

Linear growth of children with celiac disease after the first two years on gluten-free diet: a controlled study

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Summary. *Background:* Celiac disease (CD) is a lifelong disorder with gluten-induced manifestations in different organs especially growth. Gluten free diet (GFD) is required to achieve remission and prevent abnormal growth. Study reports on growth of children with celiac disease on long-term GFD are not consistent. *Objective:* We evaluated the effect of GFD on growth of children with the classical form of CD (diagnosed by serology and small intestine mucosal biopsy) on long-term GFD (>2 years). *Methods:* We studied growth parameters (weight gain/day, BMI and BMI-SDS, height growth velocity, Ht-SDS) and lab data in 30 pre-pubertal children, aged 7.4±2.6 years, with CD, who were on GFD since the age of 3.2±1.6 years of age (>2 years on GFD) for duration of 1 year. The anthropometric data of 30 randomly selected normal, age and sex matched, children were used as control. Lab investigations of CD children included complete blood count (CBC), renal and liver functions (aspartate transaminase - AST, alanine aminotransferase - ALT, and alkaline phosphatase- ALP, serum albumin, fasting blood glucose, vitamin D, and thyroid function and antibodies. *Results:* The weight gain per day was on average or above, for age and sex, in 27 children and below average in 3. Two out of those 3 children had slow linear growth (decreased Ht-SDS by -0.56 and -0.1, over one year). BMI-SDS was normal in 26/30 patients (>-1.5). BMI-SDS changed from -0.36±1.1 to -0.33±1.1 during the year of treatment. BMI-SDS decreased in 9 children during the follow up period that was explained by their fast-linear growth (increased Ht-SDS) in seven of them. The Ht-SDS was <-2 in four out of 30 children at the beginning of the study (2 years after being on GFD) and in 2 children after a year of follow-up (catch-up growth). Ht-SDS remained normal or increased in 28/30 children during the year of treatment (-0.38 ±1.2 to -0.22±1.1), with a positive trend: 0.15±0.4 SDS. Only one patient crossed down 1 Ht-SDS during the year of follow up, with low weight gain/day and decreased BMI-SDS that can be explained by poor compliance with GFD. Ht-SDS and BMI-SDS increased significantly in the CD group versus controls during the year of follow-up. All patients had normal serum albumin, liver enzyme and hemoglobin levels. 33.3% of patients had low serum ferritin level and 33.3% had a vitamin D deficiency. *Conclusions:* Most of our children with CD grew normally both in height and weight during GFD. Significant catch-up growth occurred in some of them after 2 years of being on GFD. Those with low BMI-SDS and/or Ht-SDS needed further management, including reinforcement on the importance of GFD and investigations on factors affecting growth pattern. Measuring weight gain /day appears to be a sensitive indicator for monitoring growth in these children. Vitamin D and iron status should be monitored, and deficiencies corrected. (www.actabiomedica.it)

Key words: celiac disease, growth, catch-up, weight gain/day, gluten free diet

Introduction

Coeliac disease (CD) is a genetically determined gluten-sensitive enteropathy resulting in nutrient malabsorption, with an increasing incidence world-wide. Clinical presentation in early childhood may include classic malabsorption symptoms, whereas older children with CD may present extra-intestinal symptoms, including short stature and pubertal delay (1). A gluten-free diet (GFD) is expected to lead to a catch-up in growth and to normalization of the weight (1-3). Therefore, monitoring catch-up growth in children with CD is important and forecasts the effect of CD on the final adult height. A good parameter of catch-up growth, particularly when assessed over long time, is the height SDS (Ht-SDS) and its change over time (4).

