

Prevalence of combined growth hormone deficiency and celiac disease among Saudi Arabian children with short stature: a tertiary care center experience

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Celiac disease (CeD) is an autoimmune enteropathy triggered by gluten in genetically susceptible individuals.^[1] CeD may present with typical gastrointestinal symptoms, such as chronic diarrhea, abdominal distention, and poor weight gain triggered by gluten in the diet. Some children may have short stature (SS) as the sole manifestation of CeD.^[2] Transient dysfunction of the endocrine growth axis has been reported in CeD.^[3] This apparent growth hormone deficiency (GHD) is generally normalized with the introduction of a gluten-free diet (GFD).

In some cases, the dysfunction of the growth hormone (GH) axis may persist despite good adherence to a GFD. This may reflect a real permanent impairment that requires treatment with GH therapy. Several studies have reported the coexistence of GHD and CeD, with prevalence rates between 0.23% and 0.28%.^[4-6]

The study aimed to determine the prevalence of combined GHD and CeD in Saudi Arabian children with SS at a university teaching hospital, and to assess the response to GH therapy.

The study was conducted as part of larger research project looking at the impact of screening of high-risk population for CeD and was approved by the Research Committee/Biomedical Ethics Unit, King Abdulaziz University (No. 497-19).

This was a retrospective study of children with CeD and SS diagnosed between October 2006 and December 2018 at King Abdulaziz University Hospital. The patients were identified using the hospital medical records through the Health Information Coding System and manual search and review of patients' charts. The diagnosis of CeD is based on

the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria: by measuring antibodies to tissue transglutaminase (tTG), followed by intestinal biopsy in positive cases to confirm the diagnosis.^[1] Only biopsy-proven cases of CeD were included in the analysis. SS was defined according to WHO criteria.^[7] Only patients with height for age Z score (HAZ) less than 2 standard deviations below the mean were included. The Z score was estimated using an anthropometric software program (*Epi Info*TM, a database and statistics program for public health professionals. CDC, Atlanta, GA, USA, 2011). Children with known genetic conditions (eg, Turner syndrome, Down syndrome, etc), chronic diseases, and skeletal dysplasia were excluded from the study. The diagnosis of GHD is based on low GH response (<10 ng/mL) after at least two different pharmacological tests in children with SS. Clonidine (150 mg/m² body surface area [BSA] orally) and glucagon (15 mg/kg intramuscular injection) stimulation tests were performed on all patients on two different occasions in the hospital, then a timely collection of blood samples at 0, 30, 60, 90, 120, 150, 180, and 210 min after stimulation. The related GH-dependent peptide factors including insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGF-BP3) were also measured. Treatment with recombinant human GH (rhGH) was commenced following no improvement in linear growth after 12 months of a strict GFD. The statistical analysis was carried out using the Statistical Package for the Social Sciences, Version 22 (SPSS Inc., Chicago, IL, USA) for Windows, Release 2.0. Descriptive analysis was used to describe the results: mean \pm standard deviation (SD), median (range), and percentages.

Out of 683 children with SS identified during the study period, 91 (13.3%) had positive serology for CeD, 31 (4.5%) had biopsy-proven CeD, and five (0.7%)

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Table 1: Clinical and laboratory characteristics of patients with CD and growth hormone deficiency at diagnosis.

Characteristics	Patient 1	Patient 2	Patient	Patient 4	Patient 5
Gender	Female	Female	Female	Female	Male
Age (years)	7	5	13	9	4
HAZ score	-2.32	-3.01	-3.79	-2.51	-2.27
WAZ score	-2.46	-3.45	-2.85	-1.93	-1.69
BMI (kg/m ²)	13.8	13.4	17.1	14.7	15.7
Bone age delay (months)	48	26	48	28	30
GH peak (ng/mL)	6.91	3.15	8.68	5.76	6.30
IGF-1 (ng/mL)	132	92.9	163	25	37.8
IGFBP-3 (ng/mL)	3540	3260	3590	1180	1900
tTG (U/mL)	207	184	135.4	217	234

HAZ: Height for age z score; WAZ: Weight for age z score; BMI: Body mass index; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; IGF-BP3: IGF-binding protein 3; tTG: Tissue transglutaminase.

had combined CeD and GHD. The characteristics of patients with combined CeD and GHD are described in Table 1.

The median age at diagnosis of patients with combined GHD and CeD was 7 years (with a range of 4–13 years). Following diagnosis, all patients were treated with subcutaneous injections of rhGH using a daily dose of 35 mg/kg/day in addition to a GFD throughout the treatment period.

The patients treated with GH showed significant improvement in linear growth (-2.77 ± 0.65 vs. -1.27 ± 1.63 , $P = 0.07$), corresponding to the improvement in the serum levels of IGF-1 biochemical marker from the baseline (9.3 ± 59.3 vs. 282.6 ± 161.5 , $P = 0.05$). All patients showed good compliance with the GFD, as reflected by the decline of tTG serum levels (147.5 ± 60.6 vs. 80.5 ± 62.4 , $P = 0.11$).

