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Growth and Nutritional Changes in Qatari Children after Medical and Nutritional Interventions

Guest Editor: Ashraf T Soliman

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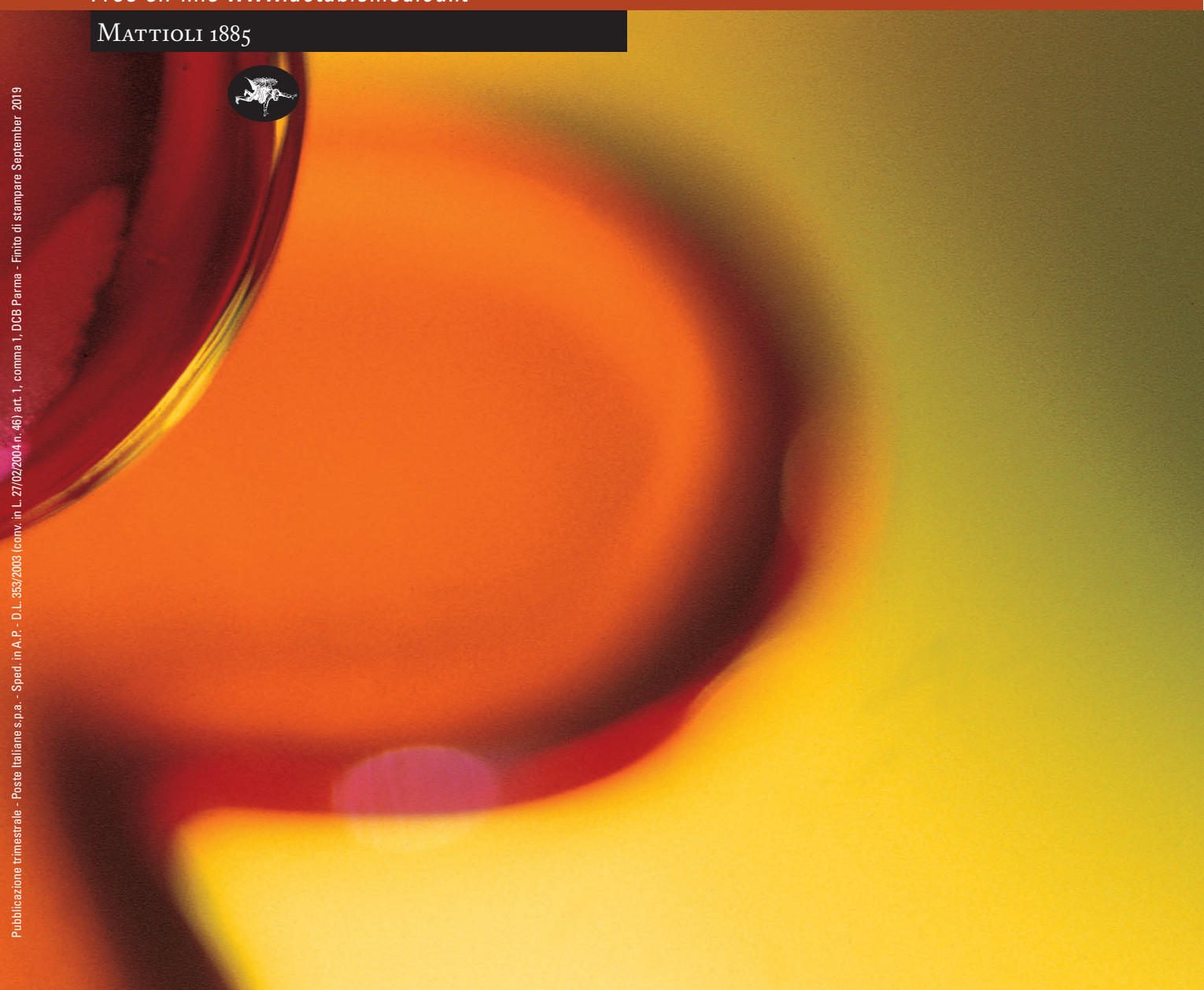

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Foreword

It is a great honor for me to introduce this supplement of Acta Biomedica on " Growth and Nutritional Changes in Qatari Children after Medical and Nutritional Interventions".

The publication focuses on the interaction between nutrition and growth in pediatric and adolescent age groups. Subjects covered include: the interplay between nutritional rehabilitation and growth in underweight children, the effects of gluten-free diet on linear growth, the postnatal growth of infants with neonatal diabetes treated with insulin pump versus multiple daily injection, the effects of thyroxin treatment on linear growth and weight gain in treated subjects with Down syndrome, and the response to growth hormone (GH) therapy in short children with normal GH secretion.

The supplement aims to bring together leading academic scientists and researchers to exchange and share their experiences and research results on different aspects of Growth and Nutrition.

Today's patients have complex health needs and typically require more than one discipline to address issues regarding their health status. In an era of information overload, two groups of opinion leaders from Qatar and Italy have contributed to the preparation of supplement, under the expert and wise guide of prof. Ashraf T. Soliman. His traits include excellent professional thinking, expert team building skills, competitive landscape, empathy and emotional intelligence for giving to children and adolescents an integral medical health care.

I believe that the supplement is ideal for pediatricians, gastroenterologists, endocrinologists, neonatologists, dieticians, nutritionists, nurses and all those involved in child development who share a passion for exchanging ideas and analysis of pediatric endocrinology and nutrition in the pediatric age group.

Finally, I wish to express my deepest thanks to the Editor in Chief of Acta Biomedica, prof Maurizio Vanelli and to the Publisher in the person of Dr. Valeria Ceci, Ph.D, for giving us this great opportunity and for the professional care and dedication in the preparation of printed version.

Vincenzo de Sanctis, MD

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Original article

Relation between changes in weight parameters and height parameters in prepubertal children: daily weight gain and BMI changes in relation to linear growth during nutritional rehabilitation of underweight children

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Summary. *Background:* Early detection of abnormal weight loss or gain in childhood may be important for preventive purposes. Variable growth response to nutrition rehabilitation have been reported in children with failure to thrive (FTT) who do not have any chronic disease or systematic illness due to different clinical and nutritional approach in their management. *Aim of the study*: To analyze the association of different body mass index (BMI) and BMI- SDS, to linear growth (Ht-SDS) in different BMI categories of prepubertal children. In addition, we studied the effect of weight changes on linear growth in a randomly selected group of prepubertal underweight children who received nutritional rehabilitation (NR) for 9±2 months. *Subjects and methods:* 102 children, between 1 and 9 years, followed at the General Pediatric Clinic, between January 2017 to December 2017, because of abnormal weight gain (decreased or increased) which was not associated with any acute or chronic illness were included in the study. Anthropometric measurements included weigh, height, Ht-SDS, BMI, and BMI-SDS. Children BMI-SDS were categorized into 4 groups: Group 1: BMI-SDS <-2, group 2: BMI-SDS <-1 but >-2, group 3 BMI-SDS >-1 but <2, group 4 BMI-SDS >2. We also evaluated the effects of weight changes on linear growth in a randomly selected group of underweight children who received nutritional counselling and oral nutritional supplementation (n = 51) for 9±months. *Results:* HT-SDS in children of groups 1 and 2 (underweight and at risk of underweight children) was significantly lower than Ht-SDS of groups 3 and 4 (normal and overweight children). Ht-SDS in children of group 4 was significantly higher than the Ht-SDS of children in group 3. A significant linear correlation was found between BMI-SDS and Ht-SDS in these prepubertal children. *Discussion:* After nutritional rehabilitation for a year, 55% of underweight children increased their BMI-SDS and 43% increased their Ht-SDS. Children who had weight gain >7g/d, over the whole period of follow-up, (n =14) increased their BMI-SDS and Ht-SDS significantly after versus before NR. The BMI-SDS and Ht-SDS did not increase significantly in the group of children who had weight gain <7 g/day. 28 children out of 51 improved their BMI-SDS after nutritional rehabilitation (group A) and 23 did not have improvement in their BMI-SDS (Group B). Group A had higher weight gain per day versus group B. Height growth velocity was significantly higher in Group B (7.4±3.6 cm/yr) versus group A (5.7±2.8 cm/yr). Ht-SDS increased significantly in the group of patients who had lower Ht-SDS before NR. Children who had faster linear growth velocity, after nutritional rehabilitation, did not increase their BMI-SDS. Linear regression showed a significant correlation between BMI-SDS and Ht-SDS supporting the notion that proper nutrition and maintaining normal BMI-SDS is essential for adequate gain in height. *Conclusion:* It appears that calculating the weight gain per day, BMI-SDS and Ht-SDS are clinically useful parameters to detect the effect of weight gain on linear growth and to monitor the nutritional management. Daily weight gain was correlated significantly to height growth rate during nutritional rehabilitation. Based on our findings and literature reports, we suggest an algorithm for follow-up of underweight/ malnourished children based mainly on anthropometric assessment. (www.actabiomedica.it)

Key words: linear growth, weight gain, nutritional rehabilitation, underweight children

Introduction

Underweight, as well as overweight and obesity, are currently highlighted as being among the most important threats to human health. According to the UNICEF, WHO and The World Bank joint report, linear growth restriction or stunting (height below minus two standard deviations from the median height for age of the reference population) due to chronic malnutrition affects an average of 25% of all children younger than five years worldwide (1). Therefore, monitoring both linear growth and weight dimensions of population is critical, because of the persistent growth failure globally as well as the emergence of obesity as a global epidemic (2-4).

It is possible not to find any specific cause for a child's apparent poor weight gain. A well looking child with normal neurodevelopmental progress, who shows apparent isolated poor weight gain, with no specific cause evident from history, examination and possibly some simple investigations, will have an excellent prognosis for future health, wellbeing and development. These children should be monitored over time to ensure that no specific causes of poor growth become evident.

A large study in the US found that most infants (77%) aged from birth to 6 months cross weight-for-age percentile lines, with 39% of infants either moving up or moving down two percentile lines. As children got older, they are much less likely to cross two weight-for-age percentile lines, but this did still happen. Six to 15% of children cross 2 percentile lines weight for height and 1-5% of children cross 2 percentile lines (weight for-age) between 2 and 5 years (5, 6).

Body mass index (BMI) as well as BMI z-scores are reasonably good references for predicting the body composition and adiposity status in children. In addition, calculation of normal weight gain/day for children according to their age and gender, although is a less used measurement, allows more precise estimation of weight growth rate and adiposity during periods of nutritional rehabilitation (7-15).

It is suggested that the content of adipose tissue influences the regulation of the biological maturation, including bone and linear growth as well as pubertal growth spurt. It has also been demonstrated that children with changes in BMI and adiposity can affect the timing and tempo of puberty and consequently the pubertal growth spurt (16, 17).

Malnutrition is considered a leading cause of growth attenuation in children. When food is replenished, spontaneous catch-up (CU) growth usually occurs, bringing the child back to its original growth trajectory. However, in some cases, the CU growth is not complete, leading to a permanent growth deficit (7).

There is no clear consensus on the correct definition of ideal body weight (IBW) (ideal weight for growth and health) in children or on the best method used to calculate IBW.

The BMI method has many advantages that include: 1) the BMI is age specific, 2) BMI-for-age accounts for "adiposity" rebound, which is the normal pattern during puberty and adolescence, 3) BMI fit well with both weight-for-height measurements and measures of body fat and, 4) BMI carries into the adult lifecycle. However, BMI cutoff values have high specificity but low sensitivity to identify adiposity. Moreover, BMI does not provide information on the proportions of multi components of weight, such as fat mass (FM), lean mass (FFM) and bone mass. BMI is correlated with each of these parameters but, it cannot differentiate between them. BMI differences among thinner children can be largely due to FFM, and it is more important in underweight children (7, 18-25).

Stunting is a primary manifestation of malnutrition (undernutrition). In malnourished and underweight children slowing of linear growth and the association between short stature and underweight has been reported in many population studies. The relation/association between weights changes (BMI-SDS and weight gain/day) and linear growth [height, Ht-SDS and growth velocity (GV)] has not been adequately studied in older children with underweight before and after nutritional rehabilitation.

The aim of this study was to analyze the effect of different BMI and BMI-SDS, if any, on linear growth (Ht-SDS) in different BMI categories of prepubertal children (n = 102). In addition, we assessed the effects of weight changes (weight gain/day, and BMI-SDS) in relation to linear growth (growth velocity and Ht-SDS) in a randomly selected group of underweight children, after nutritional rehabilitation.

Subjects and methods

All children, between 1 and 9 years, followed at the General Pediatric Clinic of Hamad Medical Centre, Doha (Qatar), between January 2017 to December 2017, because of abnormal weight gain (decreased or increased) which was not associated with any acute or chronic illness were included in the study. Physical exam and routine lab tests did not show any abnormality. Children with any organic or systematic disease were excluded from the study. The study was approved by the Institutional Review Board of Hamad Medical Centre, Doha, Qatar.

Anthropometric measurements included weigh, height, Ht-SDS, weight for height, BMI (Kg/m^2), 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 (14, 18).

We categorized Ht-SDS <–2.0 (approximately the 3rd percentile) as stunted, BMI-Z score <–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.

According to BMI-SDS our children were categorized into 4 groups: Group 1 (N=19) BMI-SDS <-2 , Group 2 (N=33) BMI-SDS >-2 - <-1, Group 3 (N=20) BMI-SDS >-1 <2, and Group 4 (N=30) BMI-SDS >2.

In addition, we evaluated the effect of nutritional rehabilitation on weight changes (weight gain g/day and BMI-SDS changes) and linear growth (height growth velocity and Ht-SDS changes) in a randomly selected group of underweight children (n = 51) who received nutritional counselling and oral nutritional supplementation.

Nutritional rehabilitation (NR) included nutrition counseling to increase energy and protein intake. 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 (18). Pamphlets were handed out for patients for education and My Plate food model was used for demonstration of 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 (18).

The effects of weight changes (g/day) and BMI on linear growth measured by height GV and Ht-SDS were studied.

Student- t test was used to compare the variables among different groups when the data was normally distributed and Wilcoxon test was used when the data was not normally distributed. ANOVA test was used to compare variables among the 4 groups categorized according to their BMI-SDS. Linear correlation equation was used to investigate possible relations between different variables. Significance was accepted when was ≤0.05.

Results

We evaluated growth parameters in 102 pre-pubertal children (age 1-9 years), with abnormal weight gain without systematic or organic illness, followed at Pediatric General Dietitian Clinic of Hamad General Hospital of Doha (Qatar).

Children were divided according to their BMI-SDS (Table 1). Ht-SDS of children in groups 1 and 2 (moderate/severe underweight and mild underweight) was significantly lower than Ht-SDS of groups 3 and 4 (normal and overweight children). Ht-SDS in children of group 4 (obese) was significantly higher than the Ht-SDS of children in group 3 (controls).

Both underweight and obese groups (1 and 4) had significantly higher percent of vitamin D insufficiency, compared to the other groups (p: <0.00001). The BMISDS was correlated significantly with Ht-SDS (r=0.72, p: <0.0001) (Table 2, Figure 1).

Serum albumin and hemoglobin concentrations were normal and did not differ among the four groups (Table 1). Vitamin D insufficiency was present in 71% of the children in group 1, 40% of the children in group 2, 23% of the children in group 3 and 75% of the children in group 4.

In the 51 children who received nutritional rehabilitation (NR) followed up for 9±2 months, the weight gain/day increased significantly between the last and first visit.