Tanner distinguished 3 different growth patterns that potentially lead to the same (normal) adult height. In the first pattern (A), the cessation of the growth restriction is followed by an increased height velocity (up to 4 times the mean velocity for chronological age), which fully eliminates the growth deficit. When the original growth curve is achieved, height velocity returns to normal. In the second pattern (B), the growth-restricted child grows slightly faster than normal for age but at a normal velocity for bone age, resulting in a longer growth period and a normal adult height. The third pattern (C) shows a growth velocity at the average level for chronological age but with delayed bone maturation, resulting in growth that goes on for longer than usual (5, 6).

Data about the occurrence and degree of catch-up growth in CD children on GFD are not consistent. Type A catch-up growth is the classic example and has been reported in some infants and young children after growth restriction, due to CD when a GFD is introduced. However, other types of catch-up were not clearly documented in older children with CD on long-term GFD. Many children have catch up growth consistent with type B.

However, some children with CD show a catch-up growth pattern inconsistent with the classic types described by Tanner. In fact, some authors described an intermediate type of catch-up growth (Type AB). This is characterized by an initial faster growth velocity than normal, which then passes into a phase of stable

height SDS, remaining below the target height (TH) SDS, until the pubertal delay causes an increase of height SDS toward TH SDS (7-10).

In addition, some CD children do not show catch-up growth during GFD, despite reversion to sero-negativity for CD markers including anti-endomysial and anti-tissue transglutaminase antibodies. Therefore, the target adult height is not attained by a high percent of these children (7, 11-14).

The existence of a higher risk of permanent growth failure makes necessary a close monitoring of growth in these children in order to detect their growth response to GFD and to diagnose and treat early any potential factors interfering with the growth development (15).

In the present paper we investigated the prevalence of growth abnormalities and studied the relation between changes in weight and linear growth for a year in children with CD who had been on a GFD for at least 2 years before the beginning of study.

Patients and methods

The study cohort comprised 30 children, aged 7.4 ± 2.6 years, with documented celiac enteropathy [positive anti-tissue transglutaminase (anti-tTG) IgA + total IgA, positive IgG-deamidated gliadin peptide (DGP) test and confirmed by intestinal biopsy] diagnosed at 3.2 ± 1.6 years of age. They were started on gluten-free diet for at least 2 years before the study. This cohort consisted of 30 consecutive cases, diagnosed during one year at the Pediatric and Dietitian Outpatient Clinic of Hamad General Hospital of Doha (Qatar). Three patients were excluded from the study, because one had type 1 diabetes mellitus, the second an autoimmune chronic hepatitis and the third a trisomy 21.

Routine lab tests [complete blood count (CBC), renal and liver functions (aspartate transaminase - AST, alanine aminotransferase - ALT, and alkaline phosphatase - ALP, serum albumin, fasting blood glucose, vitamin D, and thyroid function and antibodies] did not show any abnormality.

We assessed growth parameters (weight gain/day, body mass index - BMI, and BMI-SDS, height

growth velocity, expressed in Ht-SDS) and lab data of CD patients, who were on GFD since the age of 3.4 ± 1.6 years, and for a duration of 12.8 ± 2.6 months. Anthropometric measurements included: weight, height, Ht-SDS, weight for height, BMI, and BMI-SDS. The height-for-age Z-score (Ht-SDS) and the BMI-for-age Z-score (BMI-SDS) for each child were calculated using the WHO standard population as the reference (16).

We categorized Ht-SDS < -2.0 (approximately the 3rd percentile) as stunted, BMI-SDS < -1.00 (approximately the 15th percentile) as mild underweight, BMI-SDS < -2.00 as moderate-severe underweight, BMI-SDS > 1.00 (approximately the 85th percentile) as overweight, and BMI-SDS > 2.00 (approximately the 97th percentile) as obese.

We also evaluated the effect of nutritional rehabilitation, during GFD, on weight changes (weight gain g/day and BMI-SDS changes) and linear growth (height growth velocity and Ht-SDS changes).