In children with a history of SS, CeD must be ruled out through a process of elimination, since CeD may cause SS as a sole manifestation, without any gastrointestinal symptoms.^[4,8] The association of SS with other autoimmune diseases has been demonstrated in children with CeD; some studies have reported high titers of anti-pituitary antibodies, suggesting an autoimmune process.^[8,9] It has been postulated that autoantibodies against the pituitary gland could cause pituitary hypophysitis, which leads to suppression of GH production.^[9] This may explain the mechanism of the association between CeD and GHD.

The coexistence of both CeD and GHD has been described in a limited number of studies.^[4-6] Giovenale *et al*^[4] found that 16 (0.23%) out of 7066 children had SS that was caused by CeD and GHD. Similarly, Bozzola *et al*^[6] found 14 (0.28%) out of 1066 children had SS caused through CeD and GHD. In our study, the screening of 683 patients with SS showed a prevalence rate of 0.7% caused by CeD and GHD, which is a higher incidence than those reported by Giovenale *et al* and Bozzola *et al*. This might be attributed to the greater number of consanguineous marriages in Saudi Arabia as well as the relatively high prevalence of stunted growth.^[10]

Following GH therapy, significant improvement of linear growth was observed, similar to the responses reported by Giovenale *et al* and Bozzola *et al* after initiating GH therapy.

Serum IGF-1 remains an important biomarker of rhGH treatment, which increases in response to rhGH therapy and may be beneficial for intestinal barrier function. Therefore, the correlation between the rise of IGF-1 and the decrease in the tTG levels may reflect the better response to a GFD following the effect of rhGH on intestinal integrity.

The present study has demonstrated a predominance of incidence in the female gender (four girls, one boy), which contrasts to an extent with the study by Giovenale *et al* who reported equal gender distribution (seven boys, seven girls), and Bozzola *et al* who reported only male patients to be affected. However, taken together, these studies may indicate a general lack of gender association with this condition. The median age at diagnosis in our study was 7 years (with a range of 4–13 years), whereas in Giovenale's study, it was 6.1 (with a range of 3–7.6 years). Age was not disclosed in the Bozzola study. The growth response in our study was assessed using height for age z score (HAZ), in which patients showed a significant improvement from the median value, from -2.52 SDs to -1.58 SDs, following the results reported by Giovenale *et al*. A growth velocity calculation was used in both Giovenale *et al* and Bozzola *et al* studies to demonstrate the response to GH treatment. Our study was limited by a retrospective study design, a small cohort of patients, and the lack of a long-term follow-up program. Therefore, a prospective multi-center study is required to overcome such limitations.

In conclusion, the prevalence of combined CD and GHD in Saudi children was higher than reported in many other studies. GH therapy replacement in these patients improved the linear growth and may help in achieving the desired catch-up growth.

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Conflicts of interest

None.

References

1. Husby S, Koletzko S, Korponay-Szabo I, Kurppa K, Mearin ML, Ribes-Koninckx C, *et al.* European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr* 2020;70:141–156. doi: 10.1097/MPG.0000000000002497.
2. Nardecchia S, Auricchio R, Discepolo V, Troncone R. Extra-intestinal manifestations of coeliac disease in children: clinical features and mechanisms. *Front Pediatr* 2019;7:56. doi: 10.3389/fped.2019.00056.
3. Ferrante E, Giavoli C, Elli L, Redaelli A, Novati E, De Bellis A, *et al.* Evaluation of GH-IGF-I axis in adult patients with coeliac disease. *Horm Metab Res* 2010;42:45–49. doi: 10.1055/s-0029-1241169.
4. Giovenale D, Meazza C, Cardinale GM, Sposito M, Mastrangelo C, Messini B, *et al.* The prevalence of growth hormone deficiency and celiac disease in short children. *Clin Med Res* 2006;4:180–183.
5. Giovenale D, Meazza C, Cardinale GM, Farinelli E, Mastrangelo C, Messini B, *et al.* Growth hormone treatment in prepubertal children with celiac disease and growth hormone deficiency. *J Pediatr Gastroenterol Nutr* 2007;45:433–437. doi: 10.1097/MPG.0b013e3180de5e0a.
6. Bozzola M, Giovenale D, Bozzola E, Meazza C, Martinetti M, Tinelli C, *et al.* Growth hormone deficiency and coeliac disease: an unusual association? *Clin Endocrinol (Oxf)* 2005;62:372–375. doi: 10.1111/j.1365-2265.2005.02227.x.
7. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007;85:660–667. doi: 10.2471/blt.07.043497.
8. Iughetti L, De Bellis A, Predieri B, Bizzarro A, De Simone M, Balli F, *et al.* Growth hormone impaired secretion and antipituitary antibodies in patients with coeliac disease and poor catch-up growth after a long gluten-free diet period: a causal association? *Eur J Pediatr* 2006;165:897–903. doi: 10.1007/s00431-006-0182-4.
9. Delvecchio M, De Bellis A, Francavilla R, Rutigliano V, Predieri B, Indrio F, *et al.* Anti-pituitary antibodies in children with newly diagnosed celiac disease: a novel finding contributing to linear-growth impairment. *Am J Gastroenterol* 2010;105:691–696. doi: 10.1038/ajg.2009.642.
10. El Mouzan MI, Al Herbish AS, Al Salloum AA, Foster PJ, Al Omer AA, Qurachi MM. Prevalence of short stature in Saudi children and adolescents. *Ann Saudi Med* 2011;31:498–501. doi: 10.4103/0256-4947.84628.

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