Original Article

Utility of insulin-like growth factor-1 (IGF-1) in growth hormone-treated short children – An experience from a tertiary level center

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ABSTRACT

Introduction: Very few studies have been conducted in low-middle-income countries to assess the response to growth hormone (GH) therapy by measuring the improvement in insulin-like growth factor-1 (IGF-1) concentrations. **Objectives:** The objective is to assess IGF-1 concentrations in patients receiving GH therapy to correlate the height increment with respect to increase in the IGF-1 concentrations, including IGF-1 Z-scores as a measure of safety profile. **Methods:** Clinical and anthropometric data were extracted retrospectively from hospital records of children aged 0–18 who received GH and had IGF-1 measured during the study period. Serum IGF-1 concentrations were analyzed by a solid-phase enzyme-linked immunosorbent assay. Patients with GH deficiency (GHD) and multiple pituitary hormone deficiency (MPHD) were grouped as group A, while participants receiving GH therapy for non-GHD/MPHD were clubbed as group B. **Results:** We report a significant positive correlation between an increase in IGF-1 values and increase in height. The improvement in height Z-scores was significantly higher in participants of group A as compared to B, with no significant difference in increase in IGF-1 Z-scores between the two groups. A total of 18.75% of subjects had IGF-1 Z-scores between +2 and +3, and these were largely subjects belonging to group B. **Conclusion:** The increment in height and height velocity Z-scores in the patients on GH correlated with increase in the IGF-1 concentrations, particularly in GHD/MPHD group of patients.

Key words: Height velocity, Insulin-like growth factor-1, Recombinant human growth hormone therapy

Growth occurs by an increase in size from the accretion of tissue mass. The chief endocrine factors regulating fetal growth are insulin and insulin-like growth factors 1 and 2 (IGF-1 and IGF-2). Growth hormone (GH), IGF-1, and thyroid hormones are the primary drivers of childhood growth and play no significant role in fetal growth [1]. The secretion of GH from the pituitary gland is regulated by GH-releasing hormone secreted by the hypothalamus [2]. The GH receptor mediates the action of GH, causing transcription of GH-dependent genes and production of IGF-1, the combination of these mediates the actions of GH, including effects on cell proliferation. IGF-1 is a 7.5 kDa single-chain polypeptide hormone sharing 50% homology with insulin, which is produced in the liver and peripheral tissues and can act in both an autocrine and paracrine manner to mediate the mitogenic and anabolic effects of GH [3]. IGF-1 is widely expressed with serum concentrations reflecting hepatic IGF production, which is regulated by GH and binds to the insulin receptor as well as the IGF-1 receptor (IGF-1R).

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The binding of IGF-1 to the IGF-1R leads to phosphorylation of the receptor and activation of insulin receptor substrate-1 that activates the PI3K, AKT, mTOR, and RAS-RAF-MAPK pathways, leading to cell proliferation and gene transcription [1]. The defect in this GH/IGF-1 axis may lead to short stature. For diagnosing the etiology of short stature, growth assessment, biochemical investigation of the GH/IGF-1 axis, and imaging of the hypothalamic-pituitary area are usually performed. Consensus guidelines recommend the evaluation of the GH/IGF axis by a pharmacological GH stimulation test after the exclusion of hypothyroidism, along with the measurement of the downstream GH-dependent factors like IGF-1 [4]. Like serum GH measurements, several reference preparations have been used for the calibration of IGF-1 assays. The variability of a single measurement of IGF-1 is around ±35% [5]. A meta-analysis of studies utilizing IGF-1 or IGF-1 binding protein 3 for the diagnosis of GH deficiency (GHD) identified that a single measurement of IGF-1 has moderate sensitivity of 69% (95% CI 63–70%) and specificity of 69% (95% CI 66–72%) [6].