Nutritional rehabilitation (NR) included: nutrition counseling to comply with GFD and increase energy and protein intake to allow for catch-up. Energy requirements were calculated using catch up growth method and protein requirements were calculated using catch up growth method up to 3 g/kg/d. Pamphlets were handed out for patients, as educational support, and My Plate food model was used for demonstration of suitable GF food types and serving sizes. In addition, high energy (1:1 or 1:1.5) and high protein nutrition supplementation were monthly supplied for free to all patients who had BMI-SDS ≤ -1 . The effects of GFD on weight changes (g/day) and BMI on height changes, measured by height GV and Ht-SDS, were studied.

The compliance to GFD was also periodically assessed.

Student- t test was used to compare the growth and lab variables after versus before the follow-up period, when the data were normally distributed, and the Mann-Whitney U- test was used when the data were not normally distributed. Linear correlation equation was used to investigate possible relations between different variables. Significance was accepted when p was ≤ 0.05 .

The study was approved by the Institutional Review Board of Hamad Medical Centre, Doha (Qatar).

Results

The growth of 30 children, aged 7.41 ± 2.6 years, with verified celiac enteropathy, who had been on a GFD for at least 2 years before the beginning of study. At the study baseline, the Ht-SDS of CD children was -0.40 ± 1.2 . Four out of 30 children had Ht-SDS ≤ -2 (stunted). Their mean BMI-SDS was -0.36 ± 1.1 , 5 /30 had BMI-SDS < -1 (mild underweight) and none had BMI-SDS < -2 . One child was obese (BMI-SDS: 3.3).

The changes in BMI-SDS and Ht-SDS after the year of follow-up in CD and normal controls are shown in table 1.

During the follow up period, the weight gain per day was on average or above, for age and sex, in 27/30 children and below average in 3/30. Two out of 3 children had also a slow linear growth (decreased Ht-SDS: -0.56 and -0.1 , over one year) that was clearly explained by their poor compliance to GFD (Figure 1).

In the control group the weight gain per day was on average or above, for age and sex, in 22/30 children

Table 1. Growth data after versus before a year of follow-up in CD patients and controls

		CD-Before	CD-After	CD-Change	C-Before	C-After	C-Change
Age (years)	Mean \pm SD	7.4 \pm 3.6	8.3 \pm 3.6	0.9 \pm 0.1*	6.7 \pm 3.1	6.8 \pm 2.6	1.1 \pm 0.3*
Ht-SDS	Mean \pm SD	-0.3 \pm 1.2	-0.2 \pm 1.1	0.1 \pm -0.04 #	0.1 \pm 0.9	0.1 \pm 0.9	0.01 \pm 0.63
BMI	Mean \pm SD	16.2 \pm 2.2	16.2 \pm 2.2	0.02 \pm 0.02 #	16.1 \pm 1.4	16.0 \pm 1.6	0.09 \pm 0.7
BMI-SDS	Mean \pm SD	0.3 \pm 1.1	-0.3 \pm 1.1	0.02 \pm 0.5 *#	0.2 \pm 0.9 #	0.06 \pm 0.9	-0.1 \pm 0.4

Legend: CD = Celiac disease, C = controls; *p<0.5 before vs after 1 year of follow up (Mann-Whitney U Test), # p <0.05 CD vs controls after 1 year of follow up (Mann-Whitney U Test)

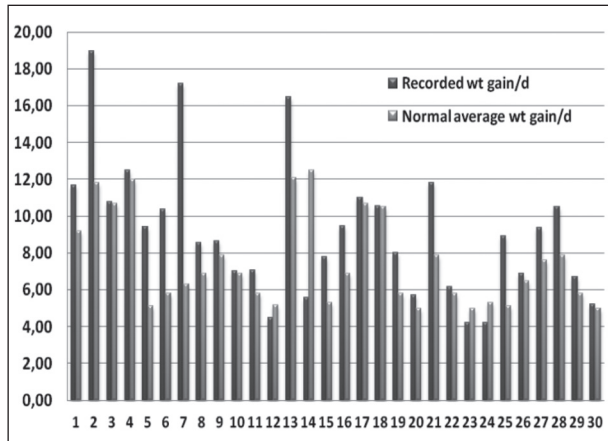


Figure 1. Daily weight gain compare to average normal weight gain for age and sex in celiac disease children on gluten free diet during follow-up (1 year)

and below average in 8/30 children. The daily weight gain was significantly lower in the control children (5.91 ± 1.5 g/day) versus CD children (9.16 ± 3.8 g/day) ($P = 0.023$).