Table 1. Anthropometric and biochemical data (mean ±SD) of children with abnormal weight gain

	N.	Age (yr)	Height SD	BMI-SD	Hb (g/dl)	Vit D (ng/ml)	Alb (g/l)
Group 1 (BMI-SDS <-2) Moderate/ severe under-wt	19	4.9±4.4	-1.5±1.3 *#	-2.8±1.0 *#	11.6±1.1	20.1±7.4	40.9±3.6
Group 2 (BMI-SDS >-2 <-1) mild under-wt	33	5.6±4.0	-1.76±0.9 *#	-1.5±0.2 *#	12.2±1.3	24.3±12.7	41.8±3.3
Group 3 (BMI-SDS >-1 <2) Controls	20	3.1±2.7	-1.26±0.9 #	-0.2±0.5 #	11.7±1.2	29.5±11.7	40.4±5.1
Group 4 (BMI-SD >2) Obese	30	8.9±3.9	1.0±0.9*	3.5±0.9 *	12.7±1.1	19.0±13.5	41.1±3.3

Legend: * P: <0.05 groups vs controls; # P: <0.05, groups vs. obese group (Group 4)

Table 2. Correlation between Body Mass Index (BMI- Kg/m^2) and Height-SDS

	Height- SDS	BMI (Kg/m^2)	BMI-SDS
Height-SDS	1.00	-	-
BMI (Kg/m^2)	0.68*	1.00	-
BMI SDS	0.72**	0.85**	1.00*

P: <0.01; ** P :<0.001

We divided the 51 children into 2 groups according to their weight gain/day response. Group A: included 14 children who had weight gain >7 g/d over the whole period of follow-up (average normal weight gain for the average age and gender is 6.5 g/d); Group B: included 37 children who gained weight <7 g/d during the follow up period.

The BMI-SDS of group A increased significantly after versus before nutrition rehabilitation, whereas, BMI-SDS did not increase significantly in group B (p: 0.06).

The Ht-SDS of group A increased significantly after 9±2 months of NR while the Ht-SDS of group B did not improve significantly (Table 3).

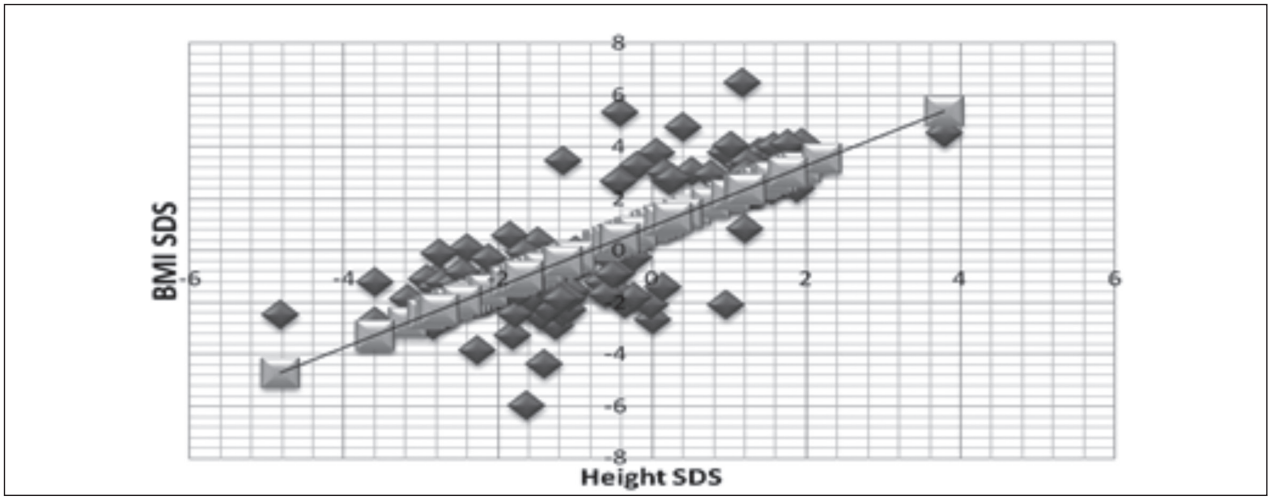


Figure 1. Regression analysis of BMI-SD score on Height SDS (r = 0.723, P: <0.0001)

When children were divided according to their BMI-SDS changes in response to rehabilitation, 28 children out of 51 improved their BMI-SDS after nutritional rehabilitation (Group A) and 23 did not have improvement in their BMI-SDS (Group B).

Group A had higher weight gain per day (8.6±5.8 g/day) versus Group B (3.3±2.2 g/day). Height growth velocity (cm/y) was significantly higher in Group B (7.4±3.6 cm/yr) versus Group A (5.7±2.8 cm/yr).

Children who had higher linear growth velocity after nutritional rehabilitation did not increase their BMI-SDS (Table 4). Weight gain/day and BMI-SDS were correlated significantly with height growth velocity (r = 0.38, p: 0.02) and (r = 0.4, p: 0.018) (Figure 2). Ht-SDS was not correlated with weight gain/day (r = 0.09) or BMI-SDS (r = -0.04).

Children who presented with Ht-SDS <- 2 (n= 17) had slightly higher height gain SDS (0.15±0.37) compared to those who presented with Ht-SDS >-2 (n = 34) (0.02±0.4) (p: 0.09). Children who presented with BMI-SDS >- 1.5 (n= 26) had an higher BMI-SDS gain (0.12 ±0.29) compared to those who presented with BMI-SDS <-1.5 (n = 25) (0.02 ±0.46) (p: 0.05), with no difference in the Ht-SDS gain between the two groups.

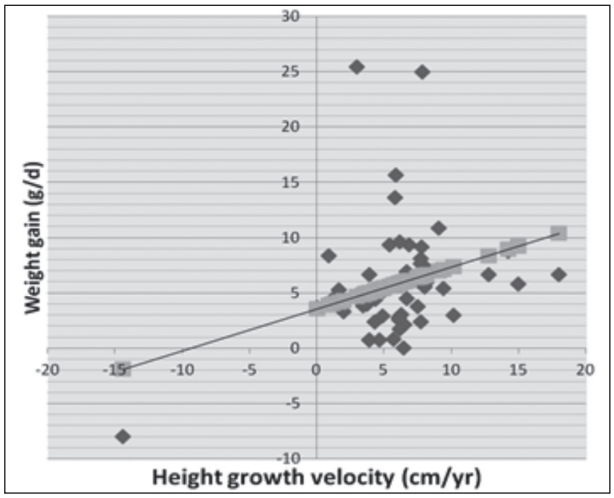


Figure 2. Correlation between growth velocity (cm/y) and weight gain g/day (r = 0.4, P: 0.02)

Table 5 shows the results of Ht-SDS changes after average of 4 and 9 months of treatment. After 4 months, 20 children increased their Ht-SDS and this was associated by decreased BMI-SDS by 0.1. They continued to have a catch- up growth also in the following 9 months of NR (0.2 at 4 months and 0.31 at 9 months associated to a decrease in BMI-SDS, after 4 and 9 months, of 0.12 and 0.13 respectively).

Table 3. Linear growth of children who gained >7g/day during nutritional rehabilitation (NR) (mean±SD)

	Age (yr)	Ht-SDS (1)	BMI-SDS (1)	Ht-SDS (2)	BMI SD (2)	GV cm/y
Wt gain >7 g/day Group A (n = 14)	7.6±3.5	-1.1±1.3 *	-1.5±0.8	1.0±1.2 *	-0.9±0.9 #*	6.9±3.0 #
Wt gain <7 g/day Group B (n = 37)	5.4±3.3	-1.7±1.04	-1.5±1.1	-1.6±0.9	-1.6±1.0	6.0±3.4

Legend: 1 = after 4 months; 2 after 9 months of nutritional rehabilitation (NR). * P: <0.05. group A vs group B; # P: <0.05. after vs before NR

Table 4. Linear growth of children who increased their mass index (BMI) SDS during nutritional rehabilitation (NR) (mean±SD)

Groups	Age	Duration months	Ht-SDS (1)	BMI- SD (1)	Ht-SDS (2)	BMI-SD (2)	GV cm/y
BMI-SDS Gain group (n:28)	6.3±3.5	9.5±2.9	-1.2±1.1	-1.3±1.2	-1.3±1.0	-1.1±1.0 #*	5.7±2.8
BMI-SDS No gain group (n: 23)	5.1± 3.3	8.5±2.4	-2.0±1.1*	-1.2±1.0	-1.8±0.9#*	-1.7±1.0	7.4±3.6*

Legend: 1 = after 4 months; 2 after 9 months. # P: <0.05, after versus before rehabilitation; *P: <0.05 between groups

Table 5. Growth data of children who increased their Height-SDS (Ht-SDS) versus those who did not during nutritional rehabilitation (NR) (mean±SD).

Ht-SDS	Age	Ht-SDS (1)	BMI-SDS (1)	Ht-SDS (2)	BMI-SDS (2)	Δ Ht-SDS (2)	Δ BMI-SDS (2)	Ht-SDS (3)	BMI-SDS (3)	Δ Ht-SDS (3)	Δ BMI-SDS (3)
Increased/ 4 mo. (n : 20)	5.3±3.8	-1.9±1.3	-1.1±1.0	-1.6±1.2	-1.2±1.3	0.3±0.3	-0.1±0.8	-1.6±1.2	-1.2±1.0	0.3±0.3	-0.1±0.5
Not increased 4 mo. (n : 31)	6.3±3.3	-1.3±0.9	-1.8±0.8	-1.5±0.9	-1.7±1.0	-0.1±0.2	0.1±0.6	-1.4±0.8	-1.6±1.0	-0.1±0.2	0.1±0.7
Increased 9 mo. (n : 28)	5.6±3.6	-1.9±1.2	-1.2±0.9	-1.7±1.1	-1.3±1.1	0.1±0.3	-0.1±0.6	-1.6±1.1	-1.3±1.0	0.3±0.3	-0.1±0.5
Not increased 9 mo. (n : 23)	6.3±3.4	-1.0±0.8	-1.9±0.9	-1.3± 0.8	-1.6±1.2	-0.2±0.2	0.2±0.7	-1.3±0.8	-1.5±1.0	-0.2±0.1	0.3±0.7

Legend: 1 = at presentation; 2= after 4 months of NR; 3 = after 9 months of NR

Children who did not increase their Ht-SDS after 4 months on NR (n = 31) had significant increase in BMI-SDS by 0.15. After 9 months of NR, 8 of them increased their Ht-SDS. Those children who didn't show catch up in height (n = 23) had increased BMI-SDS at 9 months of NR.

Discussion

We examined the Ht-SDS in 4 different BMI-SDS categories of prepubertal children. Our study showed that the Ht-SDS of children in groups 1 and 2 (children with mild and moderate/severe underweight) was significantly lower than normal and overweight children. Ht-SDS in obese children was significantly higher compared to the Ht-SDS of normal children.

Our cross-sectional data are reinforced by other studies in underweight and overweight children (26-31).

Pomeroy et al. (32) found that height was positively associated with BMI among urban lowland peruvian children. Freedman et al. (33) reported that relatively tall children had a higher BMI in early adulthood. Other authors show positive correlations between height and adiposity (34-35). Mukuddem-Petersen et al. (36) showed that stunted children living in rural areas and informal settlements, had significantly lower mean BMI than non-stunted children. However this relationship was not supported by others (37).

In support of our findings, Bonthuis et al. (38) studied BMI in children with different height distributions: short stature (mean height SDS: -1.6), normal stature (height SDS: 0), and tall stature (height SDS: +1.6). It was shown that at a given age, BMI was distributed towards lower values in short, and towards higher values in tall subjects as compared to a population with average height distribution.

In our study, the BMI-SDS was highly correlated with Ht-SDS in prepubertal children between 2 and 9 years of age (r = 0.7) (Figure 1). In addition, Kain et al. (39,40) found an association between BMI-SDS and Ht-SDS in a large cohort of children after 3 years of age.

The relation between tall stature (high Ht-SDS) and adiposity (increased BMI) can be explained by accelerated epiphyseal growth plate maturation possibly due to early estrogenization and the action of insulin

on the IGF-1 receptor. IGF-I serum values are higher in obese children compared to normal subjects for both genders. A positive relationship was found between IGF-1 SDS for serum IGF-1 and anthropometric parameters (P <0.0001) with greater effects observed for height than for BMI.In addition, the degree of body fatness may trigger the neuroendocrine events that lead to the onset of puberty; these may explain the findings that obese girls tend to mature earlier than lean girls (41-45).

Nutritional intake is an important systemic factor that strongly modulates growth. Malnutrition transiently inhibits growth, but this resolves with nutritional rehabilitation. The growth rate generally does not just return to normal but rather exceeds the normal rate for chronological age to achieve catch up growth (46). To allow for this catch-up growth, dietitian usually increase both caloric and protein intake, based on the ideal body weigh (IBW) -BMI method or other methods.

Conditional coordination of growth is observed during malnutrition. Malnutrition/undernutrition generally cause widespread inhibition of growth in multiple organs however, body proportions tend to be maintained. When growth-inhibiting conditions resolve (with nutritional rehabilitation), catch-up growth is observed in multiple organs, again tending to maintain body proportions. However, this tendency to maintain body proportions is not absolute. It appears that although the growth rates of different organs are typically affected in the same direction but not to the same extent (47-52).

One of the biological variables with the greatest impact on the long-term health of undernourished children is the recovery of stature. Most studies on growth in malnourished children have focused on weight. However, few studies have also documented a catch-up growth in height after malnutrition, either in the immediate recovery period or in the long term. We analyzed the outcome of our group of underweight children (n = 51) in response to nutritional rehabilitation (NR) according to the changes of weight (weight gain/day and BMI-SDS) and height (Ht-SDS and GV) over the period of 9±2 months.

20/51 of children started their height catch-up after 4 months of NR, whereas 28/52 of children showed increased Ht-SDS, after 9 months of NR. Children who had significant height catch-up did not increase their BMI-SDS. (i.e. the change in height was more than weight gain in the BMI equation). However, children who had weight gain >7 g/d over the whole period of follow-up (average normal weight gain for their average age and gender was 6.5 g/d), (n =14) had significant increase in BMI-SDS and Ht-SDS after versus before NR compared to those who gained weight <7 g/d (n = 37) during the follow up period. These findings suggested that during NR, weight gain more than the average weight gain for age and sex provides enough energy for catch-up in stature .

In our study underweight children who had increased BMI-SDS after NR (n = 28) had higher weight gain per day (8.6±5.8 g/day) versus children who did not increase their BMI-SDS (n = 23) with lower weight gain per day (3.3± 2.2 g/d). The height growth velocity (cm/y) was significantly higher in the latter group (7.4±3.6 cm/yr) versus the former group (5.7±2.8 cm/yr). These data denoted that children, who had faster linear growth velocity, after nutritional rehabilitation, did not increase their BMI-SDS. This effect can be clearly explained by the fact that changes in the BMI-SDS represent the relative changes in weight compared to height. Therefore, an increase of BMI-SDS can occur if an underweight child increases his weight while he is not catching-up in height or if his weight gain is relatively in excess of his height growth. In support of this view, weight gain/day was correlated significantly with height growth velocity (r = 0.4, p: 0.018). Ht-SDS was not correlated with weight gain/day (r = 0.09) or BMI-SDS (r = -0.04). Furthermore, a prospective population-based birth cohort study in Brazil found that the weight gain was positively correlated to length/height gain (height growth velocity) in the same age range (53). Stein et al. (54) analyzed a series of cross-sectional surveys, conducted between 1968 and 2007, in 4 villages in eastern Guatemala. The authors observed an improvement in child growth, as measured by Ht-SDS, without concurrent increases in BMI.