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Recombinant human GH therapy for the treatment of short stature is safe and effective and is used not only for isolated GHD and multiple pituitary hormone deficiency (MPHD) but also for Turner syndrome (TS), Noonan syndrome, Prader–Willi syndrome, chronic kidney disease, small for gestational age babies that fail to catch up and patients with idiopathic short stature (ISS) [7]. Epidemiological evidence links higher IGF-1 concentrations to increased malignancy risk, thus, one of the main concerns surrounding GH therapy has been the potential for an increased risk of malignancy, particularly since children treated with GH may have a history of brain tumors or other malignancy, such as acute lymphoblastic leukemia [8]. Apart from the growth response, IGF-1 targets have also been proposed to guide and optimize dosing. However, not many studies have been conducted to assess the response (in terms of IGF-1 concentrations) in patients administered GH therapy and its correlation with height increment. We thus conducted this study with the following objectives (1) to assess IGF-1 concentrations in patients receiving GH therapy for various indications, (2) to assess the increment in height in these patients (subset) for an increase in the IGF-1 concentrations while on GH therapy, and (3) to assess the role of IGF-1 Z-scores for the assessment of safety profile in patients receiving GH therapy.

MATERIALS AND METHODS

This retrospective study was based on data mined from a tertiary care pediatric endocrine hospital in Pune City, Maharashtra, India, from January 2017 to January 2022. Details on anthropometry and medical history of patients who were referred for short stature were collected from case records of the hospital. A total of 634 children were studied from available records on whom IGF-1 concentrations had been performed in the study period. As this was a retrospective study and data were deidentified, a waiver was granted by the Institutional Ethics Committee.

Children with any of the following growth disorders

GHD, MPHD, ISS, familial short stature, skeletal dysplasia, small for gestation age (SGA) children, TS, and others on whom IGF-1 concentrations had been assessed were included in the study. The other group of study participants included subjects with short stature due to rickets, thalassemia, syndromic short stature, chronic kidney disease, Prader–Willi syndrome, Noonan syndrome, and cystic fibrosis.

Standard dose protocol for GH therapy had been prescribed based on the diagnosis of short stature. We divided the subjects into two groups, namely group A (GH deficient groups, i.e., GHD and MPHD) and group B (non-GHD/MPHD indications of GH therapy). The dose of GH as per clinical condition used in patients in the current study is mentioned in Table 1 [9]. The flow diagram for study participants is illustrated in Fig. 1.

Data on anthropometric parameters (measured using standard protocols), bone age radiographs, and biochemical parameters were extracted from medical records. Anthropometric Z-scores were calculated using ethnic-specific reference data [10]. Height velocity Z-scores (HZZ) were derived using Indian reference data [11]. Bone age was computed from the radiograph of the left hand using the Tanner-Whitehouse method by a pediatric endocrinologist [12]. Serum IGF-1 concentrations were analyzed by a solid phase enzyme-linked immunosorbent assay with an intra-assay coefficient of variation (CV) of 4.7% and inter-assay CV of 7.2%. The IGF-1 concentrations were converted into Z-scores using Reference Intervals for IGF-1 From Birth to Senescence reference data published by Bidlingmaier *et al*. in 2014 [13].

Statistical methods

Data were analyzed using SPSS 26.0 for Windows (IBM SPSS, Bangalore, India). Descriptive statistics were used to evaluate the demographic, biochemical, and anthropometric parameters of study subjects (age, height, weight, BMI and their Z-scores, cumulative height velocity, IGF-1 concentrations, and bone age). All outcome variables were tested for normality before performing statistical analyses. Differences in means were tested using Student's *t*-test for parametric data and Mann-Whitney U test for non-parametric data. The one-way analysis of variance test was used to compare height Z-scores and IGF-1 Z-scores and to compare the difference in height Z-scores and IGF-1 Z-scores at diagnosis versus at follow-up. The Spearman correlation coefficient was used to assess the correlation between the difference in height Z-score and IGF-1 Z-score.

Table 1: Dose of GH used to treat various conditions in this study

Condition	Dose (µg/kg/day)
Growth hormone deficiency/MPHD	30
Turner syndrome	45
Small for gestational age	45
Idiopathic short stature	45
Skeletal dysplasia	50

