Original Article

# An Observational Study on Response to Growth Hormone Therapy in Indian Patients of Short Stature with Special Emphasis on Biochemical Parameters and Bone Biomarkers

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## Abstract

**Introduction:** There is a lack of Indian data on short stature treatment using recombinant human growth hormone (rhGH). We explored the effects of such treatment in eastern Indian patients, with emphasis on biochemical parameters and bone biomarkers in addition to basic anthropometry. **Methods:** Our descriptive study covered 50 short stature patients of varied aetiology attending endocrine outpatient department (OPD) of a tertiary care teaching hospital. Patients were followed up for 1 year after the index visit, and prospective data were reconciled with past medical records. A dose of rhGH used was 0.18–0.375 mg/kg as standard, starting dose mostly being 0.2 mg/kg. Dosing was adjusted if the physician judged the clinical outcome to be less favourable than expected. Anthropometric parameters (height, weight, body mass index (BMI) and skeletal age) were recorded clinically, and various biochemical parameters and bone biomarkers were estimated from blood. **Results:** Among 50 subjects, 60% had idiopathic growth hormone (GH) deficiency and 26% had Turner's syndrome. The median age at treatment start was 10 years, and the median treatment duration was 25.5 months. The height increased more in the first year of therapy. In the last 6 months, the height velocity was approximately 0.5 cm/month. Although the weight increased significantly, the increment slowed down in the last 6 months. Both remained less than age- and gender-matched references throughout. The skeletal age was on average 2 years behind chronological age (CA)—being 8.7, 9.6 and 11.3 years, respectively, at therapy start, after one year and at study end. Fasting blood glucose (FBG), total cholesterol and calcium level changes were not statistically significant. Serum cortisol and phosphate showed a modest but statistically significant rise, while thyroid-stimulating hormone (TSH) level declined. Insulin-like growth factor 1 (IGF-1) increase was relatively pronounced. Among bone biomarkers, a decrease in CTx and an increase in vitamin D were significant. Dual-energy X-ray absorptiometry (DEXA) data indicated that bone mineral density was less than that of age-matched controls despite treatment. The therapy was well tolerated. **Conclusions:** rhGH treatment leads to significant improvement in anthropometry in Indian children comparable with Western data. Bone biomarker changes indicate decreased bone resorption and increased bone formation although bone mineral density still lags behind age-matched controls.

**Keywords:** Bone biomarker, dual-energy X-ray absorptiometry, recombinant human growth hormone, short stature

## Introduction

Short stature is defined as the height below the third percentile of the general population. The most common physiological causes of short stature are familial short stature and delayed (constitutional) growth, while pathological causes include growth hormone deficiency (GHD), Turner's syndrome and chronic renal insufficiency.[1,2] Recombinant human growth hormone (rhGH) was introduced for the treatment of short stature in 1985. Studies on the safety and efficacy of rhGH have been documented through some large international databases of rhGH-treated patients, such as GENESIS sponsored by Eli Lilly[3,4] and Kabi Pharmacia International Growth Study (KIGS) sponsored by Pfizer.[5-7] However, most of these databases are focused on Western populations.

Information on rhGH therapy and its impact on Indian children are scarce. Being a costly drug, the majority of Indian patients

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cannot afford it privately and are dependent on institutional support for treatment. However, there is a considerable lack of awareness about the treatment of short stature, long latency in seeking treatment, overburdening of clinics by patients, lack of laboratory support for treatment at primary care centres and lack of standardised protocols for rhGH use. These, coupled with the relative lack of organised record keeping, impose challenges peculiar to our circumstances. Therefore, despite the Western experience, it is important to document the use and outcomes of growth hormone (GH) treatment in the Indian scenario.

Our hospital, which is a government set-up, is one of the few tertiary care institutions in India where rhGH treatments are offered to patients free of cost. This provides access to a steady cohort of short stature patients seeking treatment. Against this backdrop, we planned this study to document the modalities of use of rhGH in short stature, treatment response and safety of rhGH therapy, in terms of not only basic anthropometry but also through laboratory assessment of selected biochemical parameters and bone biomarkers and through bone densitometry. The study aimed to provide India-specific data on rhGH use for short stature, especially from eastern India.

## Materials and Methods

Ours was a descriptive observational study with a prospective follow-up. It was carried out in the endocrinology outpatient department (OPD) of our tertiary care teaching hospital after obtaining written informed consent from the parent or legal guardian and additional informed assent from minor participants above 6 years of age. Institutional ethics committee approval was obtained beforehand.

Patients of either sex receiving rhGH therapy for growth disorders, who had not yet completed natural growth and skeletal maturation, were included. Sampling was purposive in nature. Patients with a concomitant illness that could affect growth potential (e.g., malnutrition) and those with pre-existing diabetes, severe obesity, active malignancy and expressing inability to report for follow-up at 6-month intervals were excluded.

The following data were captured:

- Nature (cause) of short stature
- Dosing of rhGH
- Anthropometric measurements (height, weight, body mass index (BMI) and growth velocity)
- Bone age (BA) (skeletal maturation)
- Biochemical laboratory parameters, namely fasting blood glucose (FBG), insulin-like growth factor 1 (IGF-1), cortisol, thyroid-stimulating hormone (TSH) and fasting lipid profile
- Bone biomarkers, namely calcium, phosphate, vitamin D, intact parathyroid hormone (iPTH), C-terminal telopeptide of type I collagen (CTx), N-terminal propeptides of type I procollagen (PINP) and osteocalcin[8]
- Dual-energy X-ray absorptiometry (DEXA) assessment of bone density through total body less head (TBLH) and anteroposterior lumbar spine (LS) scans
- Sexual maturity in Turner's syndrome subjects
- Suspected adverse drug reactions (ADRs) to rhGH.

