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ORIGINAL ARTICLE

High prevalence of hypovitaminosis D in Sicilian children affected by growth hormone deficiency and its improvement after 12 months of replacement treatment

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Abstract
Purpose Although the correlation between vitamin D and growth hormone (GH)-insulin-like growth factor 1 (IGF1) axis is documented, as of date, few and conflicting studies have prospectively analyzed vitamin D before and after GH treatment. Our aim was to evaluate as to how the condition of GH deficiency (GHD) or GH treatment influences vitamin D in children.
Methods Eighty Sicilian GHD children (M/F 58/22; mean age 10.3 years), grouped according to the season of evaluation in group A (June–September; 41 children) and group B (November–February; 39 children), were evaluated at baseline and after 12 months of GH treatment.
Results Twenty-eight children (35 %) were vitamin D insufficient and 32 (40 %) deficient at baseline, and lower vitamin D levels were found in group B than in A (17.3 ± 5.3 vs. 31.1 ± 11.1 ng/ml; $p < 0.001$). A positive correlation between vitamin D and baseline GH levels ($p < 0.001$) was found. After 12 months, increased vitamin D was found both in all children (34.4 ± 16.4 vs. 24.5 ± 11.1 ng/ml; $p = 0.002$) and in group A (38.5 ± 14 vs. 31.1 ± 11.1 ng/ml; $p < 0.001$) and B (30 ± 17.7 vs. 17.3 ± 5.3 ng/ml; $p < 0.001$). Overall, only 25 (31 %) children remained insufficient and 15 (19 %) deficient, with an increase in prevalence of children with normal levels ($p = 0.001$).
Conclusions Our data demonstrated a very high prevalence of hypovitaminosis D in Sicilian GHD children, with an improvement after 12 months of GH treatment. Vitamin D assessment should therefore be considered routinely in GHD children both at diagnosis and during the follow-up.

Keywords Growth hormone · Vitamin D · GH treatment · GH deficiency

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Introduction

Vitamin D is essential for skeletal growth and the correlation between vitamin D and the growth hormone (GH)-insulin-like growth factor 1 (IGF1) axis is well documented. Treatment with GH in adult GH-deficient (GHD) patients increases bone turnover parameters [1–3], though it remains unclear whether GH acts on bone metabolism and vitamin D directly or indirectly via increased IGF1 synthesis. Indeed, the role of GH and IGF1 in the regulation of vitamin D is not fully understood. IGF1 and vitamin D influence their respective circulating concentrations. IGF1 stimulates expression and activity of the 1α-hydroxylase in the kidney, increasing the circulating levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the hormonally active and most potent metabolite of vitamin D, responsible for all the effects of the vitamin on calcium metabolism [4], but with a controversial relationship. Though the administration of both GH and IGF1 raises vitamin D in healthy subjects [5, 6], some studies show that vitamin D concentrations do not significantly change when GH or IGF1 levels vary substantially, as in acromegalic or GHD subjects after starting treatment [7, 8]. On the other hand, vitamin D seems to promote the production of IGF1 [9]. Indeed, vitamin D increases circulating IGF1 levels both in adults [10] and children [11]. As of date, few studies, and with controversial results, have prospectively analyzed the

vitamin D status in children before and after GH treatment. The aim of this study was to evaluate as to how the condition of GHD or GH treatment influences vitamin D levels in children affected by idiopathic GHD.