MPHD: multiple pituitary hormone deficiency, GH: Growth hormone

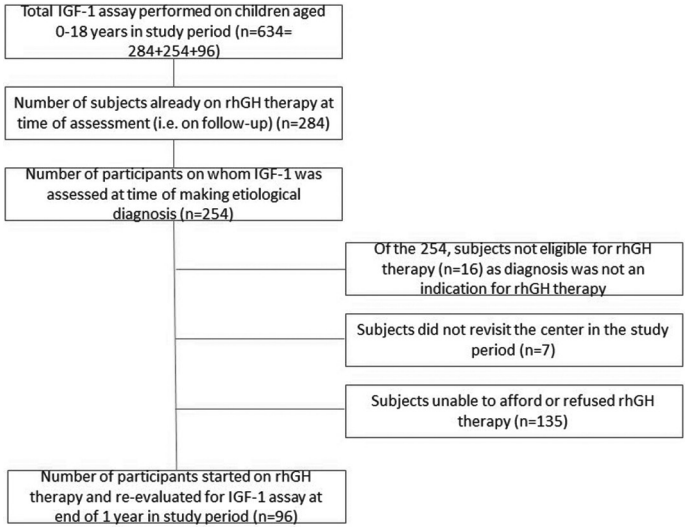

Figure 1: Flow diagram describing patient numbers included in the study

RESULTS

We present data on 634 subjects whose IGF-1 values had been assessed in the study. Of the subjects, 47.6% (n=302) were boys and 52.4% (n=332) were girls. A total of 40.2% (n=254) assessments were made at etiological diagnosis of short stature, while 59.8% (n=380) were made on follow-up. The etiological diagnosis of participants who underwent testing for IGF-1 concentrations is illustrated in Fig. 2. As shown in the figure, the highest number of subjects were diagnosed with ISS followed by GHD.

The mean and standard deviation of the chronological age, bone age, anthropometry, and IGF-1 values stratified by the timing of testing (diagnosis/follow-up) and etiological diagnosis of short stature are illustrated in Table 2. At diagnosis, the subjects with GHD and MPHD had significantly lower IGF-1 Z-scores as compared to subjects with ISS, SGA, and TS.

A subset analysis of 96 subjects (53 boys and 43 girls) on whom paired IGF-1 concentrations at baseline and follow-up (1 year after starting GH therapy) were available was performed. The correlation between improvement in height Z-score and increase in IGF-1 concentrations is illustrated in Fig. 3a. The Spearman correlation coefficient between the difference in IGF values and the increase in height was 0.232, $p<0.05$.

The mean change in height Z-score and IGF-1 Z-scores are shown in Table 3. The highest improvement in height Z-score was seen in patients with GHD and MPHD (0.8), while the highest increase in IGF-1 Z-scores was observed in patients with familial short stature (2.7). The improvement in height Z-scores was significantly higher in the GHD/MPHD group of patients than in the rest (0.8 vs. 0.5, $p<0.05$), while there was no significant difference in the increase of IGF-1 Z-scores (1.3 vs. 1.4). The correlation between HZZ and the difference in IGF-1 Z-scores is shown in Fig. 3b. The height velocity Z-score showed a linear correlation in subjects with GHD/MPHD while for other diagnoses, the correlation was not significant. A total of 18.75% of subjects had IGF-1 Z-scores above +2 but <+3 [9]. 88.9% (n=16) of these subjects belonged to group B, while only 11.1% (n=2) belonged to group A.

DISCUSSION

We report that at the time of diagnosis, the subjects with GHD and MPHD had significantly lower IGF-1 Z-scores as compared to subjects with ISS, SGA, and TS (non-GHD conditions). There was a significant positive correlation between the increase in IGF-1 values and the increase in height. Although the improvement in height Z-scores was significantly higher in the GHD/MPHD group of patients than the rest, there was no significant difference in the increase in IGF-1 Z-scores between the two groups. A total of 18.75% of subjects had IGF-1 Z-scores between +2 and +3, and these were largely subjects who received GH therapy for indications other than GHD and MPHD (group B) who received higher doses. Thus, subjects who were on treatment with GH for indications other than GHD/MPHD (group B) had lower increments in height and a higher proportion of participants with IGF1 Z-scores between +2 and +3.