At presentation, our underweight children, who started their catch-up growth as early as 4 months after NR (n = 20/51), were significantly shorter and had a higher BMI-SDS compared to those who did not

show early catch up (Table 5). In addition, our undernourished children with BMI-SDS >-1.5 at presentation, had a significantly better height gain after NR versus those with BMI-SDS <-1.5. In support of our findings, Walker et al. (55) and Doherty et al. (56) reported a catch-up growth in height and knee -heel length in a subgroup of severely malnourished children. On the other hand, Grantham-McGregor et al. (57) did not find any improvement in length /height in the immediate recovery period in their malnourished children. This may be due to the severe degree of malnutrition of their cohort that required longer time to start catch-up.

The number of children who had catch-up in Ht-SDS increased from 20/51 after 4 months of NR to 28 /51 after 9 months of NR. Similarly, Alves et al. (58) studied 51 undernourished children after nutritional rehabilitation. Height catch-up occurred in 39% of children, after 4 months, and in 55% of them after 9 months of NR. Das Neves et al. (59) reported that among their 106 malnourished children, 67.9% recovered in both weight and height after an average of 16.4 months. Almost half of their children presented a nutritional recovery of more than 0.50 in Ht-SDS (46.2%) and about 40% in weight-for-age (WAZ) (38.7%). They also found that a longer treatment was associated with a greater gain in both WAZ and Ht-SDS. Picot et al. (60) reported a significant height gain (0.2±0.33 mm/day) and weight gain (3.7±4.3 g/kg/day) in malnourished children (n = 532) during their first 8 weeks of home-based nutritional rehabilitation.

Long-term studies on height prognosis, after an episode of severe malnutrition, have produced conflicting results. Studies from Guatemala, India, and Brazil have reported that rapid infant weight and length gain are positively associated with subsequent height and lean mass rather than adiposity (61-64). A complete recovery to a normal adult height was reported in some studies (65, 66).

The assumption that full catch-up growth is possible is supported by observations that the retardation of bone maturation is not significantly different from the height retardation (65-71). However, other investigators have suggested that severe malnutrition results in a permanent height deficit (67-70). The discrepancy between the outcome of these studies may be attributed to factors such as the control group with which previously malnourished children were compared, the degree of inadequacy of the home environment to which the children returned after discharge from hospital, and the more general problem that follow-up studies in human subjects cannot be conducted under fully controlled experimental conditions, thereby making isolation of malnutrition as an independent variable practically difficult to assess. However, relatively recent studies reported continuation of catch-up in height for years in malnourished children after NR (72, 73).

In addition, das Neved et al. (59) found that malnourished children (n = 94) who recovered from malnutrition had normal body composition. These results showed that height recovery fostered a normalization of the body composition and was followed by appropriate gain in lean body mass and bone mineral content. Therefore, it reduces the risk of chronic diseases in the adult life for previously malnourished children (59).

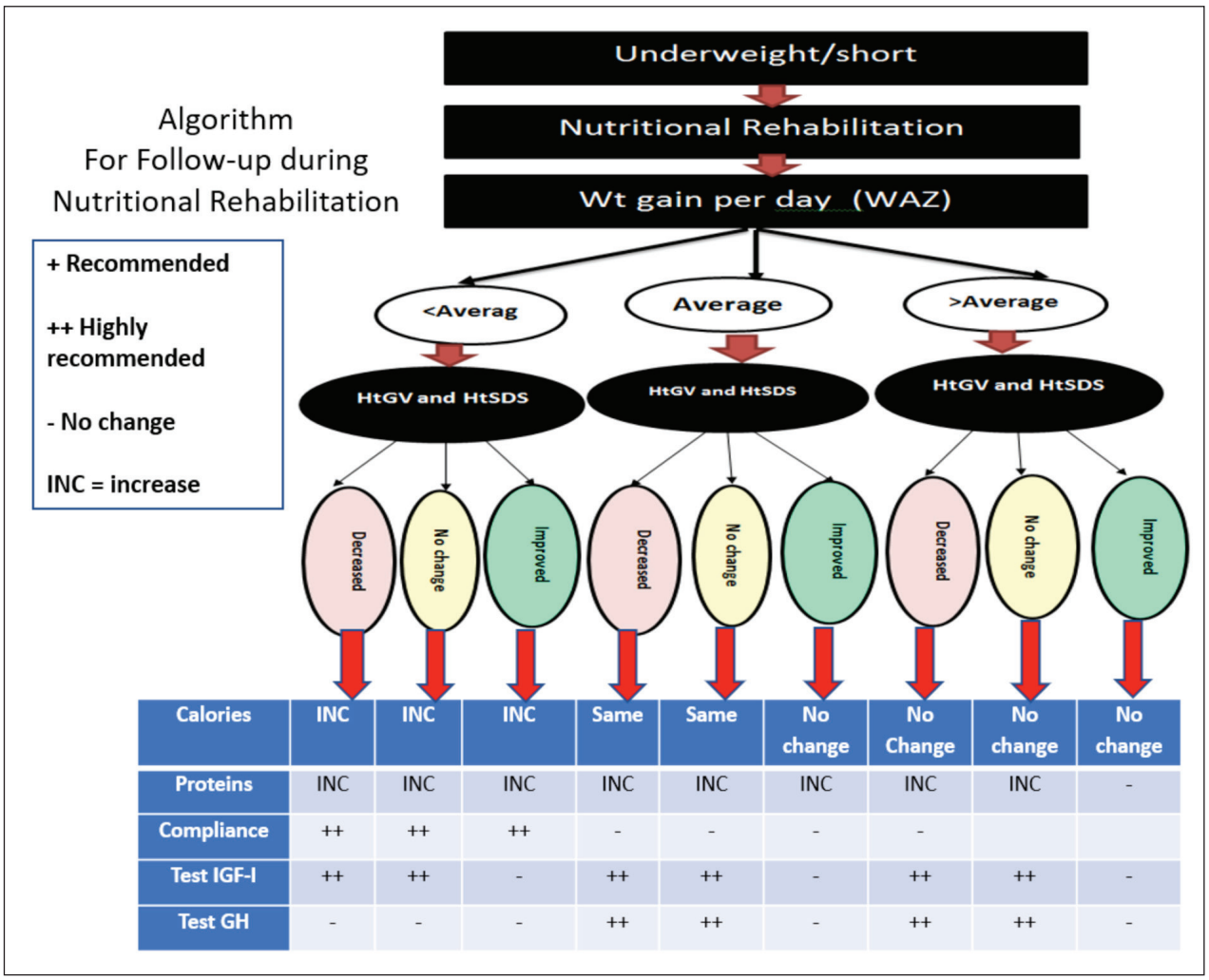
An important question is “why some children increase their height early during recovery of undernutrition while others recover later despite increased BMI and normal weight gain? “ It has been suggested that three different types of catch-up growth can be distinguished (14, 15). In type A, when growth restriction ceases, height velocity increases to such an extent that the height deficit is swiftly eliminated. In type B, when growth restriction ceases, a delay in growth and somatic development persists. However, growth continues for longer than usual, so that ultimately the growth arrest is compensated. This type of catch-up growth has only a small or no increase of height velocity compared with the mean velocity for chronological age. Type C is a mixture of types A and B. When growth restriction ceases, there is an increase in height velocity as well as a delay and prolongation of growth. Although this subdivision of catch-up growth in different types appears reasonable, the borderlines between types A, B, and C are not sharply delineated and in practice a distinction cannot always be made (46-51, 74).

Studies in rats, rabbits, and humans, after various growth-inhibiting conditions, suggest that this local catch-up growth occurs because growth-inhibiting conditions (e.g. malnutrition) slow the normal loss of proliferative capacity in the growth plate. Thus, the

loss of growth capacity in the skeletal growth plate is driven, not simply by time, but rather by growth itself (75-78).

Recent findings suggest that body growth deceleration is driven by a growth-limiting genetic program that occurs in multiple organs. This growth-limiting program, which involves the down-regulation of a large set of growth-promoting genes, depends not simply on age but also on organ growth itself. Therefore, the adult body size limit appears to be imposed by a negative feedback loop. Organ growth leads to progression of a genetic program, which in turn causes growth of the organ to slow and eventually cease. Different organs seem to use different types of information to precisely target the adult body size. This genetic growth-controlling program appears to be important during the growth-limiting periods as well as during catch-up periods (79).

Another fundamental biological variable with the greatest impact on the recovery of stature in undernourished children is the quality of the diet, especially the quality of protein and the essential amino acids consumed, to enable a gain in stature without an unwanted increase in energy provision that might favor the later development of obesity. As an example, a study in children of school age provided a protein-rich diet to one group while a second group received a diet with added oil. The group given a protein-rich diet



Calories	INC	INC	INC	Same	Same	No change	No Change	No change	No change
Proteins	INC	INC	INC	INC	INC	INC	INC	INC	-
Compliance	++	++	++	-	-	-	-		
Test IGF-I	++	++	-	++	++	-	++	++	-
Test GH	-	-	-	++	++	-	++	++	-

Figure 3. Algorithm for follow-up of underweight/ malnourished children based on anthropometric assessment.
Legend: INC = increase, ++ highly recommended, + = recommended; - no change recommended, weight-for-age (WAZ)

exhibited an increase in height directly related to the quantity of supplementary protein, while no detectable effect was present in the group consuming a diet with added oil (80).

It was also shown that the quantities of both protein and energy are important in the regulation of IGF-1, because these factors were essential in the restoration of the serum levels of IGF-1 (81-83). In one study, refeeding with a normo-caloric and normoproteic diet after 5 days of fasting raised the levels of IGF-1 by up to 70% above basal levels before food restriction, meanwhile, refeeding with an iso-caloric but hypoproteic diet delayed the recovery in the levels of IGF-1 by 2 days, and the levels of this hormone failed to reach 50% of the values before restriction. In addition, refeeding with a low calorie and low protein diet, for more than 5 days, reduced the levels of IGF-1 even further (84). In India, Aykroyd and Krishnan (85) found that school children supplemented with skim milk grew faster in height. Malcolm (86) and Lampl et al. (87) showed that a skim milk supplement increased the height of stunted, low-protein-fed children in New Guinea. In the United States, Fomon et al. (88) found that infants fed skim milk (low energy, high protein) showed the same length growth but less weight gain than those fed the high energy formula. In Bangladesh, Kabir et al. (89) found that animal-source protein at 15% energy increased IGF-1 and linear growth more than did animal-source protein at 7.5% protein in children recovering from shigellosis.

A meta-analysis on the effect of protein intake on length gain in low-birthweight infants reported small but measurable effects of higher protein intake on improved linear growth. In very-low-birthweight babies, energy and the protein: energy ratio interacts synergistically to increase IGF-1 at high levels of both. The effect of protein on IGF-1 could be used as a marker of linear growth (90,91).

It has to be mentioned that inadequate compliance with nutrition regulations and/or supplement intake can explain some of the failures to achieve the proper weight gain in a number of our children. More intensive interference including hospital admission and/or tube feeding may be required in these cases.

In summary, different mechanisms and factors appear to control the process of catch-up during recovery from different degrees of undernutrition. Genetic control of catch up in the individual, the degree of his undernutrition at the beginning (BMI-SDS), the quantity and quality (energy: protein) offered during rehabilitation as well as compliance to the nutritional advice all share in the outcome. Frequent monitoring of weight changes (weight gain/day and WAZ), height changes (GV and Ht-SDS) and the BMI-SDS greatly help in tailoring the process of NR.

Based on our findings and literature reports, we suggest an algorithm for follow-up of underweight/malnourished children based mainly on anthropometric assessment (Figure 3).

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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Original article

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 log-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 prepubertal 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-SD 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 diety

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 chronologic 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 chronologic 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, remaing 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 interferring 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: weigh, 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±SD	7.4±3.6	8.3±3.6	0.9±0.1*	6.7±3.1	6.8±2.6	1.1±0.3*
Ht-SDS	Mean±SD	-0.3±1.2	-0.2±1.1	0.1±-0.04 #	0.1±0.9	0.1±0.9	0.01±0.63
BMI	Mean± SD	16.2±2.2	16.2±2.2	0.02±0.02 #	16.1±1.4	16.0±1.6	0.09±0.7
BMI-SDS	Mean± SD	0.3±1.1	-0.3±1.1	0.02±0.5 *#	0.2±0.9 #	0.06±0.9	-0.1±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)

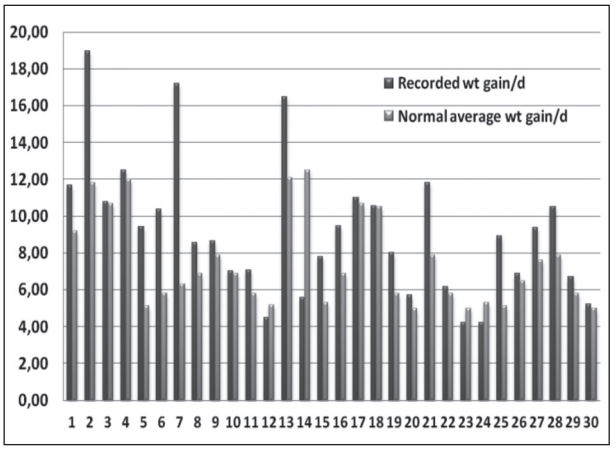

Figure 1. Daily weight gain compare to average normal weight gain for age and sex in celiac disease children on gluten free diet during follow-up (1 year)

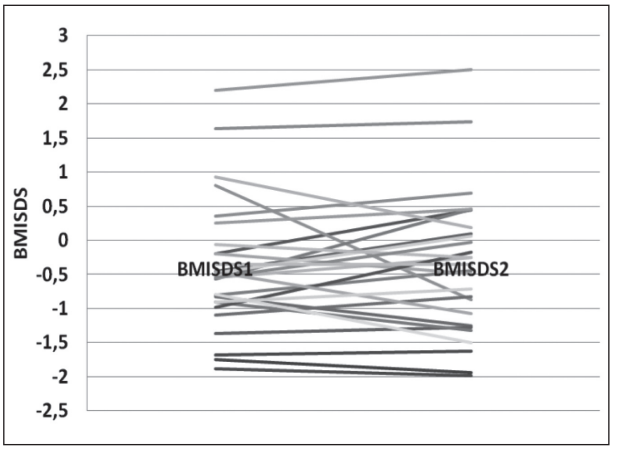

Figure 2A. BMI-SDS changes in children with celiac disease on gluten free diet during follow-up. Legend: 1- Before follow up; 2- After a year of follow up

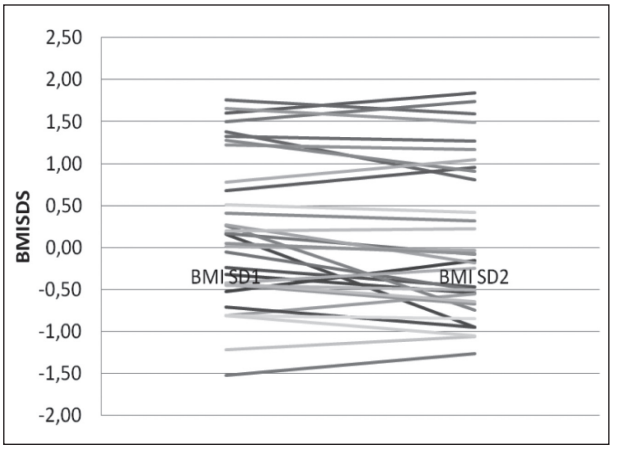

Figure 2B. BMI-SDS changes in the control group. Legend: 1- Before follow up; 2- After a year of follow up

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 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.