Materials and methods

This prospective study was located in Southern Italy (Sicily, latitude 37°N). We studied 80 prepubertal children (58 M, 22 F; mean age 10.3 ± 3 years; range 4.3–16) with isolated idiopathic GHD consecutively admitted to the Section of Endocrinology of the University of Palermo during the years 2011 and 2012 and treated with GH for at least 12 months. We excluded children with any medical condition or on any medications known to affect skeletal metabolism, and those affected by multiple pituitary hormone deficiency or receiving any other kind of hormonal replacement treatment or drug and with a follow-up of <12 months. All children, even the older ones, were in the first or second stage of sexual development according to the criteria of Marshall and Tanner [12]. The diagnosis of GHD was established by the clinical, auxological and biochemical criteria of the GH Research Society [13]. GHD was demonstrated by failure of GH to respond to the two stimuli, with GH peaks below 10 μg/l. During the tests, the area under the curve of GH (AUC_{GH}) was calculated and the average value between the two tests was reported. The patients received GH once daily at bedtime with a pen injection system. The initial daily dose was 0.025 mg/kg. During the study, the GH dose administered was adjusted in order to maintain serum IGF-I levels within the normal range for sex and age. In all patients, at baseline and after 12 months of GH treatment, according to our fixed internal protocol, we measured body height [standard deviation (SD)], height-velocity (HV), waist circumference (WC), IGF1, serum calcium (Ca), phosphate (P), bone-specific alkaline phosphatase (AP), total 25-OH-vitamin D (25-OHD) and parathyroid hormone (PTH). Since 1,25(OH)2D levels are only a measure of renal-derived vitamin D, we measured serum concentration of 25-OHD, a good indicator of the amount of available vitamin D. Vitamin D was classified as follows: vitamin D deficiency was defined as a 25-OHD <20 ng/ml (<50 nmol/l), vitamin D insufficiency as a 25-OHD between 20 and 30 ng/ml (50–75 nmol/l) and vitamin D sufficiency as a 25-OHD >30 ng/ml (>75 nmol/l) [14, 15]. The study outcome considered bone metabolic parameters at baseline and after 12 months and their correlations with biochemical and auxological data. In order also to evaluate the impact of seasonal variations on vitamin D levels, the study was performed and the children recruited in two periods: between June and September (group A, 41 children) and between November and February (group B, 39 children). The institutional Ethics Committee of the University of Palermo approved this study. At the time of hospitalization, an informed consent for the scientific use of the data was obtained from parents.

Hormone and biochemical assays

All biochemical data were collected after overnight fasting. During the study period, in our laboratory the GH levels were assayed by immunoradiometric assay (Radim, Pomezia, Italy) and the sensitivity of the assay was 0.05 μg/l. The intra- and inter-assay coefficients of variation (CV) were 2.5–3.9 and 3.8–5.0 %, respectively. Serum total IGF1 was assayed in the same laboratory with the ELISA method (OCTEIA IGF-I kit, IDS Inc., Fountain Hills, AZ, USA). The sensitivity of the method was 1.9 μg/l. The inter- and intra-assay CV values were 7–7.1 and 2.3–3.5 %, respectively, at IGF-I levels of 90.7–186 and 66.7–120.9 μg/l, respectively. The normal ranges (males and females combined) of total IGF-I levels (μg/l) were: 12–108 (0–1 years); 13–100 (1–3 years); 26–280 (3–6 years); 85–230 (6–9 years); 98–404 (9–12 years); 142–525 (12–15 years); 146–415 (15–20 years).

Serum Ca, P, AP and PTH levels were measured in our centralized laboratory with standard methods. Serum 25-OHD was measured by total chemiluminescent immunoassay for in vitro quantitative determination of total 25-hydroxyvitamin D (D2 + D3) in human serum and plasma (Diasorin, Saluggia, Italy). The intra- and inter-assay CV was 6.9–12.7 and 2.9–5.5 %, respectively.

Statistical analysis

The Statistical Package for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± SD for continuous variables, rates and proportions were calculated for categorical data. Normality of distribution for quantitative variables was assessed with the Kolmogorov–Smirnov test. The differences between the two groups (group A and B) of patients were evaluated with the Mann–Whitney test (non-parametric test), as they were continuous variables without normal distribution.

The differences between group A and B were corrected for chronological age through a logistic regression model.The differences between paired continuous variables (before and 12 months after therapy) were analyzed by the Wilcoxon test. Correlations among continuous variables without normal distribution were determined by using the Spearman's test (non-parametric equivalent for Pearson test). For categorical variables, differences were analyzed

Table 1 Baseline clinical and biochemical parameters of GHD children in totality and grouped according to the season of evaluation