In the CD group, after a year of follow-up, the BMI-SD slightly changed from -0.36 ± 1.1 to -0.33 ± 1.1 . BMI-SDS was < -1 in 5/30 children before and in 6/30 children at the end of the year of follow-up. BMI-SDS decreased in 9 children during the follow up period that can be explained by the fast linear growth (increased Ht-SDS) in seven of them.

Conditional change in BMI SDS is an alternative method to evaluate BMI changes, which provides more accurate information relative to a reference population. In the control group, BMI-SDS was < -1 in 1/30 children and in none after the follow up period denoting normal weight gain in respect to height gain. The BMI-SDS changed from 0.20 ± 0.9 to 0.06 ± 0.93 . The change in BMI-SDS was significantly higher in the CD group versus the control group ($p = 0.0139$) (Figure 2 -A and B) The BMI-SDS was significantly lower in the CD group at the beginning of follow up period ($p = 0.029$) but not statistically different after the year of follow up ($p = 0.08$).

The HT-SDS was < -2 in 4/30 children at the beginning of the study and in 2/30 children after one year of follow-up (catch up in two). The Ht-SDS of the CD group was not statistically different compared to the control group before and after the follow-up period ($p = 0.07$ and 0.126 , respectively). In the CD group, the

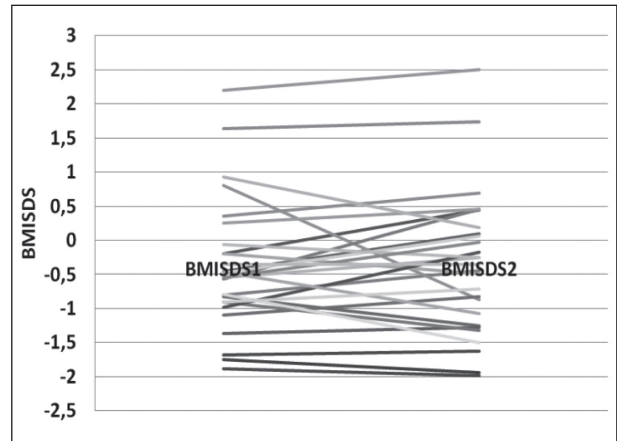


Figure 2A. BMI-SDS changes in children with celiac disease on gluten free diet during follow-up. Legend: 1- Before follow up; 2- After a year of follow up

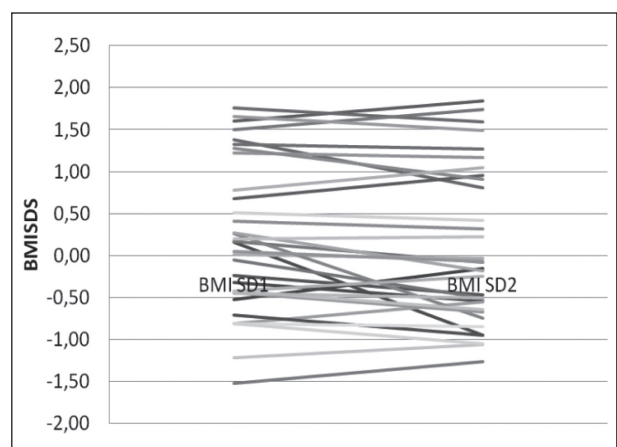


Figure 2B. BMI-SDS changes in the control group. Legend: 1- Before follow up; 2- After a year of follow up