Medical records were reviewed carefully at the screening visit, and a clinical examination was performed. Patients were followed up initially at the end of 1 year and then at 6-month intervals for anthropometry. Data earlier to index visit were obtained from medical records. Follow-up visits were scheduled earlier when required.

The height was measured with the subject standing upright, without shoes and head accessories, using a stadiometer. The weight was measured using a calibrated digital weighing machine. The subject was asked to stand firmly on the machine with minimum additional weight (dress) and without any support. BMI was estimated as weight (kg)/height (m) squared. Since growth is not continuously linear, it is important to assess its progression over a longer period of time (6–12 months). Serial measurement of height depicts an individual's pattern of growth or growth velocity. This was estimated as follows:

$$\text{Growth velocity}\left(\text{cm / year}\right) = \frac{\text{Height T2}\left(\text{cm}\right) - \text{Height T1}\left(\text{cm}\right)}{\text{Number of months between T1 and T2}} \times 12$$

Where T1 denotes an earlier time and T2 is at a later time.

The Indian Academy of Pediatrics (IAP) growth charts (revised Khadilkar's charts)[9] were used as a reference.

The growth potential for any child is largely influenced by genetic and environmental factors. A child born to short parents is expected to be short and vice versa. Based on this, the concept of determining the mid-parental height (MPH) is employed to detect stature abnormalities. The MPH (in cm) was calculated separately for boys and girls as follows:

- MPH (boy) = (father's height + mother's height + 13)/2
- MPH (girls) = (father's height + mother's height - 13)/2.

For normal stature, the target height range for boys is ± 10 cm of MPH and for girls is ± 8.5 cm of MPH.

Estimation of skeletal maturation or BA is an essential element in the workup of short stature. By convention, the left hand and wrist are radiographed and bone maturity is computed by two methods. The first is by comparison with radiographs of standard ages available as Greulich–Pyle Atlas.[10,11] The second is by scoring individual bones of the hand and wrist through the Tanner–Whitehouse method.[12,13] When BA is <2 standard deviations (SDs) of chronological age (CA), skeletal maturation is considered delayed. In familial short stature, the BA matches the CA; the height age (HA) is less than both BA and CA (i.e., HA < BA = CA). In contrast, in pathological short stature, the BA is delayed as compared to HA and is further

behind CA (i.e., BA < HA < CA). A delay of 2 years or more for BA compared with CA is clearly abnormal.

Biochemical parameters and bone biomarkers were evaluated approximately 1 year after treatment commencement and repeated after 1 year. DEXA scan was, however, performed only once towards the end of the observation period. Treatment-emergent adverse effects were carefully enquired about and looked for at each visit.

Data have been summarised by routine descriptive statistics, namely mean and SD for numerical variables that are normally distributed, median and interquartile range (IQR) for skewed numerical variables and counts and percentages for categorical variables. Changes over time in numerical variables were assessed for statistical significance by repeated-measures analysis of variance (ANOVA) or Friedman's ANOVA, as appropriate, followed by Tukey's test or Dunn's test, respectively, as a post hoc test for parametric and nonparametric data. Analyses were two-tailed, and the statistical significance level was set at $P < 0.05$ for all comparisons. MedCalc version 15.8 (Mariakerke, Belgium: MedCalc Software bvba, 2015) software was used for statistical analysis.

### Ethical clearance statement

The study was approved by IPGME&R Research Oversight Committee vide letter no. Inst/IEC/2018/174 on 26.02.2018. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follows the guidelines laid down in Declaration of Helsinki 2008.

## Results

### Demographic, socioeconomic and clinical characteristics

Among 50 recruited patients, 26 (52%) were male and the rest were female. Thirty (60%) patients were diagnosed with idiopathic growth hormone deficiency (IGHD), 13 (26%) with Turner's syndrome, two (4%) with multiple pituitary hormone deficiency, two (4%) with GHD due to craniopharyngioma, one (2%) each with Russell–Silver syndrome, GHD due to pituitary microadenoma and GHD due to empty sella syndrome secondary to viper snake bite. Most families hailed from a rural background and income-wise belonged to lower socio-economic strata.

The mean (± SD) age at the start of GH treatment was 10.4 ± 3.06 years and during the last follow-up was 13.4 ± 2.91 years. The mean treatment duration was 31.2 ± 13.03 months (median (IQR): 25.5 (23.0–36.0) months). From the first hospital visit up to the start of GH treatment, the mean duration was 2.5 ± 2.67 months (median (IQR): 2.0 (1.0–4.0) months).

### rhGH dosing

Patients received rhGH subcutaneously every night at bedtime using an insulin syringe. The starting dose of GH therapy was 0.28 ± 0.66 (median (IQR): 0.20 (0.20–0.20)) mg/kg/day or 2.03 ± 0.81 (median (IQR): 1.85 (1.40–2.50)) units/day as shown in Table 1.

### Anthropometric parameters

The mean birth weight of study subjects was 2.04 ± 0.46 kg, and most (80%) were born with low birth weight; 14% of subjects had very low birth weight—among them most were Turner's syndrome patients. The weight change over time was statistically significant. The initial mean weight at the start of GH therapy was 20.2 ± 5.86 kg, which increased to 24.9 ± 7.29 kg after one year of therapy and finally to 29.9 ± 7.44 kg. Thus, there was nearly 9.7 kg gain in mean weight slightly over the 2-year median treatment period.

The parental height distribution of the study participants is summarised in Table 2, while Table 3 depicts the changes in weight and height of the participants themselves over time. The height increased during GH therapy from a baseline of 111.9 ± 10.65 cm to finally 129.3 ± 9.89 cm, a statistically significant change. The mean height velocity was thus calculated to be 0.48 ± 0.18 cm/month (median (IQR): 0.50 (0.33–0.67) cm/month) with a range of 0.25–0.83 cm/month.