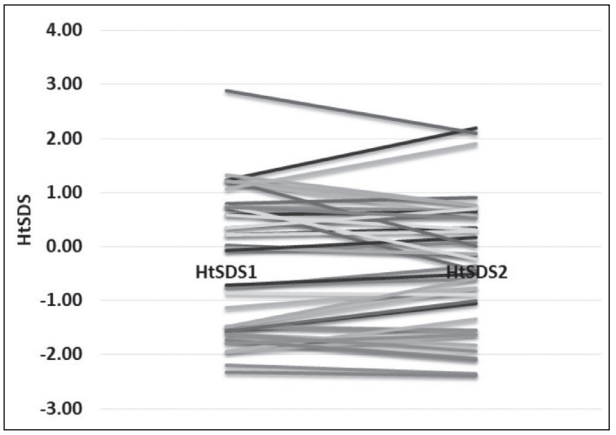

Figure 3A. Height-SDS changes in children with celiac disease on gluten free diet. Legend: 1- Before follow up; 2- After a year of follow up

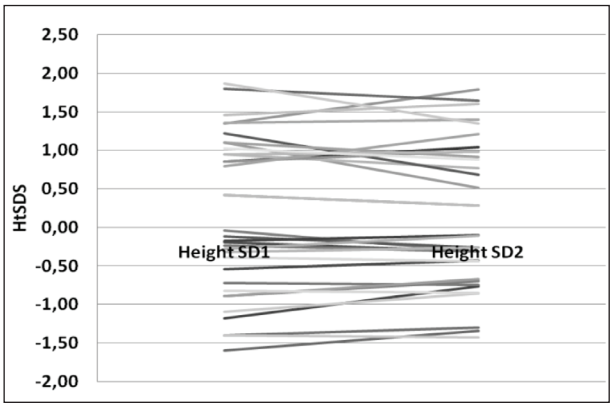

Figure 3B. Height-SDS changes in the control group. Legend: 1-Before follow up; 2- After a year of follow up

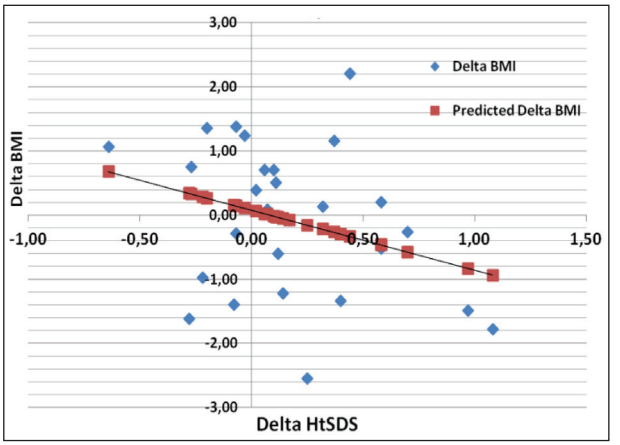

Figure 4. Correlation between Δ height-SDS and Δ BMI (r: 0.31; p: 0.08)

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 adhesion 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 impairement 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± 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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Original article

Postnatal growth of infants with neonatal diabetes: Insulin pump (CSII) versus Multiple Daily Injection (MDI) therapy

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Summary. *Background:* Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life. Their diabetes is associated with partial or complete insulin deficiency with variable degree of intrauterine growth retardation. Insulin therapy corrects the hyperglycemia and results in improvement of growth. However, no studies have reported the longitudinal growth of these infants (head circumference, length and weight gain) after starting insulin therapy. *Patients and methods:* We assessed the growth parameters weight (Wt), Length (L) and head circumference (HC) in 9 infants with PNDM, during the first 2 years of their postnatal life. Five infants were on insulin pump therapy (CSII) and 4 were on multiple doses of insulin injection (MDI) therapy. *Results:* On insulin therapy for 20±4 months catch-up growth occurred in the majority of infants. L-SDS increased from -1.45 to -0.65 , HC-SDS from -2.3 to - 0.51 and Wt-SDS increased from -1.94 to - 0.7 at the end of the 20±4 months of age, after starting insulin therapy. Two out of 9 infants had a L-SDS <-2 , in 4 Wt-SDS was <-2 and in 1 the HC-SDS was <-2 at at 20±4 months of postnatal growth. The level of HbA_{1c} was lower in infants on CSII compared to those on MDI (9.6±1%) compared to those on MDI (10.2±2%). However, growth parameters improved significantly in both groups (CSII and MDI) with no significant difference among them. *Conclusions:* Infants with PNDM with positive anti-GAD and antiTPO were diagnosed later and their intra-uterine and postnatal growth differed compared to those with negative antibodies. The majority of infants with PNDM exhibited significant catch up growth within the first two years of life irrespective of the etiology of diabetes. HbA_{1c} appeared to be better in infants with PNDM on CSII therapy when compared to those on MDI therapy. (www.actabiomedica.it)

Key words: permanent neonatal diabetes mellitus, multiple daily injections, growth parameters, body mass index

Introduction

Diabetes mellitus occurs in about 1 in 400,000 newborn infants in the first few months of life. However, in about half of these babies have a permanent form of diabetes mellitus (PNDM) (1).

Insulin deficiency leads to hyperglycemia, glycosuria with excessive loss of fluids and energy that leads to dehydration, failure to thrive and ketosis. In some cases, infants with PNDM also have certain neurological problems, including developmental delay and recurrent seizures. This combination of developmental delay, epilepsy, and neonatal diabetes is called DEND syndrome (1-6).

A small number of individuals with permanent neonatal diabetes mellitus have pancreatic aplasia or

hypoplasia. In these cases insulin and other pancreatic hormones as well as the digestive enzymes may be affected. Defective pancreatic enzymes lead to malabsorption with fatty stools and an inability to absorb fat-soluble vitamins (7, 8).

PNDM may be caused by mutations in several genes. In about 90 percent of these cases, the condition results from new mutations in the gene and occurs in people with no history of the disorder in their family. About 30% of individuals with PNDM have mutations in the KCNJ11 gene. An additional 20% of people with PNDM have mutations in the ABCC8 gene. These genes provide instructions for making parts (subunits) of the ATP-sensitive potassium (K-ATP) channel. Each K-ATP channel consists of eight subunits, four produced from the KCNJ11 gene and four from the ABCC8 gene. Mutations in the INS gene, which provides instructions for making insulin, have been identified in about 20% of individuals with PNDM. Mutations in the INS gene are believed to disrupt the cleavage of the proinsulin chain or the binding of the A and B chains to form insulin, leading to impaired blood sugar control. In addition, PNDM can also be caused by mutations in other genes, some of which have not been identified (9-14).

Insulin therapy is crucial in PNDM to obtain satisfactory weight gain and growth in these infants. A variety of methods for providing insulin such as: intravenous infusion, short–acting and long–acting subcutaneous injections, or continuous subcutaneous insulin infusion (CSII) can be used. Some authors recommended subcutaneous injection of ultralente insulin, rather than lente or isophane (NPH) insulin to avoid hypoglycemia during treatment. However, there is currently no license for its use in this age group. Insulin glargine treatment is suggested, because of its flat pharmacokinetic profile which might prove useful in this condition.

In some centers in Europe, the use of CSII in all cases of neonatal diabetes mellitus is proposed, stating that during the neonatal period, CSII therapy is safe, more physiological, more accurate and easier to manage than insulin injections (15-19).

Infants with PNDM have higher risk for defective growth because for many reasons. They lack the intrauterine anabolic effect of insulin and born small for gestational age. In addition, difficult control of their hyperglycemia may adversely affect their weight gain and linear growth. The presence of other congenital abnormalities like pancreatic aplasia or epilepsy may also compromise normal growth. However, there is scarce information about longitudinal growth of infants with PNDM (4, 18). No study assessed the growth of these infants after inulin treatment using multiple daily Injections versus CSII therapy.

The present study aimed to evaluate the growth parameters in relation to diabetes control in all children with PNDM diagnosed at Hamad General Corporation (HMC) of Doha, (Qatar).

Patients and methods

Children diagnosed with PNDM within the first 6 months of life, attending to the Diabetes Clinic of Hamad General Hospital of Doha (Qatar) between January 2006 and January 2016 were enrolled in the study. The study protocol was approved by the ethical committee of Hamad Medical Centre.

The longitudinal growth data [weight (wt), length (L) and head circumference (HC)] at the time of the diagnosis and after 12 and 24 months were recorded. Their diabetes control, monitored by the level of HbA_{1c} every 3-4 months, was also recorded. Their insulin requirement and the mode of insulin delivery (pens versus pump) were evaluated Exclusion criteria included infants diagnosed with Type 1 DM after 6 months of life and those with other congenital abnormalities or systemic disorders. Growth data were correlated to birth size, mid-parental height-SDS and average HbA_{1C} concentration. The growth data published by the WHO were used as reference for our infant's growth.

Patient anthropometric data are presented as means±SD and were compared to the appropriate population (WHO) growth standards of the same age and sex. Correlations between anthropometric and clinical variables were assessed using linear regression equations. A p value of <0.05 was considered to be statistically significant (20).

Results

At the age of diagnosis (2.7±1.9 months), our infants with PNDM (5 males and 4 females) had persistent hyperglycemia which continued for more than 6 months and required early insulin therapy.

They were born from a consanguineous marriage. None had clinical or immunological evidence of congenital viral infection.

Five infants were treated with insulin pump (CSII) and 4 with MDI, using Detemir and Humalgue insulin.

At presentation, all infants with PNDM had low or absent circulating C-peptide (0.45±0.53 ng/ml; normal range: 0.9-4 ng/ml) and low insulin levels (1.54±1.7 µU/ml; normal values: 14.6±7.2 - mean 8 µU/ml) during the episodes of hyperglycemia. Their mean HbA_{1C} concentration was 8.82±0.96 % (normal values: 5.3±0.24 %, range 4.8-6.0%). One infant had a low free thyroxine level and a high thyroid-stimulating Hormone (TSH) value. All patients were negative for anti-tissue transglutaminase. During the observational period of study, none of them had exocrine pancreatic deficiency or developmental delay.

In 4 out of 6 infants with negative anti-GAD antibodies, genetic testing did not document mutations in the *ABCC8* and *KCNJ11* genes encoding respectively the SUR1 and Kir6.2 subunits of the voltage-dependant potassium channel.

At diagnosis, the 9 infants with PNDM had compromised growth (Wt-SDS: -1.9±1.5, L-SDS: -1.46±1.2, and HC-SDS: -2.3±0.89). On insulin therapy, for 20±4 months, catch-up growth occurred in most infants. At the end of the second year of life, Wt-SDS increased from -1.94 to -0.7, L-SDS increased from -1.46 to -0.65, and HC-SDS from -2.3 to -0.51. Two out of 9 had LSDS <-2 and 4 had Wt-SDS <-2, and 1 infant had HC-SDS <-2 at 20±4 months of postnatal growth. (Figures 1 and 2). The HC-SDS was the most affected growth parameter at diagnosis (HC-SDS = -2.2) with a catch-up of 1.7 SD in the first 20 months of insulin therapy. WT-SDS was also markedly affected at diagnosis (Wt-SDS = -1.95) with significant improvement of 1.22 SD on insulin therapy. Length SDS improved 0.79 SD during the 20 months of insulin therapy (Table 1, Figures 1 and 2).

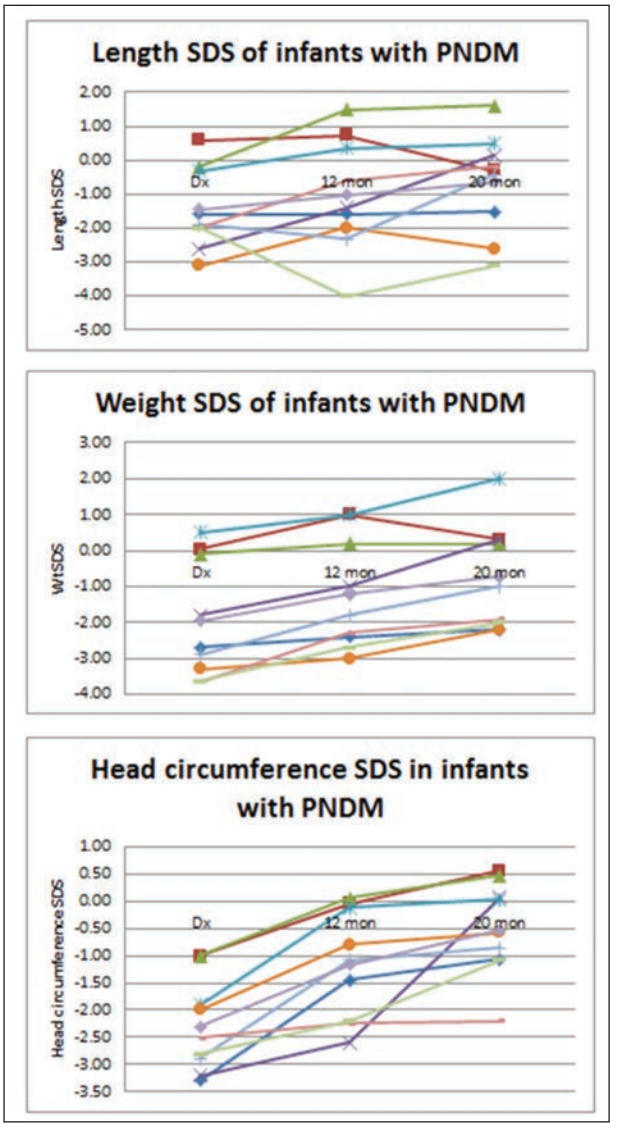

Figure 1. Growth parameters in infants with neonatal diabetes mellitus (PNDM) on insulin therapy

All infants with positive antibodies were diagnosed between 2 and 6 months of age. The diagnosis of PNDM was later in infants anti-GAD negative. The birth size (L, Wt and HC) of infants with PNDM, positive anti- GAD and anti-TPO antibodies (n= 4) was markedly better than those without antibodies. Both groups had improved growth during insulin therapy (Table 2, Figure 3).