HT-SDS remained stable to -0.25 in 14 /30 (canalization) or increased in 15/30 children (catch-up), during the year of follow up, with a positive trend in the CD group: 0.16 ± 0.4 SD. 15/30 of CD children showed increased Ht-SDS by (0.4 ± 0.2 ; range: $0.27 - 1$ SD), during the year of follow-up (denoting a catch-up growth). Only one patient had a Ht-SDS de-canalization of 1SD during the year of follow up, associated with a low weight gain/day and decreased BMI-SDS that was explained by poor compliance with the GFD and non-healing of his disease, documented by intestinal biopsy.

In the control group none of the children had Ht-SDS < -2 . 18 /30 children increased their Ht-SDS by 0.37 ± 0.32 while 12 decreased their Ht-SDS by

-0.21±0.19. The change in the Ht-SDS, after a year of follow up, was significantly higher in the CD group (P=0.02) (Figure 3- A and B)

The change in the Ht-SDS (-0.12±0.6) in children with CD, below 5 years of age (3.7±1.5 years) was not statistically different compared to the observed changes of Ht-SDS (0.14±0.39) in older children (8.2±1.8 years) with CD (Figure 3- A and B).

In the CD group, the change in Ht-SDS was correlated with the change in BMI (Figure 4) but not with the weight gain per day or BMI-SDS, during the year of follow up.

All patients had normal serum albumin, liver enzymes and hemoglobin levels. 10/30 had low ferritin level and 10/30 had vitamin D deficiency at the beginning of the study.

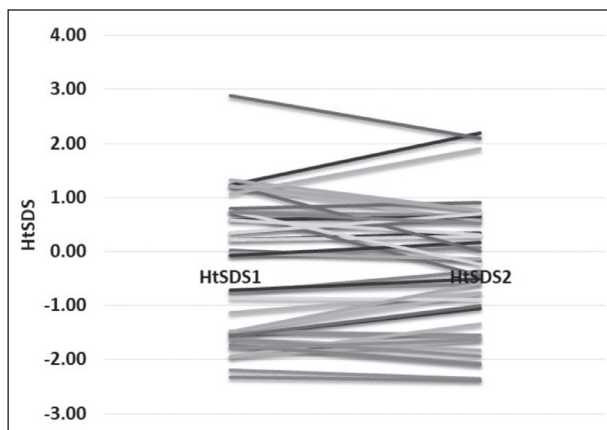


Figure 3A. Height-SDS changes in children with celiac disease on gluten free diet. Legend: 1- Before follow up; 2- After a year of follow up

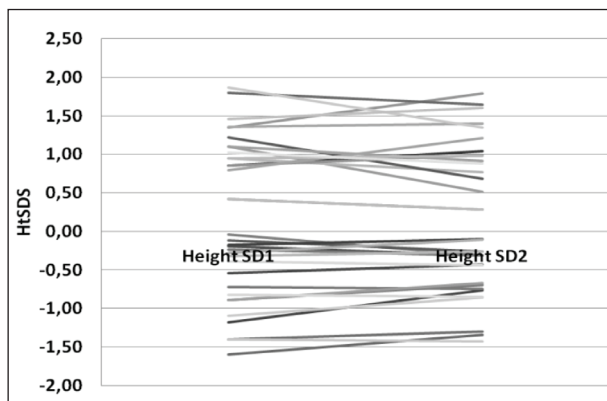


Figure 3B. Height-SDS changes in the control group. Legend: 1-Before follow up; 2- After a year of follow up

