consumption of certified gluten-free oat, naturally gluten-free grains (rice, corn, sorghum, minor or pseudo-cereals such as millet, teff, amaranth, quinoa, buckwheat) and commercially produced gluten-free foods.

While gastrointestinal and extra-intestinal symptoms improve on a gluten-free diet, some nutritional deficiencies could persist or even get worse (fiber, folate, niacin, vitamin B12) [17]. Indeed commercially gluten-free products tend to be low in a wide range of important nutrients, such as vitamin B, calcium, iron, zinc, magnesium and fiber [17]. Moreover, sugar or fat is added to gluten-free substitute flours to improve the palatability, leading to a high energy content. Commercial GF foods tend to contain more fat, including saturated,

and salt, but fewer minerals and vitamins than their gluten-containing equivalents [18]. The absence of gluten has been shown to increase the postprandial glycemic response. However, in recent years, the increased fiber content and improved manufacturing processes of these foods have modified the glycemic responses from these foods. Indeed, it has been demonstrated that several Italian commercial GF products have low or medium GI values [19]. The main nutritional characteristics of some naturally gluten-free grains are summarized in Table 1 [17, 20].

Therefore, naturally gluten-free grains, mainly minor and pseudo-cereals, may be healthy alternatives for improving the nutritional imbalances observed when only commercially produced gluten-free foods are consumed. Nevertheless, a further improvement of the nutritional quality of commercial GF products is a desirable goal.

It is very important to carry out nutrition education sessions during the follow-up of celiac children because it is necessary, in addition to the elimination of gluten, to evaluate the overall diet and improve the quality of the celiac diet in order to achieve optimal health. Indeed, in children and adolescents diagnosed with CD, dietary counselling over time is recommended, targeting nutritional imbalances in addition to monitoring adherence to a GFD.

Gut permeability: New challenges

A minority of CD patients do not respond to a GFD. Refractory celiac disease (RCD) patients fall into this category. RCD is characterized by persistent malabsorption symptoms despite strict adherence to a GFD (confirmed by an expert dietician) for at least 6-12 months and in the absence of other causes of non-response [21]. An abnormal tight junction structure and increased intestinal permeability have been shown as an early effect of gluten in CD patients [22, 23]. New techniques and research on the effect of permeability regulators may improve the current understanding of the altered gut barrier in CD, particularly as a possible co-factor in the growth

Table 1. Main nutritional characteristics of minor and pseudo-cereals.

	Minor and pseudo-cereals (millet, teff, amaranth, quinoa, buckwheat)	
	Common characteristics	**Specific characteristics**
Carbohydrates and fiber	Good source of carbohydrates; rich in fiber, especially soluble fiber.	
Glycemic index	Except for millet, low or medium glycemic index.	
Protein and essential amino acids	Higher protein content and better quality compared to wheat. They contain essential amino acids like methionine and cysteine and a higher lysine level (the limiting amino acid in cereals).	Amaranth, quinoa: high source of arginine and histidine.
Minerals	The total mineral content in amaranth, quinoa and oats is about twice as high as in other cereals.	Amaranth: good source of iron, phosphorus, magnesium and calcium. Quinoa: good source of phosphorus, copper, magnesium, potassium and iron. Buckwheat: good source of magnesium, manganese, phosphorus, potassium, copper, selenium, iron and zinc. Teff: good source of calcium, magnesium, manganese, phosphorus, potassium, iron and zinc.
Vitamins	Amaranth, quinoa: good sources of riboflavin, folic acid, vitamin C and vitamin E.	Buckwheat: good source of vitamins B2 and B6.

failure observed in some celiac subjects despite a strict adherence to GFD, due to a derangement of nutrients' absorption.