	All children Nos. 80	Group A (June–September) Nos. 41 (51 %)	Group B (November–February) Nos. 39 (49 %)	*p*	*p**
Gender					
Males	58 (72.5)	26 (63)	32 (82)	0.081	–
Females	22 (27.5)	15 (37)	7 (18)		
		Mean ± SD	Mean ± SD	Mean ± SD	
Chronological age (years)		10.3 ± 3	10 ± 2.9	10.7 ± 3.2	0.315	–
Height (SD)		−2.1 ± 0.7	−2.0 ± 1.3	−2.1 ± 0.5	0.782	–
Weight (kg)		29.3 ± 11.5	26.9 ± 9.2	31.9 ± 13.2	0.058	–
Waist circumference (cm)		60.9 ± 10.8	58.6 ± 8.7	63.7 ± 12.6	0.079	–
AUC_{GH} (μg/l)		242.4 ± 157.6	286.9 ± 145.4	195.5 ± 158	0.009	0.022
IGF-I (μg/l)		135.9 ± 64.6	139.1 ± 61.3	132.4 ± 69.3	0.722	–
Serum Ca (mg/dl)		9.6 ± 0.4	9.6 ± 0.4	9.5 ± 0.3	0.448	–
Serum P (mg/dl)		4.6 ± 0.5	4.5 ± 0.5	4.6 ± 0.4	0.342	–
Serum AP (IU/l)		161.2 ± 70.6	148.6 ± 33.5	175.8 ± 97	0.270	–
Serum 25OHD (ng/ml)		24.4 ± 11.1	31.1 ± 11.1	17.3 ± 5.3	<0.001	<0.001
Serum PTH (pg/ml)		32.5 ± 13.4	31.1 ± 10.8	33.8 ± 15.7	0.400	–

Ca calcium, *P* phosphate, *AP* bone-specific alkaline phosphatase, *25OHD* vitamin D, *PTH* parathyroid hormone

p difference between group A and group B

*p** difference between group A and group B corrected for chronological age

Table 2 Vitamin D levels in GHD children in totality and grouped according to the season of evaluation (group A: between June–September; group B: between November-February) at baseline and after 12 months of GH treatment

	All at baseline Nos. 80 No (%)	All at 12 months Nos. 80 No (%)	Group A at baseline Nos. 41 No (%)	Group A at 12 months Nos. 41 No (%)	Group B at baseline Nos. 39 No (%)	Group B at 12 months Nos. 39 No (%)	*p*	*p**	*p***
25OHD <20	32 (40)	15 (19)	7 (17)	5 (12)	25 (64)	10 (26)	0.005	0.754	0.001
25OHD 20–30 ng/ml	28 (35)	25 (31)	14 (34)	9 (22)	14 (36)	16 (41)	0.736	0.325	0.816
25OHD >30 ng/ml	20 (25)	40 (50)	20 (49)	27 (66)	–	13 (33)	0.001	0.180	<0.001

25OHD: vitamin D

p difference between baseline and 12 months in all children

*p** difference between baseline and 12 months in group A

*p*** difference between baseline and 12 months in group B

by means of the χ^2-test and Fisher's exact test when appropriate. A *p* value <0.05 was considered statistically significant.

Results

The baseline auxological and biochemical parameters of children are shown in Table 1.

In the entire cohort of children, the mean vitamin D levels at baseline were 24.4 ± 11.1 ng/ml (IR 8–73.4 ng/ml), with Ca, P, AP and PTH concentrations in the normal range. Twenty-eight (35 %) children at baseline were vitamin D-insufficient and 32 (40 %) vitamin D-deficient. Only 20 (25 %) children showed normal vitamin D levels (Table 2).

Grouping all children according to the season in which the analysis was done, we found significantly lower vitamin D levels in group B than in group A (17.3 ± 5.3 vs. 31.1 ± 11.1 ng/ml; $p < 0.001$). This significance was confirmed when we corrected the *p* value for chronological age. No difference was found in other auxological and biochemical parameters between the two groups of patients, with the exception of AUC_{GH}, which was significantly higher in group A than group B (286.9 ± 145.4 vs. 195.5 ± 158; $p < 0.001$) (Table 1).

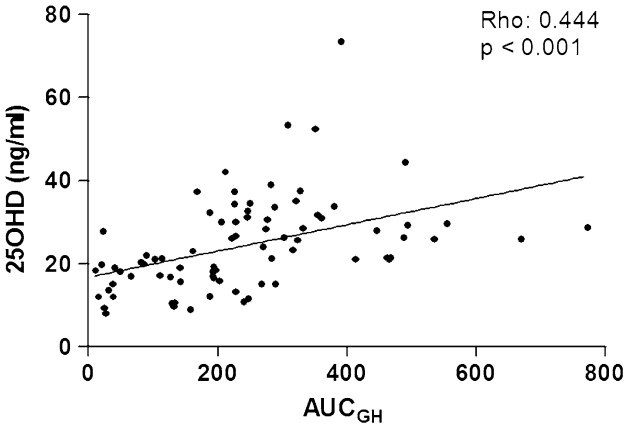

Fig. 1 Correlation between vitamin D levels and area under the curve (AUC) of GH (μg/l) at baseline in all patients