Although most fathers and mothers were of normal build, having normal height profile according to the reference Indian population, the subjects' height was considerably less than the respective MPH. Even after GH treatment, most failed to achieve target adult height within the study period.

During our first observation, the mean BMI was 15.8 ± 2.90 kg/m$^2$, which increased to 17.7 ± 3.04 kg/m$^2$ at the end of observation. In the initial one year, the mean BMI change

**Table 1: Recombinant human growth hormone (rhGH) dosing in the study participants**

| | Starting dose ($n$=50) | First change in dose ($n$=50) | Second change in dose ($n$=37) | Dose at last follow-up ($n$=50) |
|---|---|---|---|---|
| In mg/kg/week | | | | |
| Range | 0.10–0.37 | 0.15–0.40 | 0.16–0.40 | 0.18–0.38 |
| Mean±SD | 0.23±0.07 | 0.24±0.07 | 0.26±0.07 | 0.22±0.05 |
| Median (IQR) | 0.20 (0.20–0.20) | 0.20 (0.20–0.26) | 0.25 (0.20–0.30) | 0.20 (0.20–0.25) |
| In units/day | | | | |
| Range | 1.00–4.50 | 1.00–4.50 | 1.30–4.50 | 1.50–3.50 |
| Mean±SD | 2.03±0.81 | 2.26±0.83 | 2.57±0.83 | 2.25±0.52 |
| Median (IQR) | 1.85 (1.40–2.50) | 2.00 (1.50–2.50) | 2.50 (2.00–3.00) | 2.00 (2.00–2.50) |

was statistically significant, but this was not so during the last 6 months of therapy.

The initial mean skeletal age (according to the growth percentile chart) at the start of GH therapy was 8.8 ± 3.36 years, which increased to 9.6 ± 3.45 years after one year of therapy and further to 11.4 ± 3.14 years at the study end. The increase in skeletal age was statistically significant overall, as well as every 6 months. This implies BA increased steadily for rhGH therapy.

## Laboratory parameters

The changes in laboratory parameters are summarised in Table 4. Evidently, there was a modest but statistically significant rise in serum cortisol and phosphate levels by the end of the observation period and a small decrease in triglyceride and TSH. The rise in IGH-1 was, however, pronounced and significant [Table 4 and Figure 1]. Changes in fasting glucose, total cholesterol and calcium were not statistically significant.

## Bone markers

The changes in bone biomarkers are depicted in Table 5 and Figure 2. These estimations were carried out twice—after 1 year from the commencement of treatment and after another year of further treatment. The increase in vitamin D level from 31.8 ± 11.41 nmol/L to 35.7 ± 11.70 nmol/L was statistically significant ($p = 0.003$), as was the decrease in CTx value from 1.9 ± 0.59 ng/ml to 1.7 ± 0.51 ng/ml ($p < 0.001$). However, changes in osteocalcin, iPTH and PINP were minimal or modest and not statistically significant.

## DEXA scan for bone density

The data obtained towards the end of our observation period are depicted in Table 6. Due to logistical constraints, we could not do DEXA scans initially. The Z-score is the number of SDs above or below the mean of age-matched controls. Despite two years of treatment, the Z-scores indicated bone mineral density far less than in age-matched controls.

## Changes in sexual maturity in Turner's syndrome subjects

This is summarised in Table 7, the data indicating a progressive increase in sexual maturity.

## Adverse events

No serious adverse events were encountered. Only two (4%) subjects encountered mild lipodystrophy at the injection site

**Table 2: Summary of parental height distribution of the study participants**

| Parameter | Father's height ($n=50$) | Mother's height ($n=50$) | Mid-parental height ($n=50$) |
|---|---|---|---|
| Range | 149.00–175.00 | 143.00–167.00 | 144.50–169.50 |
| Mean±SD | 164.1±7.02 | 151.7±4.27 | 158.2±7.38 |

Height measurements are in cm

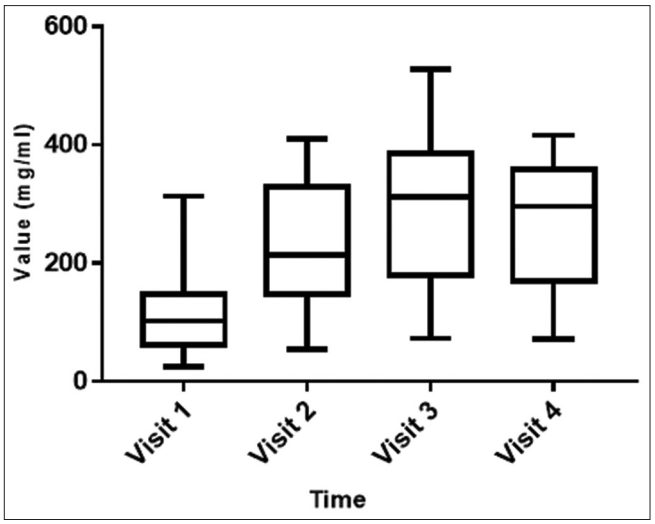


**Figure 1:** Insulin-like growth factor-1 change over time. Intervals between the successive visits are around 1 year, 6 months and 6 months, respectively, making up a 2-year observation