Proposal for an approach to growth failure in CD

The effect of gluten-free diet on growth should be evaluated mainly in biopsy-proven celiac patients who show a poor response to growth despite a strict adherence to dietary restrictions. After starting a GFD, catch-up growth is generally observed and the celiac child usually returns to the normal growth curve for weight and height within 1-2 years. To confirm dietary compliance, annual monitoring of anti-tTG-IgA is recommended. If after 1-2 years of GFD, the subject does not show a clear pattern of catch-up growth, in the presence of seronegativity for specific celiac antibodies, an evaluation of GH secretion in response to at least pharmacological stimuli is mandatory. In fact, GH deficiency could be coexistent with CD as previously reported [24, 25]. However, only 0.23% of patients with short stature show an association between CD and GH deficiency (GHD) suggesting that this association is uncommon. In CD patients with GHD, substitutive therapy with GH should be promptly started and administered at standard doses to achieve complete catch-up growth. The long-term effects of GH treatment in patients who follow a strict GFD are similar to those observed in children with idiopathic GHD.

In patients with a resistance to gluten-free diets, the introduction of gluten-like foods should be scrupulously avoided, including those used to increase the consistency of fruit beverages and contaminants mixed to other permitted foods. The degree of villous atrophy has been found to predict a higher probability of micronutrient deficiencies [26]. Thus, the negative effect of gluten and gluten-like components on linear growth may be suspected at two strategic points in time, i.e. before the diagnosis of CD and after the introduction of a GFD when patient' catch-up growth is not observed. Insulin-like growth factor I (IGF-I) which is the peripheral GH mediator, is low in GH-deficient patients, although it is not a discriminating factor in the evaluation of GH, since its secretion is also affected by the subject's nutritional status. In individuals who do not show a clear pattern of catch-up growth after a strict GFD and who test negative for antitransglutaminase and anti-endomysium antibodies, GH evaluation after pharmacological stimuli is mandatory.

In cases of GH deficiency, an association with deficiency of other hormones including thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), should be investigated before starting GH substitutive treatment. The evaluation of LH and FSH can be assessed only in pubertal period when pituitary gonadotropins increase, in age and sex-matched controls. CD patients with GH deficiency (GHD) may be treated with the same GH dosage as subjects with idiopathic GHD and with other hormones in case of associated hormonal deficiencies including levothyroxine, hydrocortisone estradiol or testosterone enanthate. The response to substitutive treatment is similar to that of idiopathic GHD patients. After starting GH therapy, GHD patients show a significant increase in growth velocity, which declines progressively in the subsequent years despite adherence to the substitutive treatment. This phenomenon is known as a waning effect. Compliance to GFD is important in order to obtain a good growth response to GH therapy. If CD patients with GHD do not respond with a significant increase in growth rate, the hypothesis of poor adherence to GFD or a waning effect of GH treatment may be raised. Seronegativity for antitransglutaminase and antiendomisium antibodies may rule out the first possibility.

Finally, the existence of a relationship between CD and autoimmune diseases such as thyroid disorders suggests that short stature may be due to impaired thyroid function.

Therefore, reasons for nonresponse may be noncompliance to the GFD or other underlying comorbidities. Special attention should be given to children who are unresponsive to the GFD. Nonresponse should prompt physicians to re-evaluate compliance to the GFD or search for underlying comorbidities in patients with extraintestinal manifestations of CD that are failing to respond to GFD.

CD patients should be monitored to verify normal growth and pubertal development, occurrence of symptoms and adherence to GFD.

CONCLUSION

In conclusion, the pathogenesis of short stature associated with CD is still not completely known although it has traditionally been attributed to generalized or selective malnutrition, such as zinc malabsorption [27]. On the other hand, poor catch-up after starting a GFD, in the presence of seronegativity, may be due to insufficient GH secretion and can be improved by an appropriate substitutive GH therapy. However, very few CD subjects present with GHD, suggesting that growth failure is not always related to hormonal insufficiency. We believe that in short CD subjects, strict adherence to GFD increases the intestinal absorption of both macro and micronutrients, leading to an increase in height and weight, in the absence of hormonal deficiencies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ABBREVIATIONS

GH: growth hormone; CD: celiac disease; GF: gluten-free; GFD: gluten-free diet; RCD: refractory celiac disease; TSH: thyroid stimulating hormone; ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; GHD: GH deficiency.

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