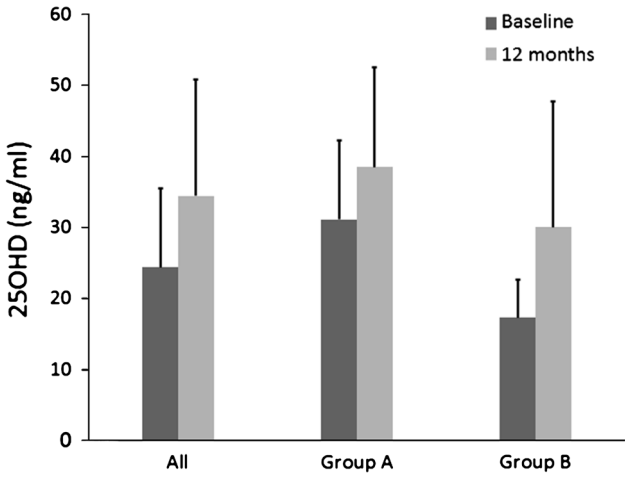

Fig. 2 Change in 25OHD levels from baseline to 12 months in all children (*left*), in children enrolled between June and September (group A) (mean) and in children enrolled between November and February (group B) (*right*)

In group A, at baseline, 14 (34 %) children were vitamin D-insufficient and 7 (17 %) vitamin D-deficient, while in group B 14 (36 %) were vitamin D-insufficient and 25 (64 %) vitamin D-deficient (Table 2).

A significant correlation was found between vitamin D levels at baseline and AUC_{GH} (ρ 0.444; $p < 0.001$) (Fig. 1), while no significant relationships were found between vitamin D levels and IGF1 or auxological parameters (data not shown).

After 12 months of GH treatment, height SD, weight, WC and IGF1 significantly increased in all children, as expected. An increase in serum vitamin D was found both in all children (34.4 ± 16.4 vs. 24.4 ± 11.1 ng/ml; $p = 0.002$) and in group A (38.5 ± 14 vs. 31.1 ± 11.1 ng/ml; $p < 0.001$) and group B (30 ± 17.7 vs. 17.3 ± 5.3 ng/ml; $p < 0.001$) (Fig. 2). A concomitant increase in AP was found both in the whole population (266.1 ± 60.6 vs. 161.2 ± 70.6 IU/l; $p = 0.016$) and in the two groups of children (244.8 ± 65.9 vs. 148.6 ± 33.5 IU/l; $p = 0.042$ in group A and 291.8 ± 47.6 vs. 175.8 ± 97 IU/l; $p = 0.035$ in group B, respectively). No significant difference was found in Ca, P and PTH levels (Table 3). When we grouped all children into those who showed an increase in vitamin D (Nos. 67 with positive delta) and those who failed to increase it (Nos. 13 with negative delta), we found no significant difference in all clinical or biochemical characteristics (data not shown). Overall, after 12 months of GH treatment, only 25 (31 %) children remained vitamin D-insufficient and 15 (19 %) vitamin D-deficient, with a significant increase in prevalence of children with normal vitamind D levels ($p = 0.001$) (Fig. 3). In group A, after 12 months, 9 children (22 %) were vitamin D-insufficient and 5 (12 %) vitamin D-deficient, without significant change in prevalence of each category of vitamin D status from baseline. Conversely, in group B we found a significant decrease in prevalence of children with vitamin D-deficiency (26 vs. 64 %; $p = 0.001$) and a significant increase in those with normal vitamin D (33 vs. 0; $p < 0.001$) (Table 2).

Discussion

Our data demonstrated a very high prevalence of hypovitaminosis D in Sicilian children affected by GHD, with an improvement in vitamin D levels after 12 months of GH treatment.

Hypovitaminosis D is a prevalent disorder in developing countries and its prevalence varies widely between and within regions, ranging between 30–90 %, according to the cut-off value used within specific regions and independently of latitude [16]. Our data showed a higher prevalence of hypovitaminosis D in children evaluated in the winter seasons, in line with the data already known. Indeed, a high prevalence of children and adolescents also showed insufficient vitamin D levels in the winter in European countries [17–19] and older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure and dietary habits are the main factors that are significantly associated with lower vitamin D levels [20, 21].