**Table 3: Changes in basic anthropometry over time in the 50 study participants**

| Parameter | Visit 1 Baseline ($n=50$) | Visit 2 After 1 y ($n=50$) | Visit 3 After 1.5 y ($n=50$) | Visit 4 After 2 y ($n=50$) | *P* |
|---|---|---|---|---|---|
| Height (cm) | | | | | Overall: <0.001 |
| Range | 84.0–137.0 | 96.0–145.4 | 105.0–150.0 | 107.0–153.5 | Visit 2 vs visit 1: <0.001 |
| Mean±SD | 111.9±10.65 | 120.4±10.28 | 126.4±9.39 | 129.3±9.89 | Visit 4 vs. visit 3: <0.01 |
| Weight (kg) | | | | | Overall: <0.001 |
| Range | 8.9–34.7 | 10.0–45.0 | 12.0–42.0 | 14.0–52.0 | Visit 2 vs visit 1: <0.001 |
| Mean±SD | 20.2±5.86 | 24.9±7.29 | 27.4±6.31 | 29.9±7.44 | Visit 4 vs. visit 3: <0.01 |
| BMI (kg/m$^2$) | | | | | Overall: <0.001 |
| Range | 9.2–23.9 | 9.6–24.3 | 10.5–23.7 | 11.6–25.0 | Visit 2 vs visit 1: <0.001 |
| Mean±SD | 15.8±2.90 | 16.9±3.32 | 16.9±2.88 | 17.7±3.04 | Visit 4 vs. visit 3: NS |
| Bone age (y) | | | | | Overall: <0.001 |
| Range | 2.0–16.0 | 3.0–17.0 | 4.0–17.0 | 5.0–18.0 | Visit 2 vs visit 1: <0.001 |
| Mean±SD | 8.8±3.36 | 9.6±3.45 | 10.7±3.19 | 11.4±3.14 | Visit 4 vs. visit 3: <0.01 |

BMI: Body mass index, Visit 2 vs visit 1 denotes change over the first 1 year of observation, Visit 4 vs visit 3 denotes change over the last 6 months of observation

**Table 4: Changes in laboratory parameters over time in the 50 study participants**

| Parameter | Visit 1 Baseline (*n*=50) | Visit 2 After 1 y (*n*=50) | Visit 3 After 1.5 y (*n*=50) | Visit 4 After 2 y (*n*=50) | *P* (over time) |
|---|---|---|---|---|---|
| Fasting glucose (mg/dL) | | | | | Overall: NS |
| Range | 65.0–115.0 | 62.0–125.0 | 67.0–115.0 | 65.0–115.0 | Visit 2 vs visit 1: NS |
| Mean±SD | 89.7±12.77 | 86.1±14.12 | 89.2±10.98 | 89.6±12.88 | Visit 4 vs. visit 3: NS |
| Cortisol (mcg/dL) | | | | | Overall: <0.05 |
| Range | 4.1–18.60 | 3.4–17.80 | 4.6–24.10 | 8.2–21.30 | Visit 2 vs visit 1: NS |
| Mean±SD | 11.7±2.89 | 11.3±2.86 | 13.6±4.31 | 12.4±3.20 | Visit 4 vs. visit 3: NS |
| Total cholesterol (mg/dL) | | | | | Overall: NS |
| Range | 75.0–215.0 | 75.0–216.0 | 116.0–215.0 | 108.0–203.0 | Visit 2 vs visit 1: NS |
| Mean±SD | 155.3±35.66 | 157.9±35.23 | 166.9±29.20 | 155.2±28.66 | Visit 4 vs. visit 3: NS |
| Triglyceride (mg/dL) | | | | | Overall: <0.001 |
| Range | 52.0–162.0 | 50.0–143.0 | 47.0–103.0 | 57.0–100.0 | Visit 2 vs visit 1: NS |
| Mean±SD | 101.9±28.54 | 99.2±24.67 | 79.0±16.80 | 75.7±12.96 | Visit 4 vs. visit 3: NS |
| TSH (micro-unit/mL) | | | | | Overall: <0.05 |
| Range | 0.75–7.14 | 0.73–6.00 | 0.10–7.10 | 0.03–7.10 | Visit 2 vs visit 1: NS |
| Mean±SD | 3.75±2.04 | 3.19±1.77 | 2.27±1.36 | 2.49±1.38 | Visit 4 vs. visit 3: NS |
| Median (IQR) | 3.64 (0.75–7.14) | 3.05 (0.73–6.00) | 2.10 (1.41–2.80) | 2.32 (1.30–3.14) | |
| Calcium (mg/dL) | | | | | Overall: NS |
| Range | 8.1–10.1 | 8.1–10.5 | 6.1–10.2 | 6.1–9.9 | Visit 2 vs visit 1: NS |
| Mean±SD | 9.2±0.58 | 9.4±0.69 | 8.6±0.94 | 8.8±0.83 | Visit 4 vs. visit 3: NS |
| Phosphate (mg/dL) | | | | | Overall: <0.01 |
| Range | 2.60–5.10 | 2.60–5.10 | 3.10–5.40 | 3.20–5.60 | Visit 2 vs visit 1: NS |
| Mean±SD | 3.77±0.76 | 3.78±0.73 | 4.31±0.59 | 4.50±0.41 | Visit 4 vs. visit 3: NS |
| IGF-1 (mg/dL) | | | | | Overall: <0.001 |
| Range | 25.0–313.0 | 54.0–410.0 | 73.0–527.0 | 72.0–416.0 | Visit 2 vs visit 1: <0.001 |
| Mean±SD | 107.0±60.09 | 234.3±105.66 | 296.3±126.09 | 272.2±104.65 | Visit 4 vs. visit 3: NS |

FBG: Fasting blood glucose, IGF: Insulin-like growth factor, IQR: Interquartile range, SD: Standard deviationm, Visit 2 vs visit 1 denotes change over the first 1 year of observation, Visit 4 vs visit 3 denotes change over the last 6 months of observation