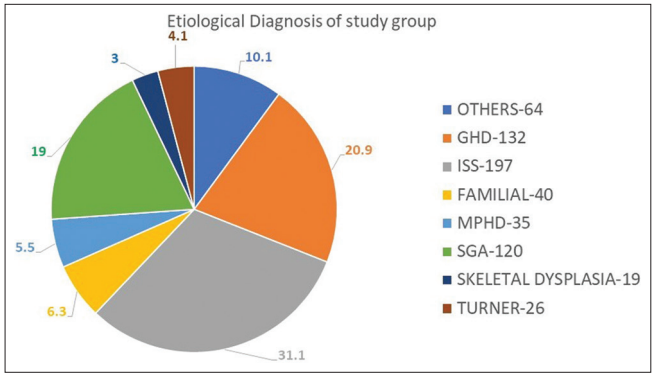

Figure 2: Etiological diagnosis of subjects enrolled in the study

As other disorders wherein GH therapy is indicated are not primarily related to the GH-IGF-1 axis such as SGA and TS, the baseline IGF-1 Z-scores in these conditions are usually higher than in GHD/MPHD, as found in our study. Specifically, children with ISS have normal birth weight and are GH-sufficient, and even though there are no accepted biochemical criteria for initiating GH treatment in ISS, it is strongly recommended that IGF-1 concentrations be obtained as part of the evaluation [14]. Similar to our study, Cohen *et al*. report that the changes in height-SDS from baseline for all the patients on GH therapy demonstrated a significant positive correlation ($r=0.5$, $p<0.01$) with changes in IGF-1 SDS. They also noted that the rise in the IGF-1 SDS significantly impacted height outcomes along with the GH dose and the pretreatment peak-stimulated GH concentration. However, theirs was a 2-year, open-label, randomized, IGF-1 concentration-controlled trial wherein only pre-pubertal short children with low IGF-1 concentrations were studied [15]. Another study also noted that IGF-1 SD scores significantly correlated with the gain in height SD scores ($r=0.33$, $p<0.01$) [16]. Thus, even though the improvement in height SD score in patients on GH therapy is multifactorial, IGF-1 response is a valid independent predictor and should be considered separately. IGF-1 SDS has been used as a parameter to predict response to GH therapy by various models such as Gothenburg and Cologne [17]. A review on the clinical use of growth prediction models observed that IGF-1-based dose titration also led to a decrease in the variation in growth response, thereby suggesting its utility in monitoring response to therapy [18].

We also report that the improvement in height Z-scores was significantly higher in GHD/MPHD group (group A) patients than the non-GHD indications of GH therapy (group B). Bakker *et al*. in 2008 demonstrated that subjects with GHD showed a 1st-year height velocity of 1.3 to 1.5 SD as compared to ISS and TS which showed 1.0 and 0.7 SD, respectively [19]. Ranke and Lindberg reported that responses in terms of improvement in height velocity at the end of the 1st and 2nd years were significantly higher in patients with severe GHD as compared to TS and in children with SGA on GH therapy [20]. Our results are thus in line with the observation that children with severe GHD are more responsive to GH replacement than patients with normal GH secretion, like ISS who respond less [21]. Similar to our results,

Table 2: Comparison of clinical, anthropometric, bone age and IGF-1 parameters by etiology at diagnosis and follow-up