The average HbA_{1c} of infants on insulin pump (CSII) therapy (n = 5) was significantly lower than

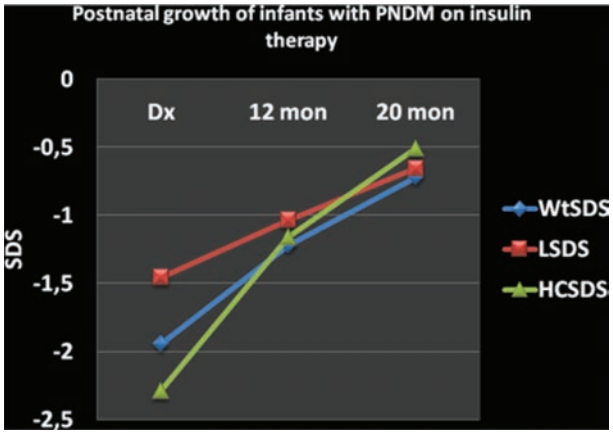

Figure 2. Growth parameters in infants with permanent neonatal diabetes mellitus (PNDM) on insulin therapy (mean values)

Table 1. Postnatal growth parameters in infants with permanent neonatal diabetes mellitus (PNDM)

Postnatal Growth	At diagnosis	At 12 months	At 20±4 months
Wt-SDS	-1.9456	-1.2211	-0.7222
L-SDS	-1.4556	-1.0367	-0.6567
HC-SDS	-2.2889	-1.1611	-0.5111
Growth MDI vs Pump			
L-SDS (Pump)	-1.28	-1.01	-0.80
L-SDS (MDI)	-1.68	-1.07	-1.07
Wt-SDS (Pump)	-1.95	-1.12	-0.62
Wt- SDS (MDI)	-1.94	-1.12	-0.95
HC-SDS (Pump)	-2.22	-1.11	-0.72
HC-SDS (MDI)	-2.38	-1.22	-0.25

Legend: Weight (Wt), Length (L) and head circumference (HC). MDI: multiple doses of insulin injection

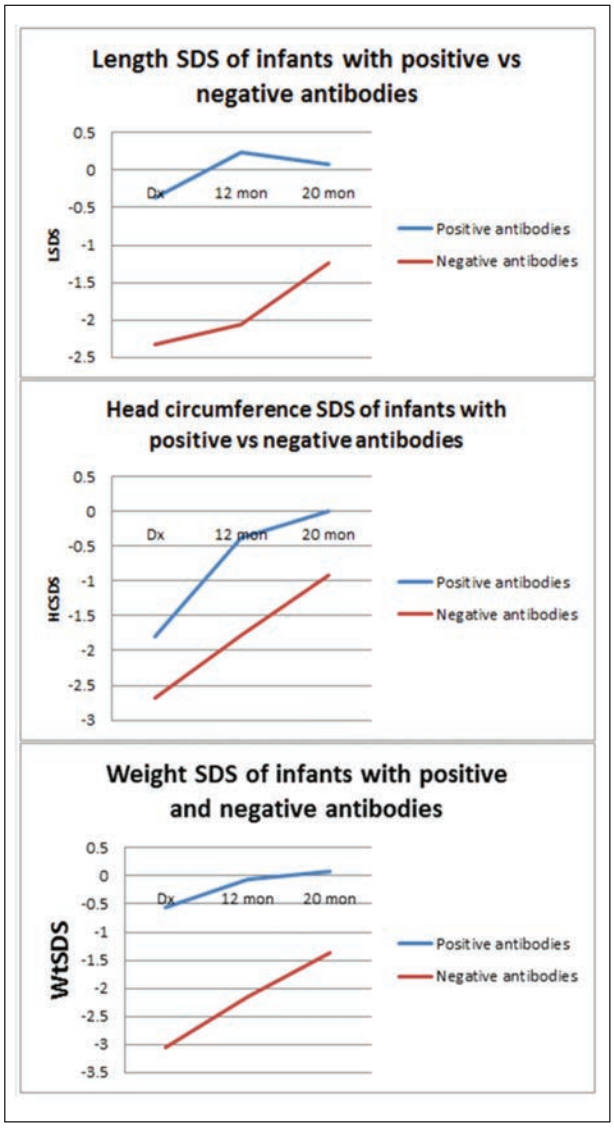

Figure 3. Growth parameters in infants with permanent neonatal diabetes mellitus (PNDM) with positive versus negative antibodies

Table 2. Postnatal growth in infants with permanent neonatal diabetes mellitus (PNDM), positive and negative antibodies

Wt-SDS	At diagnosis (Dx)	At 12 months	At 20±4 months
Positive antibodies	-0.5625	-0.05	0.075
Negative antibodies	-3.05	-2.16	-1.36
L-SDS	Dx	At 12 months	At 20±4 months
Positive antibodies	-0.375	0.2425	0.075
Negative antibodies	-2.32	-2.06	-1.242
HC-SDS	Dx	At 12 months	At 20±4 months
Positive antibodies	-1.8	-0.385	0.005
Negative antibodies	-2.68	-1.782	-0.924

Legend: Weight (Wt), Length (L) and head circumference (HC)

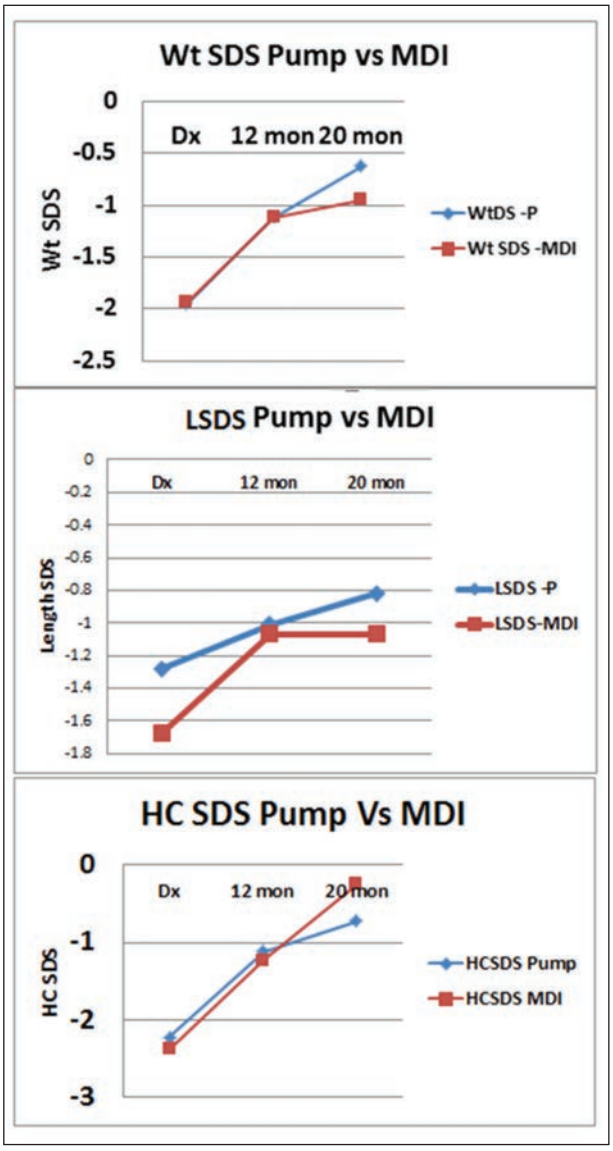

Figure 4. Growth in infants with neonatal diabetes mellitus (PNDM) on insulin pump versus multiple doses of insulin injection (MDI). Legend: Weight (Wt), Length (L) and head circumference (HC).

those on MDI (n = 4) (9.6±1% versus 10.2±2%, respectively). The mean Wt-SDS and L-SDS of infants on pump therapy were higher than those on MDI. However, the differences did not achieve a statistical significance (p = 0.09 and 0.15, respectively), probably due to the small number of patients (Figure 4).

HbA_{1c} at 20 months of age was correlated significantly with L-SDS and HC-SDS (r: -0.55 and -0.43, respectively; p<0.01).

Discussion

Permeant neonatal diabetes mellitus (PNDM) is defined as persistent hyperglycemia (plasma glucose concentration >150-200 mg/dL) in infants younger than age six months. Neonatal diabetes mellitus (NDM) is an infrequent cause of hyperglycemia in the newborn period. Typically, infants are of low birth weight and develop hyperglycemia requiring exogenous insulin within the first 6 weeks. Intrauterine growth retardation, failure to thrive, fever, dehydration, hyperglycemia, acidosis with or without ketonuria are the clinical features of the disease.

In-utero growth retardation is due to loss or defective insulin secretion by the fetal pancreas that negative affect fetal growth and metabolism especially during the last half of gestation. All our patients with PNDM, with negative anti-GAD antibodies reported here had intrauterine growth retardation and had low levels of insulin and C-peptide (21, 22).

Our PNDM patients with negative antibodies presented with growth retardation at birth, as well as in other studies, denoting impaired intrauterine growth. Insulin-like growth factor 1 (IGF-1) axis is the major hormonal mediator of growth in utero, and levels of IGF-1 are often very low after preterm birth (23, 24). Umbilical cord IGF-1 concentrations reflect fetal IGF-1 levels at birth and correlate with birth weight. Cord serum IGF-1 concentrations are lower following intrauterine growth restriction. Infants with NDM have low concentration of IGF-1 that improves on insulin therapy (25-29).

In the majority of our infants with PNDM, the correction of insulin deficiency state lead to significant catch up growth in all growth parameters (Wt, L, and HC). In the newborn infant, hepatic IGF-1 generation is controlled by nutrition and insulin and not dependent on growth hormone secretion. The acid labile subunit levels are reduced, and this means that much of the circulating IGF-1 is in binary complexes. Insulin through IGFBP-1 plays an important role in regulating IGF-1 bioactivity. Finally there is evidence, that in the newborn infant IGF-1 signaling through the IGF1 receptor may have a role in maintaining pancreatic β-cell function. We can assume that insulin therapy increased linear growth in our patients with

PNDM through its effect on IGF-1 secretion and indirectly through improving nutrition (4, 5, 29).

As a result of the scarcity of PNDM case reports, no universal clinical guidelines exist for PNDM. Though genetic etiologies of many cases of PNDM have been identified, there has been no consensus on its management. Various modalities reported as effective include oral sulfonylureas, intravenous regular insulin, continuous subcutaneous insulin infusion pump therapy, neutral protamine Hagedorn (NPH) insulin, and subcutaneous insulin glargine (30-32).

The treatment of neonatal hyperglycemia must be based on the diagnosis and suspected etiology of the condition in each case. If severe hyperglycemia persists, exogenous insulin administration may be warranted. Guidelines about when to use insulin treatment and how to provide this form of therapy remain highly controversial and vary widely among clinicians and institutions. The treatment is complex because: 1) dietary compromises the caloric provision; 2) there is a lack of a pharmacokinetic profile for subcutaneously administered insulin in neonates; 3) the use of small insulin doses are highly error-prone; 4) there are limited data for dilution of commercially available insulin formulations; and 5) there is a lack of subcutaneous fat deposits in a small gestational age (SGA) neonate for the subcutaneous insulin administration (33-36). Furthermore, hypoglycemia is a potentially severe problem if insulin is administered through a single IV line.

Insulin Detemir is a long-acting basal insulin analogue manufactured by recombinant DNA technique. The prolonged action of insulin Detemir is the result of reversible binding of the fatty acid residue to serum albumin, which slows release of active insulin monomers into systemic circulation following subcutaneous injection. From a pharmacokinetic perspective, the duration of action of insulin Detemir is dose-dependent, ranging from 5.7 to 23.2 hours, with onset of action at approximately 1 to 3 hours and with peak effect occurring between 3- and 10-hours post-administration. Lack of subcutaneous fat and /or hypoalbuminemia could have profound effects on the pharmacokinetics of insulin Detemir. No studies have evaluated the efficacy in terms of release pattern or stability of diluted long-acting insulin products. However, our 4 infants with PNDM had fairly good response to Detemir (basal) twice daily and lispro insulin (at prandial time) (37, 38).

Continuous subcutaneous insulin infusion (CSII) in our 5 cases of PNDM proved effective with lower HbA_{1c} concentration compared to MDI therapy. CSII can control blood glucose with few hypoglycemic events, which are particularly frequent and dangerous at this age. Infants tolerated the subcutaneous infusion lines well and we did not observe any side effect. In addition, postnatal linear growth appeared better compared to MDI (L-SDS and Wt-SDS). Therefore, our result support the safety and benefit of CSII reported in other studies in treating this group of infants (39,40).

In summary:

Infants with positive anti-GAD antibodies were diagnosed between 2 and 6 months of age. The diagnosis of PNDM was later in anti-GAD negative infants. Infants with PNDM who had positive anti-GAD and anti-TPO were diagnosed later that those negative for antibodies and they had also a different growth pattern. Insulin therapy using CSII appears to be better than MDI in treating PNDM infants because of achieving lower HbA_{1c} levels.

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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Original article

Prevalence of thyroid dysfunctions in infants and children with Down Syndrome (DS) and the effect of thyroxine treatment on linear growth and weight gain in treated subjects versus DS subjects with normal thyroid function: a controlled study

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Summary. *Background:* Individuals with Down syndrome (DS) are at an increased risk of developing thyroid disease, primarily autoimmune, with a lifetime prevalence ranging from 13% to 63%. Unfortunately, there are few studies systematically examining the frequency of thyroid disease in very young children. *Aim of the study:* The aim of the present study was to investigate the prevalence of different thyroid dysfunctions (TD) in a cohort of infants and children with DS and the growth parameters in subjects with normal versus abnormal thyroid function, followed for 3 years. *Patients and methods:* All children (n = 102; 48 males and 54 females, aged 2.3±3 years) with the diagnosis of DS who were seen at the General Pediatric Clinic of Hamad General Hospital in Doha (Qatar) from 2014 to 2018 were enrolled in our study. We recorded thyroid function and linear growth parameters [BMI, length/height SDS (Ht-SDS) and weight gain/day] and divided them into 3 groups according to their thyroid function. Group 1: (n = 36 subjects) with normal free T4 (FT4) and TSH; Group 2 (n = 44 subjects) with high TSH >5 and <12 mIU/L, and normal FT4, and Group 3 (n = 22 subjects) with TSH >12 mIU/L and/or FT4 <9 pmol/L. We also compared linear growth parameters in subjects with DS and thyroid dysfunction versus those with normal thyroid function at diagnosis and after treatment with L- thyroxine, for an average of 3 years. *Results:* In infants with DS (<1 year of age; n = 47, mean age: 5±3.5 months) we documented a higher prevalence of hypothyroidism (HT) (7/47 = 14.9%), both primary (5/47; 10.6%) and secondary (2/47; 4.3%). Subclinical hypothyroidism and positive thyroid antibodies were found in (13/47; 27.7%) and (9/47;19%, respectively). Before treatment with L-thyroxine, DS infants of Group 3 had significantly lower BMI-SDS but were not significantly shorter compared to other two Groups (p= 0.03 and p =0.14, respectively). After an average of 3 years of treatment the BMI- SDS and Ht-SDS did not differ among the treated and not treated infant groups. In the older group (>1 year; n=55; mean age: 5.5±3.3 years) primary HT was detected in 7/55 (12.7%). Subclinical HT was diagnosed in 20/55 (36.4%) and positive thyroid antibodies were found in 26/55 (47.3%). Before treatment with L-thyroxine, using the CDC growth charts for DS, we found that the groups with high TSH (Groups 2 and 3) were significantly shorter and heavier compared to the group with normal TSH (Group 1). After treatment with L-thyroxine, the Ht-SDS and Wt-SDS did not differ between the two groups. The linear growth of those diagnosed early during the first year of life was compared to growth parameters of children who were diagnosed with thyroid dysfunction later in life. *Conclusion*: Our data provided more evidence to support the findings that L- thyroxine treatment can improve growth of infants and young DS children with high TSH (>5 mIU/L), especially in those with TSH >12 mIU/L. (www.actabiomedica.it)

Key words: Down syndrome, thyroid function, growth, L- thyroxine treatment, associated morbidities

Introduction

Down syndrome (DS) is one of the most common encountered human chromosomal disorder.

It occurs in ~1 in 700 births in the United States and is associated with a spectrum of physical and cognitive disabilities (1).

Advances in medical care, and increased access to care, have improved health and well-being of individuals with DS in the United States such that life expectancy has risen from 35 years in 1982 to 53 years in 2007 (2, 3).

However, DS subjects are at an increased risk of developing thyroid disease, primarily autoimmune, with a lifetime prevalence ranging from 13% to 63% (4). Beyond the newborn period, the incidence of elevated TSH values in DS increases and has been reported to be as high as 85% of infants under the age of 12 months (5). Sub-clinical hypothyroidism (SH) was the most common thyroid abnormality detected in children with DS by Unachak et al. (6).