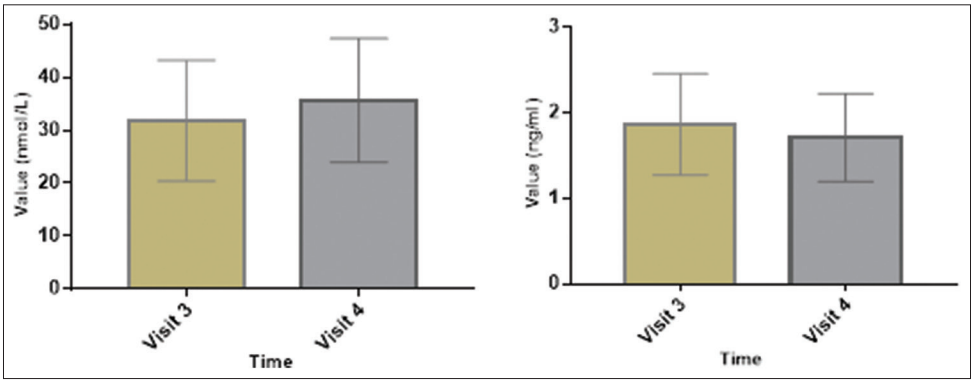


**Figure 2:** Changes in selected bone-related biomarkers over time (1 year): left panel—vitamin D and right panel—C-terminal telopeptide of type I collagen (CTx)

that was noted within a few weeks of commencement of the subcutaneous injections but disappeared spontaneously approximately 3–4 months after starting site rotation. There were no premature drug withdrawals.

A comparison of the major indications of GH therapy (IGHD and Turner's syndrome) is summarized in Tables 8–10.

While comparing the two major groups of GH recipients, it was observed that the mean (±SD) height improved from 112.2 ± 11.38 cm to 127.2 ± 10.31 cm in the IGHD group and from 111.7 ± 7.20 cm to 128.8 ± 5.19 cm in Turner's syndrome after 2 years of treatment ($P < 0.001$ for both). However, the final height between the two groups was not different.

The BA improved from 9.0 ± 3.34 years to 11.2 ± 3.41 years in the IGHD group and from 8.1 ± 2.72 years to 11.4 ± 1.89 years in Turner's syndrome during the same period ($P < 0.001$ for both).

Though there were no significant changes in calcium and 25(OH) D level from a baseline to the end of the study in either

group, phosphate level improved significantly in both groups implying phosphate retaining effects of GH.

The TBLH Z-score at the end of the study was not different between the two groups. The median (with IQR) for TBLH Z-score was –1.60 (–1.80 to –1.00) for IGHD and –1.60 (–2.50 to –0.80) for Turner's syndrome. Whereas the bone formation markers, for example osteocalcin and PINP, did not improve in either group, the bone resorption marker decreased significantly in both groups.

**Table 5: Changes in bone markers over time in the 50 study participants**

| Parameter | After 1-year treatment (*n*=50) | End of observation (*n*=50) | *P* |
|---|---|---|---|
| iPTH (pg/mL) | | | |
| Range | 3.0–93.7 | 11.2–84.0 | 0.618 |
| Mean±SD | 43.0±18.30 | 43.8±14.04 | |
| 25(OH) Vit D (nmol/L) | | | |
| Range | 11.1–70.0 | 16.5–62.5 | 0.003 |
| Mean±SD | 31.8±11.41 | 35.7±11.70 | |
| Osteocalcin (ng/mL) | | | |
| Range | 39.2–288.9 | 57.5–292.7 | 0.937 |
| Mean±SD | 144.04±56.03 | 144.21±49.75 | |
| CTx (ng/mL) | | | |
| Range | 0.8–3.4 | 0.7–2.8 | 0.001 |
| Mean±SD | 1.9±0.59 | 1.7±0.51 | |
| PINP (ng/mL) | | | |
| Range | 159.5–1200.0 | 321.3–1432.6 | 0.268 |
| Mean±SD | 986.3±281.23 | 965.9±243.51 | |
| Median (IQR) | 1100.0 (902.7–1200.0) | 1046.8 (864.3–1145.3) | |

CTx: C-terminal telopeptide of type I collagen, iPTH: Intact parathyroid hormone, PINP: N-terminal propeptides of type I procollagen, Vit D: Vitamin D

## Discussion

An unrestricted supply of human GH became available with the introduction of the recombinant variety in 1985, and since then, various studies have been conducted in the west[14,15] and international databases[3-7] have been set up to document the benefits and adverse effects of rhGH use for the treatment of short stature of varied aetiology. Being expensive, its use is limited in India and Indian data on rhGH are less compared with Western data. It is possible that given genetic differences in Indian children, the response to rhGH treatment may not be uniform for all Indian children and may not be comparable to Western data. This, therefore, calls for studies on the effectiveness and adverse effects of rhGH use in different parts of India. In this study, we have addressed this gap for eastern India and there are no comparable studies from this region. The approach to a patient of short stature includes anthropometric measurements and plotting of standard growth curves, BA estimation, laboratory measurements and genetic assessments to diagnose the underlying diseases. Patients may need provocative GH testing, IGF-1 and insulin-like growth factor-binding protein 3 (IGFBP3) testing and neuroimaging for diagnosis. We adopted most of these approaches for our cohort of short stature patients.