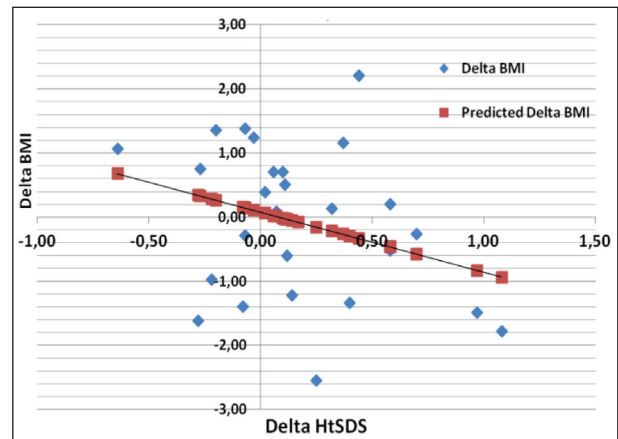


Figure 4. Correlation between Δ height-SDS and Δ BMI (r: 0.31; p: 0.08)

Discussion

Linear growth appears to be under the control of a dynamic and complex system that makes the growing child return to its path of growth after deviation. This tendency to keep to a narrow and predictable track of growth has been called “canalization” and is a prerequisite for catch-up growth. In clinical terms, canalization means that the individual growth curve parallels the centile curves (same Ht-SDS) on growth charts.

In the prepubertal period canalization is clearly recognizable. Within one individual, the degree of canalization varies among the various growth parameters. Head circumference, height, and skeletal maturation tend to parallel the centiles more closely than weight and skinfold thickness.

Catch-up growth is characterized by an increase of percentile position (increase of Ht-SDS) and thus requires that height velocity exceeds the statistical limits of normality for age and/or maturity at some point (6, 17, 18).

In normal children, shifts in growth rates are common from birth to 6 months of age, somewhat less common for children 6 to 24 months of age, and least common for children 24 to 60 months of age (19). Growth velocity is normal if growth is maintained along an isobar line (same Ht-SDS). When growth velocity is abnormally decreased, height measurements will progressively fall across isobars (decreased Ht-SDS), sometimes termed ‘falling off the curve’.

Conversely, acceleration of growth velocity results in crossing the upper isobars (increasing Ht-SDS) (20).

There is no agreed cut-off criterion for catch-up growth, and it is suggested that a sustained increase in height SDS toward the Ht-SDS before the start of growth retardation is acceptable definition (14,21).

After gluten withdrawal, a prompt onset of catch-up growth follows. This catch-up growth is characterized by a height velocity above the statistical limits of normality for age during a defined period of time (increasing Ht-SDS). So that within 6-12 months the child usually returns to his/her normal growth curve for weight and within 2-3 years complete catch-up growth for height is achieved (7, 22). However, many authors reported that the catch-up growth is not always complete and final height remains below the mean notwithstanding the early treatment, the carefully follow-up and the good adherence to the dietary rules of the patients (11-13).

In this study 50% of children with CD on GFD were still increasing their Ht-SDS (crossing up height centiles), documenting continuous slow catch-up, even after an average of 2 years or more after the beginning of GFD. Their Ht-SDS were significantly higher than normal age matched children. In support of our results, de Wit et al. (14) reported a catch-up growth pattern inconsistent with the classic types described by Tanner. Instead the authors described an intermediate type of catch-up growth (Type AB). This is characterized by an initial faster growth than normal, which then passes into a phase of stable height SDS, which remains below target height (TH) SDS, until the pubertal development causes an increase of height SDS toward TH SDS.

Bosio et al. (12) studied a cohort of 24 short children with delayed diagnosis of CD. Their follow up showed an increased height velocity and weight velocity during the first 3 years of GFD, with maximum growth velocity occurring during the first year. Nevertheless, the catch-up growth was incomplete over 3 years (mean Ht-SDS: 1.77 ± 0.6). Puberty began in all patients at a normal age. The 12 patients who completed pubertal development reached their target height, denoting continuous catch-up during late childhood until puberty.