Vitamin D physiologically stimulates intestinal absorption of calcium and phosphate and renal reabsorption of calcium and inhibits PTH from the parathyroid glands [22, 23]. A positive association between vitamin D and GH/IGF1 axis is documented. Both GH and IGF1 increased the production of vitamin D by cultured kidney cells and IGF1 stimulated vitamin D synthesis by the placenta [24]. IGF1 stimulates renal production of active vitamin D, which

Table 3 Change in clinical and biochemical parameters of GHD children in totality and grouped according to the season of evaluation (group A: between June–September; group B: between November–February) from baseline to 12 months of GH treatment

	All children at baseline nos. 76 Mean ± SD	All children at 12 months nos. 76 Mean ± SD	Group A at baseline nos. 39 Mean ± SD	Group A at 12 months nos. 39 Mean ± SD	Group B at baseline nos. 37 Mean ± SD	Group B at 12 months nos. 37 Mean ± SD	*p*	*p**	*p***
Height (SD)	−2.1 ± 0.7	−1.6 ± 0.7	−2.0 ± 1.3	−1.5 ± 0.3	−2.1 ± 0.5	−1.6 ± 0.3	<0.001	0.001	<0.001
Weight (kg)	29.3 ± 11.5	35.6 ± 12.7	26.9 ± 9.2	33.9 ± 8.6	31.9 ± 13.2	33.6 ± 12.5	<0.001	0.015	<0.001
Waist circumference (cm)	60.9 ± 10.8	64.9 ± 9.8	58.6 ± 8.7	65.8 ± 8.2	63.7 ± 12.6	65.2 ± 10.3	<0.001	0.015	0.015
Height velocity (cm)	–	8 ± 2.7	–	7.9 ± 3	–	8.2 ± 2.4	–	–	–
IGF-I (μg/l)	135.9 ± 64.6	308.7 ± 172.4	139.1 ± 61.3	313.3 ± 116.1	132.4 ± 69.3	280.5 ± 162.6	<0.001	<0.001	<0.001
Serum Ca (mg/dl)	9.6 ± 0.4	9.3 ± 1.3	9.6 ± 0.4	9.5 ± 1.3	9.5 ± 0.3	9.4 ± 0.5	0.364	0.557	0.446
Serum P (mg/dl)	4.6 ± 0.5	4.8 ± 0.5	4.5 ± 0.5	4.8 ± 0.3	4.6 ± 0.4	4.8 ± 0.6	0.181	0.813	0.079
Serum AP (IU/l)	161.2 ± 70.6	266.1 ± 60.6	148.6 ± 33.5	244.8 ± 65.9	175.8 ± 97	291.8 ± 47.6	0.016	0.042	0.035
Serum 25OHD (ng/ml)	24.4 ± 11.1	34.4 ± 16.4	31.1 ± 11.1	38.5 ± 14	17.3 ± 5.3	30 ± 17.7	0.002	<0.001	<0.001
Serum PTH (pg/ml)	32.5 ± 13.4	31.3 ± 12.9	31.1 ± 10.8	33.3 ± 9.7	33.8 ± 15.7	30 ± 15.9	0.491	0.780	0.124

Ca calcium, *P* phosphate, *AP* bone-specific alkaline phosphatase, *25OHD* vitamin D, *PTH* parathyroid hormone

*p** difference between baseline and 12 months in group A

*p*** difference between baseline and 12 months in group B

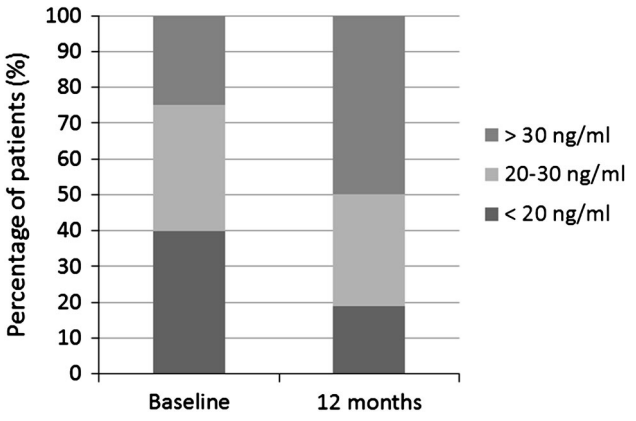

Fig. 3 Percentage of vitamin D sufficiency (>30 ng/ml), insufficiency (20–30 ng/ml) and deficiency (<20 ng/ml) in GHD children at baseline and after 12 months of GH treatment

increases calcium and phosphate availability in the body and inhibits PTH secretion [25, 26]. These actions could be responsible for bone status in active acromegaly, characterized by significantly higher serum vitamin D and by an increase in plasma calcium and phosphate and urinary calcium excretion [7, 27]. In addition, a better vitamin D status seems to contribute to the achievement of normal IGF1 levels in children affected by GHD [10].