Diagnosis	Age	Bone Age	Skeletal maturity	Height in cm	Height z-score	Weight in kg	Weight z-score	BMI in kg/m²	BMI z-score	IGF-1 in ng/ml	IGF-1 z-score
GHD											
Diagnosis (n=42)											
Mean	7.8	8.2	−1.3	102.3	−3.6	17.7	−2.8	15.0	−0.4	82.1	−1.9
SD	4.3	4	1.1	26.9	3.2	10.1	2.1	3.8	1.3	108.7	1.6
Follow-up (n=90)											
Mean	10.4	12.8	−0.7	124.6	−2.1	27.2	−1.5	16.3	−0.4	200.9	−0.6
SD	4.0	2.8	1.2	20.8	1.1	13.8	1.2	3.4	1.1	162.3	1.8
MPHD											
Diagnosis (n=11)											
Mean	8.6	11.8	−3.0	107.2	−3.3	20.2	−2.7	16.1	−0.3	41.3	−2.9
SD	5.3	1.6	3.5	28.4	1.5	10.4	2.7	2.5	1.1	41.5	2.1
Follow-up (n=23)											
Mean	11.4	12.4	0.1	133.2	−1.4	34.5	−0.6	18.4	0.2	213	−0.4
SD	4.2	3.3	2.2	22.1	1.5	13.5	1.1	3.6	0.8	127.1	1.6
ISS											
Diagnosis (n=94)											
Mean	11.1	11.0	−0.3	130.2	−1.8	30.1	−1.3	16.9	−0.3	230.9	−0.3
SD	2.8	3.1	1.3	17.3	1.0	11.6	1.3	3.2	1.0	168.2	1.7
Follow-up (n=103)											
Mean	11.8	13.2	−0.1	136.1	−1.5	33.9	−1.2	17.1	−0.3	359.8	0.9
SD	3.2	1.7	1.5	20.1	1.3	12.8	2.1	3.6	1.0	186.8	1.7
FAMILIAL											
Diagnosis (n=14)											
Mean	10.2	11.0	−0.5	123.1	−2.2	25.4	−1.7	16.1	−0.4	153.8	−1.2
SD	3.6	2.7	0.9	20.9	0.8	10.1	1.1	2.6	0.9	117.1	1.1
Follow-up (n=26)											
Mean	11.6	12.8	0.3	136.3	−1.3	32.1	−1.1	16.7	−0.4	382.5	1.1
SD	2.8	1.5	1.2	16	0.5	9.7	0.7	2.4	0.7	168.2	1.4
SGA											
Diagnosis (n=57)											
Mean	8.1	7.5	−0.5	110.7	−2.5	18.5	−2.6	14.2	−1.1	123.1	−1.2
SD	3.3	3.7	1.3	19.6	1.1	8.4	1.6	2.2	1.1	109.2	1.5
Follow-up (n=63)											
Mean	8.7	12.0	0.6	118.6	−1.8	21.7	−2.1	14.5	−1.1	268.6	0.8
SD	3.2	2.3	1.2	20.3	1.1	10.1	1.6	2.6	1.2	170.4	1.6
Skeletal dysplasia											
Diagnosis (n=6)											
Mean	7.7	10.0	0.4	98.3	−4.2	19.5	−2.4	18.8	1.4	110.3	−0.7
SD	4.1	0.7	0.1	17.9	0.5	11	1.6	4.3	1.3	43.5	1.2
Follow-up (n=13)											
Mean	8.5	12.3	0.5	106.8	−3.5	23.0	−1.4	19.1	1.1	271.4	1.1
SD	3.9	0.2	1.0	21.1	0.8	10.0	1.6	2.8	1.3	127.1	1.6
Turner syndrome											
Diagnosis (n=6)											
Mean	9.8	8.1	−0.1	121.6	−2.1	30.2	−0.1	20	1.1	219.8	0.1
SD	1.7	1.0	0.1	11.2	0.5	8.5	0.6	2.2	0.5	181.8	2.2
Follow-up (n=20)											
Mean	10.8	12.6	0.4	124.6	−2.2	28.6	−1.1	17.8	0.1	272.9	0.5
SD	3.0	0.8	0.5	13.6	0.9	9.5	1.3	3.1	1.0	153.5	2.1

(Contd...)

Table 2: ***(Continued)***

Diagnosis	Age	Bone Age	Skeletal maturity	Height in cm	Height z-score	Weight in kg	Weight z-score	BMI in kg/m²	BMI z-score	IGF-1 in ng/ml	IGF-1 z-score
Others											
Diagnosis (n=24)											
Mean	11.4	12.9	1.1	132.2	−1.4	33.1	−1.1	18	−0.1	215.3	−0.4
SD	3.5	0.7	2.5	16.6	1.6	17.1	2.3	6.1	1.7	163.3	2.1
Follow-up (n=40)											
Mean	10.6	12.4	0.7	132.4	−1.1	31.1	−0.6	17.3	0.1	287.3	0.3
SD	2.9	1.8	2.1	19.2	1.7	11.7	1.9	4.4	1.3	173.9	1.8

SD: Standard deviation, BMI: Body mass index, IGF-1: Insulin like growth factor-1, GHD: Growth hormone deficiency, MPHD: Multiple pituitary hormone deficiency, ISS: Idiopathic short stature, SGA: Small for gestational age