Nevertheless, there are few studies systematically examining the frequency of thyroid disease in very young children and the effects of L-thyroxine treatment in subjects with DS with SH (7-11). Recently, it has been shown that the best cut-off level for prediction of persistent hypothyroidism for initial TSH level was 11.6 mIU/L.

The aim of the present study was to investigate the prevalence of different thyroid dysfunctions (TD) in a cohort of infants and children with DS and the growth parameters in DS subjects with normal versus abnormal thyroid function.

Patients and methods

DS infants and children (n = 102; 48 males and 54 females; aged 2.3±3 years) followed at the General Pediatric Clinic of Hamad General Hospital of Doha (Qatar), from 1-1-2014 to 1-1-2018, were enrolled in the study. Thyroid tests, including free thyroxine (FT4), thyroid stimulating hormone (TSH), anti TPO antibodies (thyroperoxidase), and growth parameters [weight, height, BMI, lenght/height SDS (Ht-SDS)] were assessed and registered in all subjects.

The diagnosis of thyroid dysfunctions were based on the following criteria:

1. Primary hypothyroidism (HT) is diagnosed when FT4 was <9 pmol/L, and TSH is >5 mIU/mL
2. Subclinical hypothyroidism (SH) was diagnosed when FT4 is normal, and TSH is >5 mIU/mL and <12 mIU/L .
3. Central hypothyroidism (CH) was diagnosed when FT4 is <9 pmol/l and basal TSH is low or normal.

Infants and children with DS were divided into 3 groups according to their thyroid function. Group1: n = 36 infants /children with normal FT4 and TSH; Group 2: n = 44 infants/children with high TSH >5 and <12 mIU/L, and normal FT4; Group 3: n = 22 infants/ children with TSH >12 mIU/L and/or FT4 below the lowest normal range (<9 pmol/L).

Children with high TSH >5 mIU/l and /or FT4 <9 pmol/L were treated with L-thyroxine.

Linear growth parameters in infant and children with DS and thyroid dysfunction were compared, at diagnosis and after treatment with L- thyroxine for an average of 3 years, to DS infants/children with normal thyroid function .

Growth charts for DS subjects were used to assess growth parameters (12).The longitudinal linear growth of patients diagnosed with thyroid dysfunction, during the first year of life, was also compared to linear growth of those diagnosed with thyroid dysfunction later in life.

FT4 was measured by radioimmunoassay, and TSH was measured by immune-radiometric assay using kits purchased from Genprice Inc, Santa Clara, CA 95054. The inter-assay and intra-assay coefficients of variations of FT4 were 6.6%, and 3.9%, respectively, and those of TSH were 6.1%, and 2.4%, respectively. The normal range for FT4 was 9.5 -17.5 pmol/L and TSH was 0.25-4.5 mIU/L.

Student- t test was used to compare the growth and lab variables when the data was normally distributed and the Mann-Whitney U test was used when the data were not normally distributed. Linear correlation 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 prevalence of thyroid disorders in 102 infants and children with DS is shown in table 1. Congenital hypothyroidism was diagnosed in 3/102 children by neonatal screening program. The prevalence of thyroid dysfunction, both HT and SH, did not differ significantly between DS infants <1 year of age and >1 year of age. The prevalence of positive thyroid antibodies (TPO) was significantly higher in the older group of DS subjects. Central hypothyroidism was diagnosed in 2/47 infants with DS but not in the older group. The prevalence of HT (low FT4 and/or high TSH) was higher in females compared to males (29 versus 18 subjects). Primary hypothyroidism occurred in 7 out of 68 of DS children with congenital heart disease (CHD) and in 5 out of 46 DS children without CHD.

Thyroid function did not differ between the two groups of DS subjects with and without CHD (FT4 = 13.8±3.2 and 13.6±4.8 pmol/L, respectively) .

Table 2 shows the TSH and FT4 values before and after treatment in infants and children with DS, and the mean dose of L- thyroxine used during the follow up period (~3 years). After treatment with L-thyroxine the TSH and FT4 levels did not differ significantly between the two groups of DS infants and children (treated with L- thyroxine versus normal thyroid function).

Before treatment with L-thyroxine, DS infants of Group 3 had significantly lower BMI-SDS but were not significantly shorter compared to other two Groups of DS subjects (p = 0.03 and p = 0.14, respectively). After an average of 3 years of treatment with L-thyroxine the BMI-SDS and Ht-SDS did not differ among the treated and not treated infant groups (Table 3).

Table 1. Prevalence of thyroid dysfunction in infants and children with Down Syndrome (DS) and associated disorders

	DS <1 yr	DS >1 yr	Total	P value
Number	47	55	102	
Age (years); mean and SD	0.5 ±0.3	5.5 ±3.5	2.3 ±3	
Primary hypothyroidism (low FT4 pmol/L and/or TSH >12 mIU/L)	5/47 (10.6%)	7/55 (12.7%)	12/102 (11.8%)	0.74
Central hypothyroidism	2/47 (4.4%)	0	2/102 (1.96%)	0.12
TSH >5 and <12 mIU/L (subclinical hypothyroidism)	13/47 (27.7%)	20/55 (36.4%)	33/102 (32.4%)	0.34
Positive anti thyroid antibodies (TPO)	9/47 (19%)	26/55 (47.3%)	35/102 (34.3%	0.003
Type 1 diabetes mellitus	1/47 (2%)	1/55 (1.8%)	2/102 (1.96%)	0.91
Congenital Heart Disease (CHD)	36/47 (76.6%)	26/55 (47.3%)	62/102 (60.8%)	0.0025

Table 2. Thyroid function (Mean ± SD) in 2 groups of Down Syndrome (DS) subjects before and after treatment with L- thyroxine versus DS subjects with normal thyroid function

Groups		Age (1) yr	TSH (1) mIU/L	FT4 (1) pmol/L	L-thyroxine µg/day	Age (2) yr	FT4 (2) mIU/L	TSH (2) pmol/L
TSH >12 mIU/L or FT4 <9 pmol/L	Mean	3.86	50.75	10.93	34.38	7.73	13.85	6.05
Treated	SD	5.63	38.80	3.47	16.93	5.52	2.14	4.00
TSH >5 and <12 mIU/L	Mean	2.88	9.50	13.88	29.32	8.88	14.29	6.14
Treated	SD	2.70	4.83	4.13	9.34	5.04	4.00	3.80
Normal thyroid function	Mean	1.64	4.80	15.16	NT	4.15	14.16	5.77
	SD	2.03	2.06	3.33	NT	2.81	2.45	2.73
p value		0.077	0.000035	0.0032	0.65	0.0008	0.973	0.45

Abbreviations: 1 = before treatment, 2 = after treatment with L-thyroxine

In the older group of DS subjects (>1 year; n = 55; mean age: 5.5±3.3 years) HT was detected in 7/55 (12.7%). Subclinical HT was diagnosed in 20/55 (36.4%) and positive thyroid antibodies were found in 26/55 (47.3%). Before treatment with L-thyroxine, using the CDC growth charts for DS (8), we found that the groups with high TSH (Groups 2 and 3) were significantly shorter and heavier compared to the DS group with normal TSH (Group 1). After treatment with L-thyroxine, the Ht-SDS and Wt-SDS did not differ between the two groups (Tables 4 and 5).

The dose of L- thyroxine did not correlate with

Table 3. Anthropometric data (Mean± SD) in the 2 groups of infants (<1 year) with Down Syndrome (DS) before and after treatment with L-thyroxine compared to DS of Group 1 (normal thyroid function)

Groups		Age (1) (yr)	Ht-SDS (1)	BMI-SDS (1)	Age (2) (yr)	HT-SDS (2)	BMI-SDS (2)	Delta Lenght-SDS	Delta BMI-SDS
TSH >5 and <12 mIU/L	Mean	0.48	-1.46	-1.04	4.4*	-1.99	0.43	-0.53	1.43
Treated	SDS	0.38	1.28	1.38	4.25	0.81	1.14	1.16	1.63
TSH >12 mIU/L	Mean	0.29	-2.43	-2.77*	4.4*	-2.24	0.69	0.20	3.46#
Treated	SDS	0.31	1.70	1.76	4.69	0.74	0.75	1.72	2.33
TSH <5 mIU/L	Mean	0.54	-1.75	-0.99	2.5*	-1.82	0.33	-0.07	1.32
Not Treated	SDS	0.39	2.51	1.33	1.00	1.53	1.62	1.43	2.14

Abbreviations: 1 = before treatment, 2 = after treatment with L-thyroxine .*p <0.05 Wilcoxon test before vs after; # p <0.05 ANOVA test between the 3 groups.

Table 4. Anthropometric data (Mean± SD) in 2 groups of children with Down Syndrome (DS) (>1 yr) with high TSH before and after treatment with L-thyroxine compared to DS subjects with normal thyroid function

Groups		Age-1 (yr)	Ht-SDS (1)	BMI-SDS (1)	Age-2 (yr)	Ht-SDS (2)	BMI-SDS (2)	Δ Ht-SDS	Δ BMI-SDS
TSH >12 mIU/L or FT4 <9 pmol/L	Mean	3.86	-2.15	-0.77	7.73	-2.39	0.66*	-0.24	1.43
Treated	SD	5.63	1.46	2.63	5.52	1.01	1.69	1.32	2.49
TSH >5 and <12 mIU/L	Mean	2.88	-1.57	0.38	8.88	-2.18	1.37*	-0.62	1.23
Treated	SD	2.70	1.04	1.82	5.04	1.27	1.98	1.09	3.25
Normal thyroid function	Mean	1.64	-1.90	-0.13	4.65	-2.08	0.59*	-0.17	0.69
	SD	2.03	1.36	1.68	2.81	0.93	1.48	0.97	1.41
P value		0.08	0.1182	0.089	<0.00	0.47	0.29	0.21	0.28

Abbreviations: 1 = before treatment, 2 = after treatment with L-thyroxine

Table 5. Anthropometric data (Mean ± SD), using Down Syndrome (DS) growth curves, in infants and children with DS with high TSH before and after treatment compared to DS subjects with normal thyroid function (Group 1)

	Age-1	Ht- SDS (1)	Weight- SDS (1)	Age -2	Ht- SDS (2)	Weight- SDS (2)
Treated group	3.8	-1.85	1.05	8.3	-0.8 #	0.95
N =47	2.4	0.9	0.7	3.8	0.42	0.6
Untreated group	2.5	-1.5	0.6	4.7	-0.7 #	1.03 #
N= 55	2.9	0.81	0.4	3.3	0.38	0.55
P value between the 2 groups	0.038*	0.013 *	0.02 *	0.01 *	0.08	0.32

Abbreviations: 1 = before treatment, 2 = after treatment with L-thyroxine; #p<0.05 t test before vs after; *p <0.05 between 2 groups

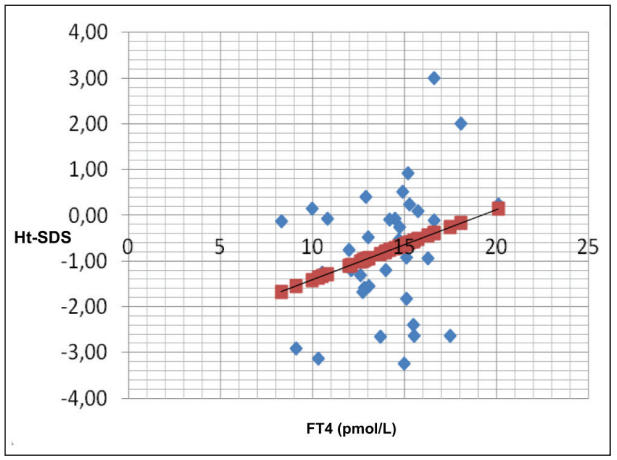

Figure 1. Correlation between FT4 and change in Ht-SDS (r = 0.32; p = 0.05)

the height growth velocity in the treated group (r = 0.08; p = 0.61). The change in Ht-SDS was correlated with the level of FT4 (r = 0.32; p = 0.05) (Figure 1).

At first examination (age = 2.3±2.5 years), 16 out of 102 DS children (15.7%) were overweight (BMI-SDS >1.5) and 17 out of 102 (16.7%) were underweight (BMI-SDS <-1.5). At age of 5±3.1 years, 33/102 DS children were overweight (BMI-SDS >1.5) and 7 /102 were underweight.

There was no significant difference in the thyroid function or linear growth in DS children with CHD when compared to those without CHD (Table 6).

Discussion

The increased prevalence of hypothyroidism in patients with DS has been well documented (4,6-11). The female:male ratio of approximately 3:2 (13). In our young patients with DS (n = 102) the prevalence of thyroid abnormalities (low FT4 and/or high TSH) was 47/102 (46%) with a female to male ratio of 29/18 (1.6:1).

In our patients, congenital hypothyroidism (CH) was diagnosed in 3/47 (prevalence of 1/141 compared to the incidence in our newborn screening of 1: 2150) Ultrasonography did not show athyrosis or ectopic gland in any of the patients.

The incidence of CH in newborn without DS recorded by the neonatal screening in Qatar, during the same periods of study, was 1/2150. These data confirm the higher prevalence of CH in neonates with DS compared to normal population of newborns. Fort et al. (14) found that CH was about 28 times more common among infants with DS than in the general population with an incidence of 1% (0.7% permanent and 0.3% transient congenital hypothyroidism) detected by newborn screening.The authors concluded that DS are at high risk for CH and should have careful follow-up to prevent further deterioration of their mental development or growth (14).

During the first year of life two of our DS infants developed HT and in 2 a CeH was diagnosed. In the following years, primary HT was diagnosed in 12.5% and SH in 36.4% of 55 DS children followed in our clinic. The older group had also a significant higher prevalence of thyroid antibodies and 4 out of the 7 DS children with positive thyroid antibodies developed primary HT. Therefore, it would seem that thyroid autoimmunity could have a clinical impact in DS from early age. This is in contrast to a previous observation reporting a gradual increase in the concentrations of thyroid autoantibodies from the age of 8 years (15).

Table 6. Linear growth and thyroid function in children with Down Syndrome (DS) with (n = 62) and without (n = 40) congenital heart disease (CHD).

	Age (yr) (1)	Ht-SDS (1)	BMI-SDS- (1)	TSH mIU/L	FT4 pmol/l	Age (yr) (2)	Ht-SDS (2)	BMI SDS (2)
CHD								
Mean	2.43	-1.95	-0.15	8.57	13.76	5.5	-2.13	0.90
SD	3.09	1.70	1.95	12.7	3.24	3.7	1.21	1.47
No CHD								
Mean	3.37	-1.70	0.22	13.5	13.6	7.6	-2.00	0.96
SD	3.90	0.94	1.72	16	4.78	5.7	0.91	1.02

Abbreviations: 1 = before treatment, 2 = after treatment with L-thyroxine

These findings support the view of an increased autoimmune aggression with age. A genetic predisposition and a propensity to acquire autoimmune disorders seem to be possible factors, though their causal relation remains unclear (16). The occurrence of type 1 diabetes mellitus with positive anti-GAD antibodies in two of our hypothyroid children with DS and positive anti-thyroid antibodies is in favor of this view.

We treated with L- thyroxine DS infants and children with TSH >5 mIU/L and /or FT4 <9 pmol/L. Doses of L thyroxine required to keep TSH = or <5 mIU/L and FT4 in the normal range, did not differ significantly between those with HT and with SH. The linear correlation between FT4 levels and growth parameters expressed in Ht-SDS suggests also a positive effect of treatment on the linear growth. Our data also put in evidence that treatment with L-thyroxine in DS children with high TSH prevented also an excessive weight gain, that was observed in DS children with normal thyroid function (Group 1).