However, to date, there are no current definitive prevalence estimates available for vitamin D status in GHD children and data about the effect of GH and IGF1 on vitamin D in GHD children are controversial [8, 28–30].

In our cohort, a high percentage of children (75 %), regardless of the season, showed low vitamin D levels (<30 ng/ml) with normal serum levels of Ca, P and PTH, despite a much higher prevalence in the winter seasons. These data are partially in agreement with existing studies on prevalence of hypovitaminosis D performed in children grouped according to the seasons of evaluation [31], although in our study the condition of GHD seems to amplify this trend already documented in healthy children of the above-mentioned study. Instead, if the overall prevalence of low vitamin D in our cohort of children at baseline in the winter seasons is not higher than those detected in healthy young subjects living in the South of Italy [32] (64 vs. 70 %), in summer seasons it is higher than expected (17 vs. 4.4 %), although after GH treatment the difference becomes smaller (12 vs. 4,4 %). Indeed, 12 months of GH treatment has proven effective in increasing vitamin D levels, suggesting the main role of GH in influencing it. In our opinion, probably a longer GH treatment could lead to more similar prevalences. However, the possibility that the negative influence of GHD on vitamin D levels is concealed in the absence of light exposure and is more pronounced in the summer seasons, for example due to the relatively high melanin content of the skin, can not be excluded. In addition, notably, in the above-mentioned study the subjects enrolled were young adults with a mean age of 38 years, while we enrolled children with a mean age of 10 years, which are then more comparable to the healthy schoolchildren of the other study [31].

We found no effect of GH treatment on serum Ca, P and PTH levels and these data are partially in line with the literature. A few years ago Wright et al. [33] showed that GH increases serum vitamin D levels independently of circulating PTH in healthy subjects, assuming this as a potential mechanism by which GH stimulates increases in bone mass. Conversely, Ahmad et al. [34] demonstrated a regulatory effect of GH on bone mineral metabolism by an increase in serum calcium, phosphate and vitamin D and a decrease in PTH in adult GHD patients. In these subjects a PTH resistance status with increased serum PTH levels has been documented and GH replacement seems to restore PTH secretion rhythm in addition to increasing vitamin D concentration [35]. Conversely, in line with our data, Bianda et al. [5, 36] demonstrated the effect of GH on vitamin D without changes in other bone parameters in both healthy and GHD adult subjects. In addition, in support of our data, the effect of GH replacement on bone turnover seems to be independent of PTH, as some studies have failed to observe any consistent change in PTH levels [28, 37]. Conversely, the change in AP levels, documented in healthy children during growth as a result of osteoblast activity [38], has also been confirmed in our study. A limitation of this study is represented by the lack of data regarding more specific bone apposition and resorption markers and bone mineral density, whose data were not available for all patients.

The absence of correlation between vitamin D and IGF1 levels both in baseline and after 12 months of GH treatment further suggests a direct stimulatory effect of GH on vitamin D, not necessarily mediated by IGF1 increase. This finding is supported by the evidence that children with lower GH values (expressed by the AUC of GH during stimulation tests), and not IGF1, at baseline showed concomitant lower vitamin D levels. However, regardless of the season of evaluation, in the entire cohort we found that children with lower concentrations of vitamin D did not have lower growth velocity after 12 months of treatment or lower IGF1 concentrations both before and after 12 months of GH treatment, probably because in all children GH dose was modulated to steadily maintain IGF1 levels in the normal range and a comparable growth velocity.

The relatively high prevalence of low vitamin D levels remaining after 12 months of GH treatment, regardless of the season, lead to the idea that GHD children could also profit from vitamin D supplementation. Future prospective interventional studies that include a control group, the absence of which is a limitation of our study, may better clarify this point.

In conclusions, even in a sunny country hypovitaminosis D is common in GHD children, more so in the winter, and 12 months of GH treatment slightly improves this condition. Vitamin D assessment should therefore be considered routinely in GHD children both at diagnosis and during the course of follow-up. Additional prospective studies with longer follow-up will demonstrate whether long-standing GH treatment can further reduce the high prevalence of low vitamin D levels in GHD children.

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Conflict of interest All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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