Our study cohort had a mix of various aetiologies for short stature, though 60% of the subjects were diagnosed with idiopathic GHD and 26% had Turner's syndrome. The age of GH treatment commencement was around 10 years. From the first hospital visit to starting of GH treatment, the delay was around 2 months; this latency is of acceptable duration. Till the

**Table 6: DEXA scan findings at the end of the observation period in study participants**

| Parameter | TBLH Z-score (*n*=49) | TBLH BMD (*n*=49) | AP-LS Z-score (*n*=49) | AP-LS BMD (*n*=49) |
|---|---|---|---|---|
| Range | –3.30 to –0.20 | 0.58 to 0.92 | –4.40 to 0.50 | 0.44 to 0.95 |
| Mean±SD | –1.53±0.765 | 0.80±0.080 | –1.95±0.958 | 0.75±0.108 |
| Median (IQR) | –1.60 (–1.95 to –0.80) | 0.82 (0.75 to 0.87) | –2.10 (–2.70 to –1.20) | 0.75 (0.72 to 0.81) |

BMD: Bone mineral density, TBLH: Total body less head, AP-LS: Anteroposterior lumbar spine

**Table 7: Changes in sexual maturity in Turner's syndrome (*n*=13) subjects**

| Baseline | | 1 year after the start of treatment | | 1.5 years after the start of treatment | | End of observation at 2 years | |
|---|---|---|---|---|---|---|---|
| Stage | Count (%) | Stage | Count (%) | Stage | Count (%) | Stage | Count (%) |
| B0P0A0 | 9 (69.23%) | B0P0A0 | 6 (46.15) | B1P0A0 | 4 (30.77 | B1P0A0 | 1 (7.69) |
| B1P0A0 | 4 (30.77%0 | B1P0A0 | 4 (30.77) | B1P1A0 | 1 (7.69) | B1P1A0 | 3 (23.08) |
| | | B1P1A0 | 1 (7.69) | B1P1A1 | 1 (7.69) | B1P2A1 | 1 (7.69) |
| | | B2P0A0 | 1 (7.69) | B2P0A0 | 1 (7.69) | B2P1A0 | 2 (15.38) |
| | | B2P1A0 | 1 (7.69) | B2P1A0 | 3 (23.08) | B2P2A0 | 1 (7.69) |
| | | | | B2P1A1 | 1 (7.69) | B3P1A0 | 2 (15.38) |
| | | | | B3P1A1 | 1 (7.69) | B3P2A1 | 2 (15.38) |
| | | | | B3P2A0 | 1 (7.69) | B4P3A0 | 1 (7.69) |

end of the observation period, the median duration of treatment of our study subjects was 25 months. Attending physicians used a standard dose (mostly 0.2 mg/kg/week) for starting rhGH treatment. The dose was calculated on weekly basis and then converted to daily dosing in units. Dose adjustments were carried out according to the response of the patient and changes in anthropometry and laboratory parameters. There was no specific time period at which dose changes were effected. Per day dose (IU) changed as patients gained weight over time, but the weekly dose remained constant. Sometimes, the dosage was increased to a weekly dose of 0.375–0.4 mg/kg/week if the physician suspected GH resistance and the clinical outcome was less favourable than expected. The above-mentioned findings mirror the results of previous GH studies in India[16-20] and also the GH dosing reported by Western authors.[21]

Regarding anthropometry, despite mostly having parents of normal height profile according to the reference Indian population, the subject height was considerably less than the respective MPH in this study. The height remained less than age- and gender-matched references (IAP height–weight chart) throughout the observation. Even after rhGH treatment continuously for two years, most failed to achieve their target height. The height gain was more in the first year of therapy. In the last 6 months of observation, the height velocity was approximately 0.5 cm per month, which translates to approximately 6 cm per year. Most subjects were born with low birth weight, and absolute weight was also less than age- and gender-matched references throughout the course. However, weight gain over time was statistically significant. Weight increment also slowed down in the last 6 months. The BMI change in the first year of therapy was statistically significant but that during the last 6 months was not. Skeletal age is on average 2 years behind the subject's CA but improved steadily during therapy. Overall, we can say that there was a

**Table 8: Parental height distribution in the IGHD and Turner's syndrome subcohorts compared**

| Group | Height | Father's height | Mother's height | Mid-parental height |
|---|---|---|---|---|
| IGHD (*n*=30) | Range | 150.0–175.00 | 143.0–167.0 | 145.0–169.50 |
| | Mean±SD | 164.3±7.22 | 151.7±4.79 | 160.2±6.99 |
| Turner's syndrome (*n*=13) | Range | 152.0–172.0 | 149.0–157.0 | 144.5–157.0 |
| | Mean±SD | 163.4±6.17 | 151.8±2.77 | 151.1±3.64 |
| | *P* | 0.610 | 0.919 | <0.001 |