These data support the findings of Trotsenburg et al. (10) who demonstrated that L-thyroxine replacement in the first two years of life improve the growth in young infants with DS, and the Marchal et al. observations (9). The Authors showed that T4-treated children tended to be taller compared to placebo treated children with DS and high TSH.

Congenital heart defects (CHD) are present in patients with DS in approximately 40-50% of cases (17-20). Among the most common cardiac defects are atrioventricular septal defect (AVSD), representing approximately 45% of cases, and ventricular septal defect (VSD), representing 20-30% (17, 20).

In our study 62/102 (60.7%) had CHD. No significant difference was observed in the thyroid function or linear growth in DS children with CHD when compared to those without CHD. In support to our findings, Mıhçı E et al.(35) reported no significant relationship between CHD and TSH and FT4 levels (21).

Conclusion

Our data provided more evidence to support the hypothesis that L-thyroxine treatment can improve growth of infants and young children with DS presenting a TSH >5 mIU/L and especially in those with TSH >12 mIU/L. On treatment of these children, FT4 levels increased and this was associated with better linear growth. The onset of hypothyroidism may be associated with symptoms and clinical findings that are subtle and attributed to the underlying disorder. Therefore we recommend, according to guidelines for children with DS, to review the results of the newborn thyroid function screening, and to repeat thyroid function tests at the age of 6 months and 12 months, and then annually (22). An early treatment is also recommended for those with high TSH or low FT4 levels.

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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Original article

Responses to growth hormone (GH) therapy in short children with normal GH secretion and no bone age delay: an analysis of potential factors affecting their response to rhGH therapy. A controlled study

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Summary. *Background*: Variability still exist about the growth response to growth hormone (GH) therapy in children with idiopathic short stature (ISS). We describe the growth response to rhGH therapy for >2 years in 20 prepubertal children with idiopathic short stature (ISS) and 18 children with GH deficiency (GHD) and compared them with 15 children with ISS who did not receive rhGH therapy. *Patients and methods:* Our study included 35 prepubertal and peripubertal (Tanner 1 and 2) children with short stature (Ht-SDS <-2) and/or Ht-SDS >1SD below their mid parental height SD (MP-Ht-SDS) with slow growth velocity (<-1 SD), with normal peak GH response to provocation tests (15.5±6.5 ng/dl), normal IGF-I SDS (-0.9±0.6), and no bone age delay (± 1 year from chronological age) (ISS). 20 children were treated for 2.5±1.5 years with rhGH 0.05 mg/kg/day and 15 children were not treated with rhGH. 18 children with diagnosis of GHD, diagnosed in the same period, receiving rhGH therapy served as controls. We assessed the linear growth and IGF-I levels of all children for an average of 2 years. *Results:* Children with ISS on rhGH therapy had a height gain of 0.77 SD in 2 years versus 1.05 SD in GHD children, with significant increase in IGF-I and normal progression of bone age and puberty. Children with ISS who did not receive rhGH had no gain in the changes of Ht-SDS inspite of normal progression of bone age and puberty. The difference between children Ht-SDS and mid-parental height SDS (MP-Ht-SDS) changed significantly from -1.1±3 to -0.3±0.5 in the ISS group and from -1.35±0.5 to -0.3±0.25 in the GHD group, after an average of 2 years of treatment. In the treated ISS group, the Ht-SDS gain was correlated positively with the duration of rhGH therapy ($r = 0.82$, $p<0.0001$), negatively with the age at the start of treatment ($r = -0.544$, $p = 0.01$), and positively with the bone age ($r = -0.44$, $p = 0.04$). *Discussion*: The Ht-SDS of children with ISS on rhGH treatment closely approached their MP-Ht-SDS after 2 years of rhGH therapy while those who did not receive rhGH kept the same distance from their MP-Ht-SDS after 2 years. Analysis of possible factors affecting linear growth in children with ISS on rhGH therapy showed that children below 9 years with Ht-SDS <-2.5 SD and those with Ht-SDS >1SD below MP-Ht-SDS grew better on rhGH therapy compared to older children and those with Ht-SDS >-2.5 and were less than 1SD from their MP-HT-SD. Higher doses of rhGH (to keep IGF-I in high normal levels) and longer duration of therapy improved the Ht-SDS gain of these children. *Conclusion:* We report significant gain in Ht-SDS in prepubertal children with ISS on rhGH therapy and better response in younger children and in those with Ht-SDS > 1 SD below their MP-Ht-SDS. (www.actabiomedica.it)

Key words: idiopathic short stature, growth hormone deficiency, rhGH therapy

Introduction

A remarkable era of human growth hormone (GH) therapeutic expansion ensued, spearheaded by industry and facilitated by pediatric endocrinologists. Eagerness for increasing height in children who are short for reasons other than GH deficiency (GHD) arose from prior assumptions that: 1) severe short stature in children is a disabling condition requiring and deserving of treatment; 2) GH is safe for short children without GHD, even at escalating and supraphysiologic dosages; and 3) GH-induced height augmentation would measurably enhance quality of life. However, the validity and value of each of these assumptions are being challenged due to shortage of evidence, weakening GH therapeutic expansion and favoring limitation. An increasingly evidence-based and honest appraisal of the benefits, risks, costs and value of GH treatment is highly required (1, 2).

Idiopathic short stature (ISS) is not a specific diagnosis. It is an expressive term used to define children who are short, i.e., height ≤2 SD, with normal birth weight, absence of chromosomal defects, no dysmorphic features or chronic illnesses, and no identified endocrine abnormality. The term ISS, therefore, describes a heterogeneous group of children with many unidentified causes of short stature (2-5).

Because the causes of ISS are regarded as a combination of a decrease of sensitivity and inappropriate secretion of GH, it is thought that growth will be improved with GH (6). However, until now the management of ISS with rhGH therapy remains debatable. The FDA rather than EMA guidelines are generally followed, with approximately 20% of rhGH-treated children having ISS. In addition, during the guidelines-developing process, fundamental questions about rhGH treatment still need evidence-based answers (7-9).

The aim of this study was to measure the growth response to GH therapy for >2 years in 20 prepubertal children with ISS who had a slow growth velocity (<-1 SD), normal GH response to provocation test and who were significantly shorter than their mid-parent's height SDS (MP-Ht-SDS) (-1 difference). Their growth and IGF-I data were compared to a group of children with GHD on rhGH therapy as well as with a group of ISS children who did not receive GH therapy.

Patients, Methods and Statistical Analysis

1. Patients

This retrospective study was done by reviewing clinical and anthropometric data of children with idiopathic GHD or ISS at Hamad General Hospital (HGH), Doha (Qatar) between January 2015 to December 2018. The diagnosis of GHD was made by the presence of short stature (height <-2 SDS) and a peak GH response below 10 ng/mL after GH provocation tests. ISS (height <-2 SDS) was defined when the patient had short stature without genetic factors or other physical problems, but the peak growth hormone response was more than 10 ng/mL.

These two groups were treated with rhGH (0.03-0.05 mg/kg /day) for an average of 2 year and the dose was adjusted to keep IGF-I level in the upper quartile of normal for age. 15 age matched children with ISS diagnosed during the same period who did not receive rhGH therapy were used as controls. Patients with chromosomal abnormality, organic lesions on brain magnetic resonance imaging, or a systemic or other endocrine disease or syndrome that causes growth disorders were excluded. Patients with Tanner stage 3 or more were also precluded.

2. Methods

Body parameters of patients with idiopathic GHD and ISS were recorded at the first visit to our center. We checked chronological age, bone age (BA), height standard deviation score (Ht-SDS), body weight, body mass index (BMI), and mid-parental height (MP-Ht) at the point of diagnosis. BA was evaluated by the Greulich-Pyle method (10).

Insulin-like growth factor-1 (IGF-1) and thyroid function were also measured. All children had normal FT4 and TSH. After 2 years or more of rhGH treatment, the values of Ht-SDS, IGF-1 were recorded. MP-Ht was the average height of the parents plus 6.5 cm in boys and minus 6.5 cm in girls.

Height SDS was calculated as the patient's height minus the average height for the same age and sex divided by the standard deviation. The WHO growth data was used as normal growth reference in our study (https://www.who.int/childgrowth/standards/en/).

The protocol of the study was approved by the local Ethics Review Committees in accordance with national and international regulations.

3. Statistical analysis

Student- t test was used to compare the variables among different groups when the data were normally distributed and Wilcoxon test was used when the data were not normally distributed. ANOVA test was used to compare variables among the 3 groups categorized according to their BMI-SDS. Linear correlation equation was used to investigate possible relations between different variables. Significance was accepted when p = or <0.05. Data were analyzed by Excel statistical Package for Windows (version: 10).

Results

Clinical and anthropometric data of the study groups are presented in table 1. The results of ANOVA test used to compare variables among the 3 groups categorized according to their BMI-SDS are reported in table 2. Children with ISS on rhGH therapy had a height gain of 0.77 SD in 2 years versus 1.05 SD in GHD children, with significant increase in IGF-I associated with normal progression of puberty. Children with ISS who did not receive rhGH had no gain in the Ht-SDS associated with normal progression of puberty. The difference between children Ht-SDS and MP-Ht-SDS changed significantly from -1.1±3 at the beginning of rhGH therapy to -0.3±0.5 in the ISS and from -1.35±0.5 to -0.3±0.25 in the GHD group at the

Table 1. Growth parameters of children with idiopathic short stature (ISS) versus growth hormone deficiency (GHD) before vs after treatment. (ANOVA test among the three groups)

ISS n =20 GH-treated		Baseline	At last examination	Differences
Age (years)	Mean±SD	9.8±2.6	12.3*±2.2	2.4±1.6
IGF-I (ng/mL)	Mean	143.4±57.4	407.1*±162.4	263.7± 105
Ht-SDS	Mean	-2.3±0.41	-1.5*± 0.5	0.77±0.1
MP-HtS-DS	Mean	-1.6±0.9	-1.6±0.9	--
ISS n= 15 Not treated				
Age (years)	Mean	9.1±2	11.2±2	2±0.3
IGF-I (ng/mL)	Mean	119.2±36.1	182±57	63±38
Ht-SDS	Mean	-2.1±0.4	-2.1±0.3	0±0.3
MP-Ht-SDS	Mean	-0.9±0.6	-0.9±0.6	--
Pubertal stage	Mean	1.2±0.2	2.2*±0.5	0.9±0.6
GHD n = 18 GH-treated				
Age (years)	Mean	8.6±3.6	10.6±3.4	2.5±1.4
IGF-I (ng/mL)	Mean	99±45	350±180	251±85
Ht-SDS	Mean	-2.6±0.4	-1.52±0.22	1.05±0.3
MP-Ht-SDS	Mean	-1.2±0.5	-1.2±0.5	--

Table 2. ANOVA test used to compare variables among the 3 groups categorized according to their BMI-SDS.

	Age (1)	Ht-SDS (1)	MP-HS-DS	IGF-I (1)	GH-Basal	GH Peak	Age (2)	Ht-SDS (2)	Δ Ht-SDS	IGF-1 (2)	duration	Δ IGF-I	Bone age
P value	0.44	0.117	0.076	0.06	0.8	<.001	0.07	.0001	0.009	<.001	0.17	<.001	0.38

Legend: * p <0.05

Table 3. The effect of different factors on linear growth in children with idiopathic short stature (ISS) on treatment with rhGH

	Ht-SDS MP-Ht-SDS before GH Therapy	Ht-SDS – MP-HT-SDS after GH therapy	Ht-SDS gain after GH therapy
Ht -SDS <-2.5	-1.20	-0.20*#	0.98#
Ht-SDS >-2.5>-2	-0.93	-0.32*	0.60
More than 1SD below their MP-Ht-SDS before GH therapy	-1.5	-0.57*#	0.88#
Less than 1SD below their MP-Ht-SDS before GH therapy	-0.71	-0.1*	0.62
IGF-I increment >150%	-1.2	-0.4*	0.7
IGF-I increment <150%	-1.1	-0.25*	0.83
GH response >15 ng/dl	-1.13	-0.29*	0.8
GH response <15 ng/dl	-1.07	-0.37*	0.69
Remained as prepubertal during therapy	-1.34	-0.27*	0.71
Progression to Tanner 3 during therapy	-1.36	-0.37*	0.78
Age <9 years at the start of GH	-1.2	-0.1*#	1.1#
Age >9 years at the start of GH	-1.04	-0.45*	0.58

Legend *=p<0.05 before vs after therapy, #= p<0.05 comparing different groups

last examination. The bone age did not differ among the three groups at the beginning or after 2 years of follow-up (Table 3).

Analysis of possible factors affecting linear growth in children with ISS on rhGH therapy showed that children below 9 years with Ht-SDS <-2.5 and those with Ht-SDS >1SD below MP-Ht-SDS grew better on rhGH therapy compared to older children and those with

Ht-SDS >-2.5 and below 1SD from their MP-HT-SD (p<0.05) (Table 3).

In the treated ISS group, the Ht-SDS gain was correlated with the duration of rhGH therapy (r = 0.82, p<0.0001) (Figure 1), negatively with the age

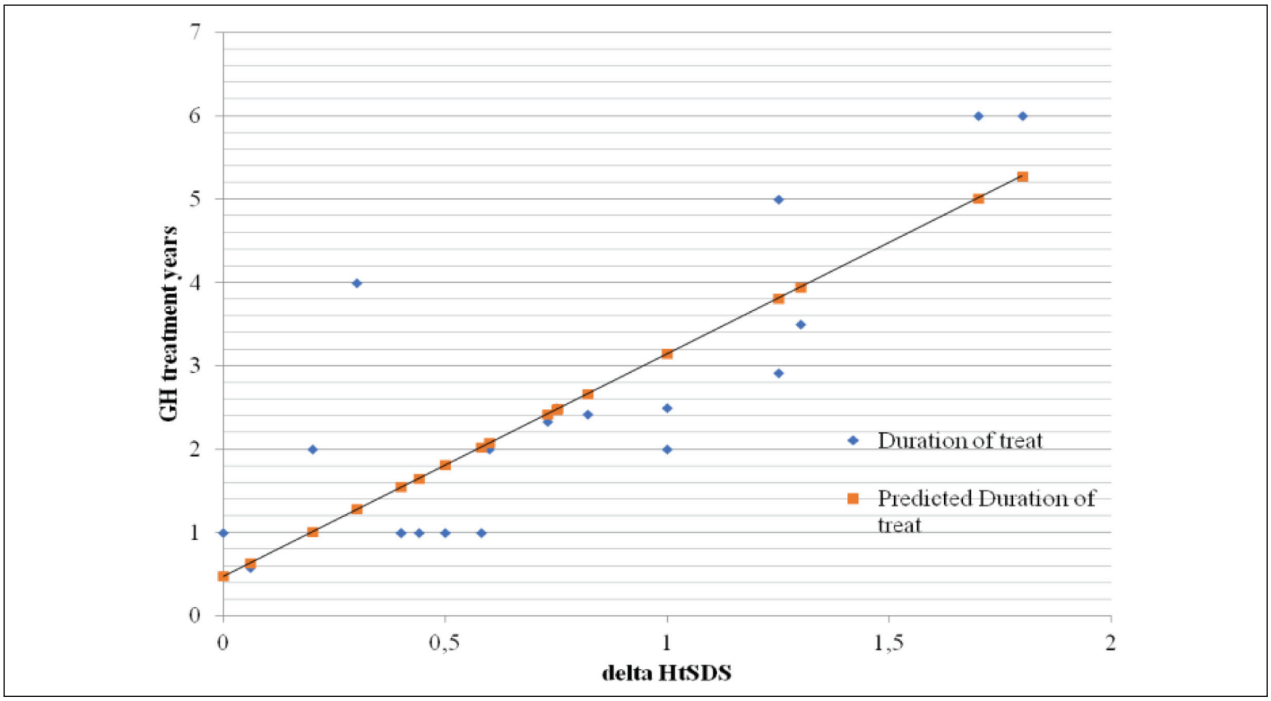

Figure 1. Correlation between Δ Ht-SDS and duration of rhGH therapy in years (r: 0.82, p:0.0001)