Damen et al.(7) studied the growth pattern of 28 girls and 32 boys with CD up to the ages of 10 and

12 years, respectively. At diagnosis, 18 of 60 patients (30%) had a height SDS below -2.0, and 45 of 59 patients (76%) had a weight-for-height below the median. The authors reported also a relatively fast catch-up growth with increasing Ht-SDS in the first year after diagnosis, but catch-up continued slowly thereafter for the following 2-3 years.

Gemme et al.(11) studied 26 patients (11 boys and 15 girls), who were younger than 2.5 years at diagnosis of CD, over a median period of 15.3 years. They reported that some patients did not catch-up completely in height and skeletal age after a dietary treatment period of 3 years. Most of them were seen to be slightly below the height average for age during childhood and adolescence with skeletal maturity retardation.

In our study, however, there was no difference in Ht-SDS between CD children on GFD and normal controls, and the change in the Ht-SDS did not differ between young (<5 years of age) and older children (>5 years of age).

The reported difference in the pattern and rate of catch-up growth in our study and other reports can be explained by the delayed growth plate senescence theory. In infants, correction of the growth restricting disorder leads to a markedly increased growth rate with catch-up growth over a brief time course (Type A). In older children, the hypothesis predicts that catch-up growth should occur gradually, over years (Type B, or AB) (23).

In our CD children, 4/30 and 2 /30 had short stature before and after nutritional rehabilitation, respectively. In the latter 2 children, the weight gain per day was lower than average for age. Therefore, a poor compliance to GFD was taken in consideration and was supported by non-healing in intestinal biopsy in one of them. This support the traditional concept that poor growth has been attributed to persistence of histological damage leading to malabsorption of essential nutrients (24, 25).

However, many other factors can lead to impairment or delayed catch-up growth and may compromise final adult height. The coexistence of anemia and other micronutrient deficiencies may contribute to poor growth. Abnormalities in the growth hormone/insulin-like growth factor-1 axis and thyroid axis may explain some of the growth delay in those who did not

attain good catch-up or in those with slow growth, despite being compliant with the GFD (26-31). Late diagnosis during childhood could be an additional factor contributing to a reduction of final adult height (32). Nevertheless, these aspects remain controversial.

Children and adolescents with CD are at risk for suboptimal bone health at time of diagnosis and after 1 year on GFD. Suboptimal vitamin D status was found in a third of our children with CD on GFD. Celiac children not following a GFD showed delays in both bone maturation and mineralization (33).

Tau et al. (34) reported a decrease of axial bone mineral density (BMD) below -1 SD in 58% of their children with CD. After about 1 year of GFD, height and weight increased significantly ($P < 0.001$) and the axial bone mass reverted to normal values in most children under the age of 4 years. The increase in bone mass was correlated positively with the increase in BMD. Mager et al. (35) reported that 43 % of their children with CD had suboptimal vitamin D status [25(OH)-vitamin D < 75 nmol/l] at diagnosis, and 21% after 1 year on the GFD. Heyman et al. (33) showed that the bone mass density increased significantly in CD children on GFD, as determined by the BMD/CA/year ($+0.05 \pm 0.3$ vs -0.34 ± 0.4 SD; $P < 0.01$).

Anemia may impair growth and catch-up in children with CD. Anemia is a frequent finding in patients with CD and may be the presenting feature. The anemia may be the only abnormality identified. The anemia is usually hypo proliferative, reflecting impaired absorption of essential nutrients, like iron and various vitamins. The prevalence of anemia varies greatly according to different reports and has been found in 12% to 69% of newly diagnosed patients with CD. In our children, 10/30 had low ferritin but none had anemia. Correction of the iron status appears to be important to support normal appetite and growth in these patients (36-38).

Conclusion

Follow up of growth of children with CD on long-term GFD, after the first two years on GFD, has proved that these children maintained normal linear growth rate, and some of them still show significant

catch-up growth. Measuring weight gain /day and changes in Ht-SDS appeared to be sensitive indicators for monitoring growth in these children. Vitamin D and iron status should be monitored, and deficiencies corrected.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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