Height measurements are in cm

**Table 9: Basic anthropometry in the IGHD and Turner's syndrome subcohorts compared**

| Group | Parameter | Visit 1 Baseline | Visit 2 After 1 y | Visit 3 After 1.5 y | Visit 4 After 2 y | Over time *P* |
|---|---|---|---|---|---|---|
| IGHD (*n*=30) | Height (cm) | | | | | |
| | Range | 84.0–137.0 | 96.0–145.4 | 105.0–150.0 | 107.0–153.5 | <0.001 |
| | Mean±SD | 112.2±11.38 | 120.3±10.12 | 124.5±9.90 | 127.2±10.31 | |
| Turner's syndrome (*n*=13) | Height (cm) | | | | | |
| | Range | 93.0–121.0 | 99.5–130.4 | 118.0–132.0 | 120.0–136.0 | <0.001 |
| | Mean±SD | 111.7±7.20 | 118.7±7.38 | 126.1±4.66 | 128.8±5.19 | |
| | *P* | 0.893 | 0.601 | 0.592 | 0.605 | |
| IGHD (*n*=30) | Weight (kg) | | | | | |
| | Range | 8.9–34.7 | 10.0–41.0 | 12.0–42.0 | 14.0–47.0 | < 0.001 |
| | Mean±SD | 20.3±6.12 | 24.9±7.29 | 26.8±6.79 | 29.3±7.39 | |
| Turner's syndrome (*n*=13) | Weight (kg) | | | | | |
| | Range | 10.0–26.0 | 12.0–32.0 | 19.0–35.0 | 18.5–39.5 | <0.001 |
| | Mean±SD | 20.2±5.14 | 24.9±6.18 | 27.6±5.45 | 29.2±6.05 | |
| | *P* | 0.990 | 0.987 | 0.727 | 0.964 | |
| IGHD (*n*=30) | BMI (kg/m$^2$) | | | | | |
| | Range | 9.3–23.9 | 9.6–24.3 | 10.5–23.7 | 11.6–25.0 | <0.001 |
| | Mean±SD | 15.7±3.08 | 16.9±3.11 | 17.1±2.92 | 17.7±2.86 | |
| Turner's syndrome (*n*=13) | BMI (kg/m$^2$) | | | | | |
| | Range | 11.6–20.3 | 12.1–23.0 | 12.6–22.1 | 11.7–23.4 | 0.055 |
| | Mean±SD | 16.0±3.02 | 17.5±3.61 | 17.3±3.20 | 17.6±3.41 | |
| | *P* | 0.816 | 0.585 | 0.793 | 0.781 | |
| IGHD (*n*=30) | Bone age (y) | | | | | |
| | Range | 3.0–15.0 | 4.0–16.0 | 4.0–17.0 | 5.0–17.0 | <0.001 |
| | Mean±SD | 9.0±3.34 | 9.8±3.47 | 10.4±1.87 | 11.2±3.41 | |
| Turner's syndrome (*n*=13) | Bone age (y) | | | | | |
| | Range | 2.0–12.0 | 3.0–14.0 | 7.0–14.0 | 8.0–15.0 | <0.001 |
| | Mean±SD | 8.1±2.72 | 9.1±2.90 | 10.7±3.19 | 11.4±1.89 | |
| | *P* | 0.369 | 0.515 | 0.839 | 0.843 | |

BMI: Body mass index, IGHD: Idiopathic growth hormone deficiency

**Table 10: Laboratory parameters in the IGHD and Turner's syndrome subcohorts compared**

| Group | Parameter | Visit 1 Baseline | Visit 2 After 1 y | Visit 3 After 1.5 y | Visit 4 After 2 y | Over time *P* |
|---|---|---|---|---|---|---|
| IGHD | Fasting glucose (mg/dL) | | | | | |
| (*n*=30) | Range | 70.0–115.0 | 62.0–125.0 | 67.0–115.0 | 65.0–115.0 | 0.326 |
| | Mean±SD | 93.5±12.11 | 90.0±14.23 | 91.7±11.49 | 92.3±12.77 | |
| Turner's syndrome | Fasting glucose (mg/dL) | | | | | |
| (*n*=13) | Range | 66.0–101.0 | 63.0–104.0 | 72.0–100.0 | 66.0–102.0 | 0.337 |
| | Mean±SD | 84.9±12.19 | 80.5±13.20 | 83.0±7.65 | 85.2±12.50 | |
| | *P* | 0.042 | 0.049 | 0.017 | 0.099 | |
| IGHD | Cortisol (mcg/dL) | | | | | |
| (*n*=30) | Range | 4.1–17.5 | 3.4–17.8 | 4.6–21.3 | 8.6–19.2 | 0.148 |
| | Mean±SD | 11.6±3.00 | 11.7±2.97 | 12.7±3.69 | 12.6±2.59 | |
| Turner's syndrome | Cortisol (mcg/dL) | | | | | |
| (*n*=13) | Range | 8.6–18.6 | 8.4–15.4 | 9.5–24.1 | 10.1–21.3 | 0.053 |
| | Mean±SD | 12.1±3.31 | 10.9±2.11 | 15.4±4.69 | 14.7±3.55 | |
| | *P* | 0.632 | 0.451 | 0.046 | 0.031 | |
| IGHD | TC (mg/dL) | | | | | |
| (*n*=30) | Range | 89.0–215.0 | 110.0–216.0 | 116.0–215.0 | 109.0–202.0 | 0.448 |
| | Mean±SD | 159.8±33.49 | 156.3±32.75 | 166.1±29.38 | 156.2±27.26 | |
| Turner's syndrome | TC (mg/dL) | | | | | |
| (*n*=13) | Range | 111.0–211.0 | 113.0–213.0 | 125.0–211.0 | 112.0–203.0 | 0.572 |
| | Mean±SD | 164.3±37.00 | 166.5±37.00 | 170.2±30.34 | 155.7±32.02 | |
| | *P* | 0.701 | 0.380 | 0.677 | 0.961 | |
| IGHD | TG (mg/dL) | | | | | |
| (*n*=30) | Range | 52.0–158.0 | 52.0–142.0 | 47.0–102.0 | 57.0–100.0 | <0.001 |
| | Mean±SD | 104.5±27.95 | 94.7±24.54 | 80.8±15.34 | 76.4±13.63 | |
| Turner's syndrome | TG (mg/dL) | | | | | |
| (*n*=13) | Range | 55.0–153.0 | 73.0–143.0 | 47.0–103.0 | 61.0–100.0 | 0.030 |
| | Mean±SD | 98.0±29.04 | 114.2±20.71 | 73.8±19.71 | 74.9±11.67 | |
| | *P* | 0.494 | 0.017 | 0.211 | 0.717 | |
| IGHD | TSH (micro-unit/mL) | | | | | |
| (*n*=30) | Range | 0.75–7.11 | 0.73–6.00 | 0.10–5.61 | 0.03–5.20 | 0.027 |
| | Mean±SD | 3.53±1.99 | 3.20±1.86 | 2.10±1.13 | 2.37±1.27 | |
| | Median (IQR) | 3.21 (1.85–4.84) | 3.19 (1.52–5.07) | 2.13 (1.45–2.31) | 2.31 (1.30–2.89) | |
| Turner's syndrome | TSH (micro-unit/mL) | | | | | |
| (*n*=13) | Range | 1.30–7.14 | 1.17–5.43 | 0.89–7.10 | 0.12–7.10 | 0.074 |
| | Mean±SD | 4.34±2.19 | 2.86±1.79 | 3.04±1.81 | 3.05±1.68 | |
| | Median (IQR) | 5.36 (2.43–6.20) | 2.04 (1.34–4.97) | 2.90 (1.54–4.33) | 3.14 (2.31–3.40) | |
| | *P* | 0.278 | 0.509 | 0.173 | 0.135 | |
| IGHD | Calcium (mg/dL) | | | | | |
| (*n*=30) | Range | 8.1–10.0 | 8.1–10.5 | 7.2–10.2 | 6.1–9.8 | 0.014 |
| | Mean±SD | 9.3±0.54 | 9.5±0.64 | 8.8±0.90 | 8.7±0.89 | |
| Turner's syndrome | Calcium (mg/dL) | | | | | |
| (*n*=13) | Range | 8.2–10.0 | 8.2–10.5 | 6.1–9.3 | 8.1–9.9 | 0.525 |
| | Mean±SD | 9.1±0.64 | 9.2±0.85 | 8.1±0.94 | 8.9±0.61 | |
| | *P* | 0.329 | 0.269 | 0.042 | 0.349 | |
| IGHD | Phosphate (mg/dL) | | | | | |
| (*n*=30) | Range | 2.60–5.10 | 2.60–5.10 | 3.10–5.40 | 3.21–4.97 | <0.001 |
| | Mean±SD | 3.65±0.77 | 3.78±0.81 | 4.30±0.55 | 4.38±0.39 | |
| Turner's syndrome | Phosphate (mg/dL) | | | | | |
| (*n*=13) | Range | 2.9–4.9 | 2.9–5.0 | 3.6–5.2 | 4.2–5.6 | <0.001 |
| | Mean±SD | 3.9±0.69 | 3.8±0.69 | 4.6±0.50 | 4.7±0.43 | |
| | *P* | 0.302 | 0.871 | 0.077 | 0.019 | |
| IGHD | IGF-1 (mg/dL) | | | | | |
| (*n*=30) | Range | 30.1–210.0 | 54.0–410.0 | 88.0–526.0 | 90.0–416.0 | <0.001 |
| | Mean±SD | 104.8±49.71 | 229.7±109.87 | 286.5±125.37 | 272.8±102.44 | |