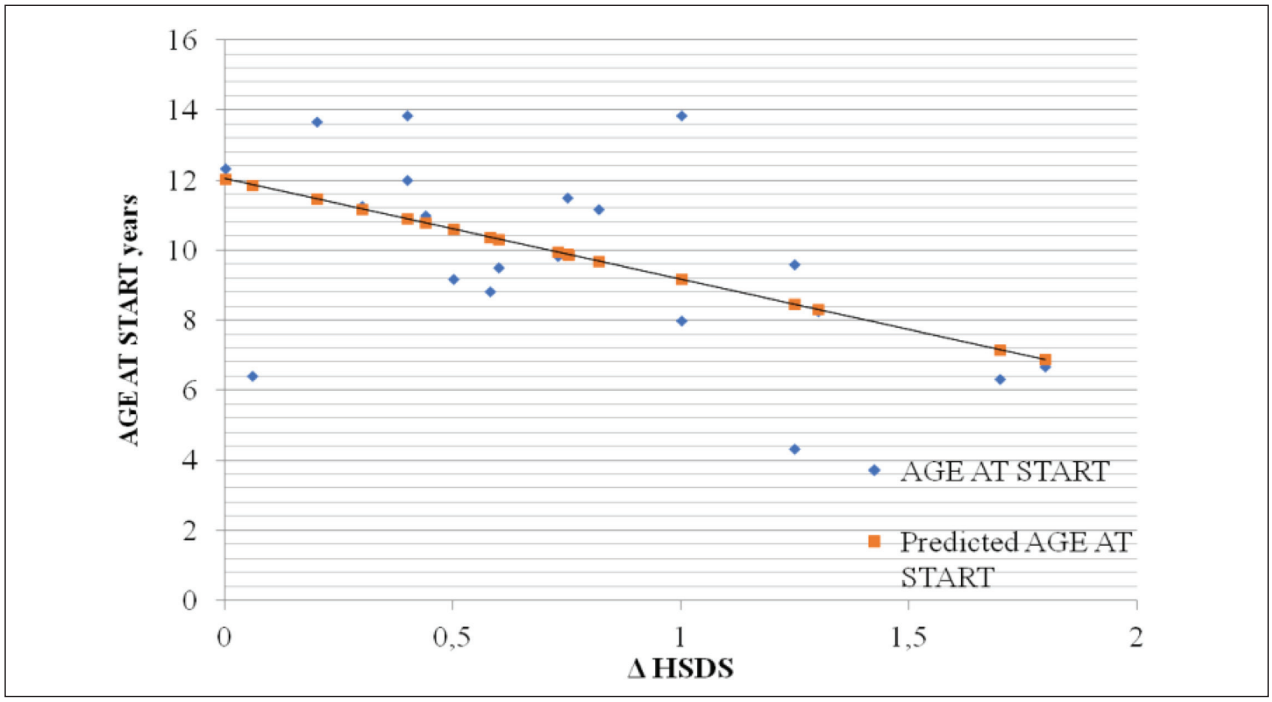

Figure 2. Correlation between Δ Ht-SDS and age at beginning of rhGH therapy in years (r: -0.544; p:0.01)

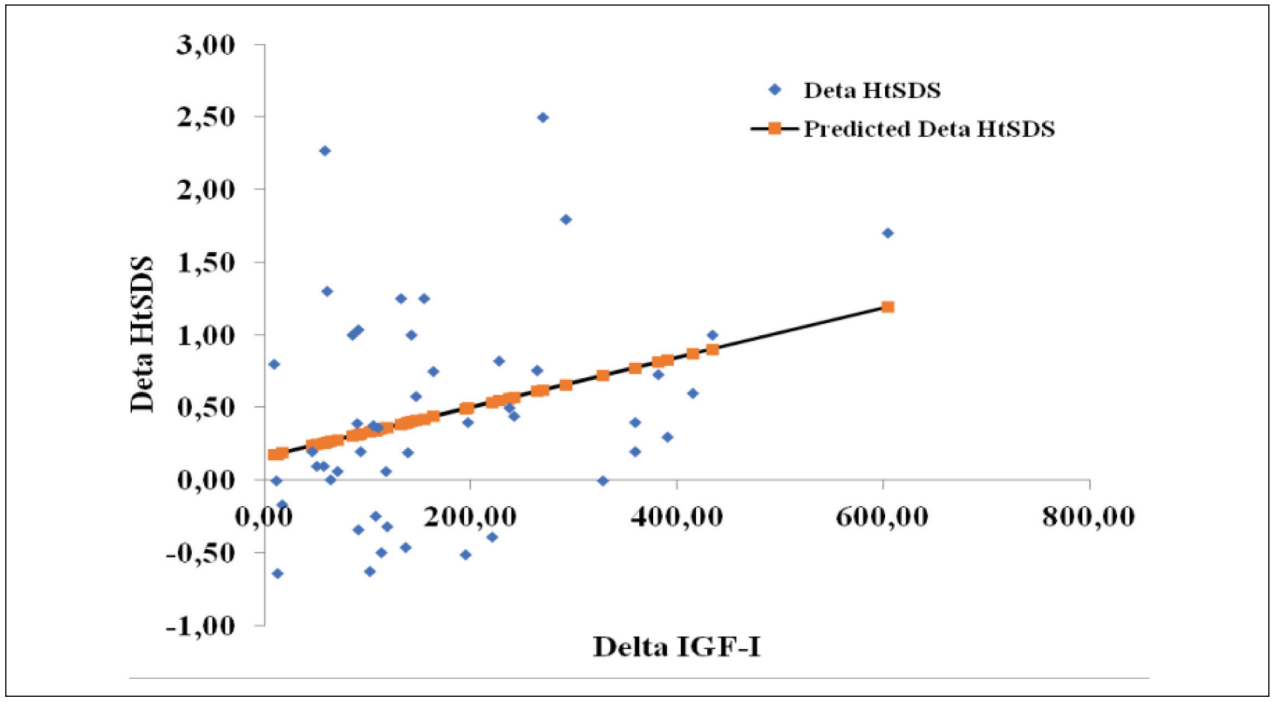

Figure 3. Correlation between Δ IGF-I and Δ Ht-SDS (r: 0.32; p: 0.02)

at the start of treatment (r = -0.544, p = 0.01 (Figure 2), and positively with the bone age delay expressed in years (r =-0.44, p = 0.04). The increase in IGF-I concentration was correlated significantly with the increase in the Ht-SDS in children with ISS (Figure 3).

There were no cases of adverse events like intracranial hypertension, slipped capital femoral epiphysis, thyroid dysfunction, dyslipidemia or type 2 diabetes mellitus. Two children had headache related to rhGH injections not requiring discontinuation of rhGH therapy.

Discussion

After rhGH was introduced in the treatment of patients with GHD and ISS, many studies have addressed the effects of rhGH treatment (11).

In our study, we compared the anthropometric measurements of patients with idiopathic GHD patients on rhGH treatment with 2 groups of children with ISS; one was treated with rhGH for 2 years and the other group was not treated. According to our results, peak GH response to provocation test and IGF-I levels at the diagnosis were significantly lower in the GHD group versus ISS group. The changes in height SDS in patients with GHD and in patients with ISS, who received GH therapy, were considered positive after treatment and when compared to the untreated group. In particular, the gain in the Ht-SDS in the of the rhGH-treated ISS group was 0.7 SD , although it was lower compared to the GHD group (1.05 SD), enabled them to approach very closely their mid-parental height SDS without acceleration of their bone age in relation to their chronological age. These data reinforce the positive effect of rhGH therapy on linear growth in children with ISS.

Data from randomized controlled trials (RCTs) and non-RCTs, from 1985 to April 2010, showed similar results. The inclusion criteria were short stature (defined as height >2 SD) below the mean), peak GH responses to provocation tests >10 ng/mL, prepubertal stage, no previous rhGH therapy, and no comorbid conditions that would impair growth rate.

Three RCTs (115 children) reported that the adult height of the rhGH treated children exceeded that of the controls by 0.65 SD score (~4 cm). The mean height gain in treated children was 1.2 SD score compared with 0.34 SD score in untreated children. In other seven non-RCTs, adult height of the rhGH-treated group exceeded that of not treated group by 0.45 SD. Longer duration of treatment appears to be more effective (12-17). On the other hand, other investigators reported that rhGH treatment improved growth velocity, but it was ultimately unhelpful because it accelerated bone maturation and pubertal progression (18-20).

In our study, the untreated ISS group did not increase their Ht-SDS over 2 years, while the treated group increased their Ht-SDS by 0.7 SD. Furthermore, there was no difference between the bone age and pubertal progression between children with ISS treated with rhGH compared to those not treated with rhGH therapy during the study period. The significant increase in the IGFI level after rhGH therapy in children with ISS was comparable to that in the GHD group, although the average dose received by the ISS group was significantly higher (0.045±0.05) compared to that received by the GHD group (0.28±0.06). This may suggest a mild degree of resistance to GH, as previously suggested by Saenger et al. (21), in children with ISS.

Our children with ISS who had increased their IGF-I to >150% of basal level had higher gain in the Ht-SDS compared to those who did not increase their IGF-I to that level (Table 2). The delta Ht-SDS gain was correlated significantly with the delta increase in IGF-I level (Figure 3) Moreover, the duration of rhGH therapy was correlated with the gain in Ht-SDS in children with ISS (Figure 1). In support to our findings, Kim et al. (22) reported that the differences in IGF-1 between their GHD and ISS groups, after 1 year of rhGH treatment, were not significant although the change in height SDS in patients with GHD was significantly higher than that in patients with ISS (0.62±0.33 vs. 0.40±0.27, respectively; p: 0.03). In addition, Wit et al. (23) and Albertsson-Wikland et al.(24) reported that the final adult height in children with ISS on rhGH therapy was dose dependent. In our study, we used a higher dose in ISS group compared to GHD to attain the required IGF-I level.

Other factors appeared to positively affect the gain in Ht-SDS of our children with ISS. These included: the younger age, the higher difference between the child Ht-SDS and the mid-parental Ht-SDS at the start of therapy, the higher dose of rhGH and the longer duration of rhGH therapy (Figures 1, 2 and 4). In support of this view, Ranke et al. (25) and Hughes

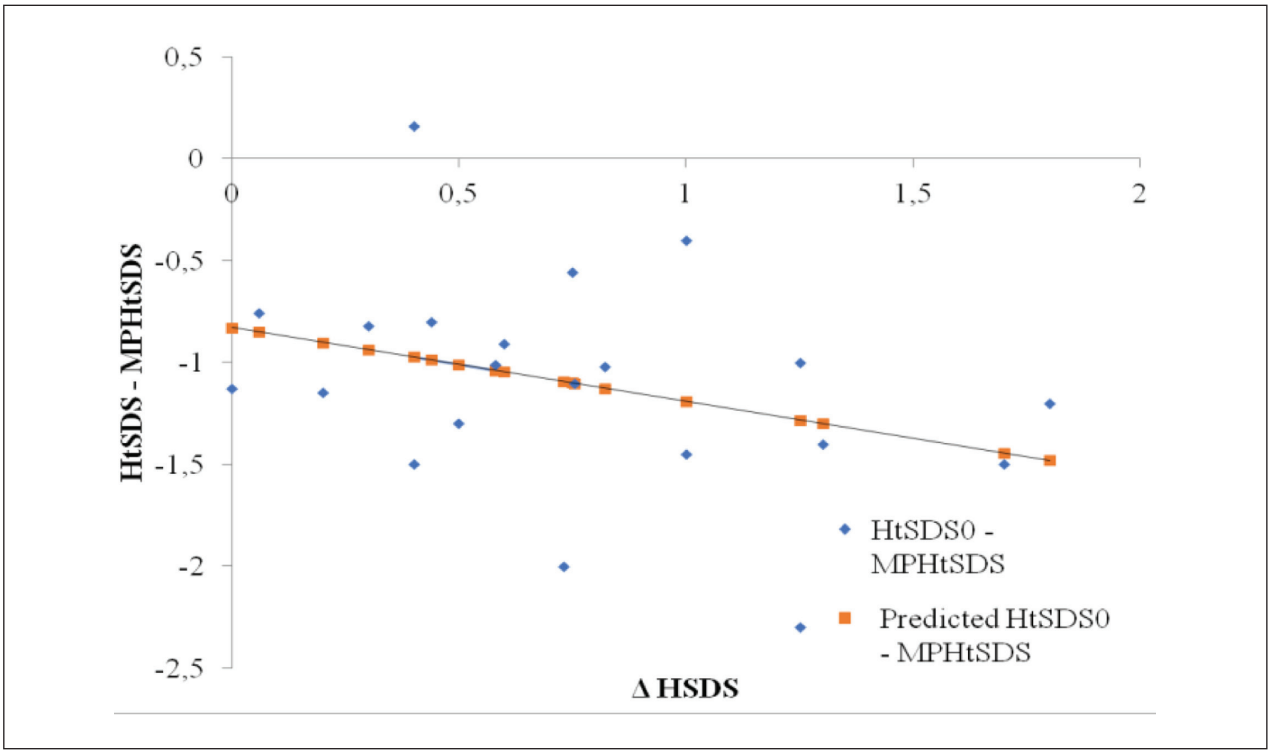

Figure 4. Correlation between Δ Ht-SDS and difference between Ht-SDS and MP-Ht-SDS at the beginning of rhGH therapy (r: -0.34; p: 0.06)

et al. (26) reported that the age at the beginning of treatment and first-year responsiveness to rhGH treatment are the major determinants of height outcome in ISS. In addition, Dahlgren et al. (27) reported that the younger age the patient and the greater difference in current height vs. parental height, at start of treatment, were good prognostic factors for height gain. Height improvement ranged from 0.5 to 1.3 SDS. Wit et al. (28) found that children with ISS on rhGH treatment increased their Ht-SDS for chronological age from -3.8±0.7 to -2.3±0.9 over 6 years, while their matched ISS controls HS-DS for age did not have any positive change**.**

Our study had some limitations, especially the limited number of patients included in the study and the short period of rhGH treatment (2 years). Therefore, more data in patients with idiopathic GHD and ISS and a prolonged period of treatment and observation are needed.

Conclusion

In this study, patients with GHD and ISS treated with rhGH showed improvement in height after 2 years of treatment. These findings do not indicate that rhGH should be used routinely to treat children with short stature, because the treatment should be limited to patients with height <2 SDS especially if their HT-SDS is >1 SD below their MP-Ht-SDS. Treatment of this group of children appears to be better if it is started early and with rhGH doses to maintain IGF-I concentrations in the upper quartile for age and sex. Finally, any benefit derived from an increase in height must be weighed against the risk of adverse events, the cost, and the discomfort of rhGH injections**.**

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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