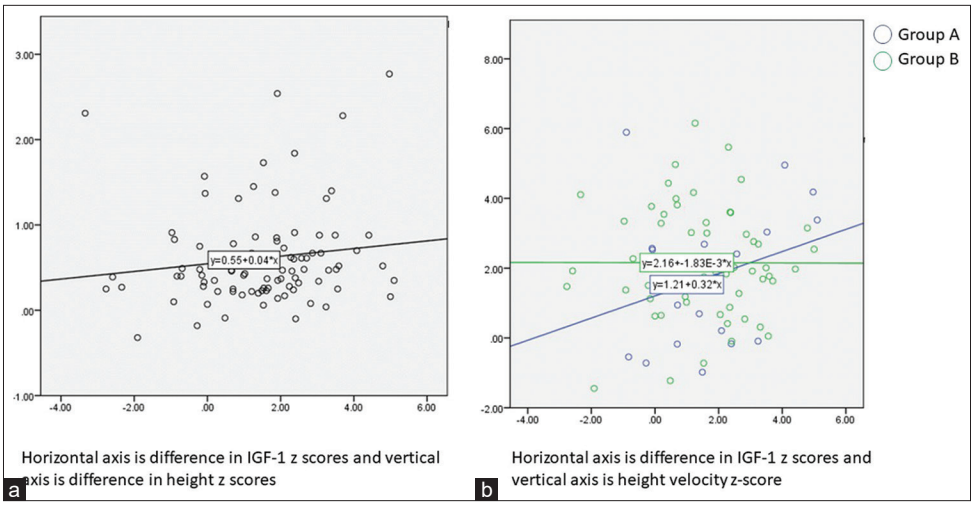

Figure 3: (a) Scatter plot showing correlation between improvement in height z-score and increase in IGF-1 concentrations. (b) Scatter plot showing correlation between height velocity z-scores and difference in IGF-1 z-scores by groups

Table 3: Comparison of difference in height and IGF-1 between baseline and endline in the study group

Diagnosis	Height difference*		Height Z-score difference*		Igf1 Z-score difference	
	Mean	SD	Mean	SD	Mean	SD
Group A (n=27)	13.3	10.3	0.8	0.7	1.3	1.8
Group B (n=69)	8.8	8.7	0.5	0.4	1.5	1.6

SD: Standard deviation, BMI: Body mass index, IGF-1: Insulin like growth factor-1, GHD: Growth hormone deficiency, MPHD: Multiple pituitary hormone deficiency, ISS: Idiopathic short stature, SGA: Small for gestational age. *Statistically significant difference between group A and group B at $P<0.05$

Bang *et al*. demonstrated that change in IGF-1 SDS during the 1st year of treatment correlated with the 1st-year change in height SDS (r=0.312, p<0.001). They also report that 1st year gain in height SDS in GHD was higher than in SGA, TS, and ISS (0.46–0.8 vs. 0.27–0.34). Short-term generation of IGF-1 and change in IGF-1 SDS during the 1st year of GH therapy did not differ among treatment groups, a finding echoed by our study [22].

We report 18.75% of subjects having IGF-1 Z-scores above +2 but <+3 without development of any clinical adverse events. In clinical practice, children with GHD need replacement of "physiological" GH, and ideal therapy would maintain IGF-1 within the appropriate levels for gender and age. On the other hand, children with growth disorders other than GHD may require supraphysiologic levels of IGF-1 to obtain the desired beneficial effects of treatment [23]. The GH Research Society guidelines published in 2019 suggest that in certain conditions characterized by partial IGF-1 insensitivity such as SGA and TS, IGF-1 concentrations above +2 SDS may be needed for effective growth [24].

To the best of our knowledge, ours is the first study from low-and middle-income countries where response to GH therapy in terms of height gain and increment in IGF-1 values for various clinical indications has been correlated. The uneven distribution of subjects across various clinical indications, the retrospective nature of the the study, and lack of uniformity in follow-up timing are our limitations.

CONCLUSION

To conclude, the increment in height and HZZ in patients on GH therapy were in line with the increase in IGF-1 concentrations particularly in the subset of GHD/MPHD group of patients. The IGF-1 Z-scores were higher in subjects of group B as they received GH therapy at higher doses but were still within safety limit of +2 to +3.

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