*Contd...*

**Table 10: Contd...**

| Group | Parameter | Visit 1 Baseline | Visit 2 After 1 y | Visit 3 After 1.5 y | Visit 4 After 2 y | Over time *P* |
|---|---|---|---|---|---|---|
| Turner's syndrome | IGF-1 (mg/dL) | | | | | |
| (*n*=13) | Range | 36.7–261.0 | 87.0–397.0 | 79.0–527.0 | 101.0–401.0 | 0.001 |
| | Mean±SD | 111.4±60.23 | 247.3±107.46 | 300.2±130.84 | 255.2±117.08 | |
| | *P* | 0.711 | 0.630 | 0.746 | 0.510 | |

FBG: Fasting blood glucose, IGF: Insulin-like growth factor, IGHD: Idiopathic growth hormone deficiency, IQR: Interquartile range, SD: Standard deviation, TC: Total cholesterol, TG: Triglyceride, TSH: Thyroid-stimulating hormone

significant improvement in anthropometric parameters over the 2-year observation period, although improvement slowed down after the initial 1½ years. These findings are also in line with previous Indian and international studies.[4,6,17,19,20] The precise quantum of improvement in an individual child will likely depend on the indication, starting age of GH therapy, treatment duration and dosage. A comparison between different aetiologies of short stature in this regard requires exploration through larger prospective studies.

Regarding laboratory parameters, there was no significant change in FBG. This is important as GH physiologically can cause glucose impairment. Cortisol and TSH were monitored meticulously and supplemented if necessary, to maintain normal value throughout the course. The change in cortisol was statistically non-significant. TSH changes in the initial one year and the last 6 months of observation were non-significant, although the overall change till the study end was statistically significant. Around 10 subjects were on levothyroxine treatment in our cohort. Levothyroxine dose was adjusted according to the thyroid profile by the physician regularly as per need. In the lipid profile, changes in total cholesterol were statistically non-significant, be it in the initial year, in the last 6 months of therapy or through the course of GH. However, overall triglyceride was significantly reduced with the course of GH treatment, which can be explained by stimulation of lipolysis in the adipose tissue, as we know from the physiology of GH effects. Serum calcium change was non-significant. Phosphate change in the initial one year and the last six months of observation was statistically non-significant; however, change in phosphate over the entire course of GH therapy was statistically significant. IGF-1 is the principal peripheral mediator of GH action. The significant rise in IGF-1 level was mostly driven by the increase in the initial year of therapy. Once again, these changes in biochemical parameters mirror the experience reported in earlier papers.[22]

Uniquely in our study, we evaluated bone markers for bone formation and resorption including 25(OH) vitamin D value. However, owing to logistical limitations these tests were carried out only in the last 6 months of observation period and baseline data are not available for comparison. During the 6 months of observation period, changes in iPTH, osteocalcin and PINP were statistically not significant. However, the CTx value declined significantly from a mean of 1.86 ng/ml to 1.71 ng/ml. An increase in 25(OH) vitamin D level from a mean of 31.8 nmol/L to 35.7 nmol/L was also statistically significant. Both point towards a decrease in bone resorption and an increase in bone formation. However, the cross-sectional DEXA Z-score (both total body and AP spine) at the end of treatment indicated that the bone mineral density remained less than in age-matched controls.

In conformity with earlier experience,[23,24] rhGH treatment was well tolerated in this study and practically no adverse events were reported. Two mild cases of injection site lipodystrophy occurred but resolved spontaneously in 3–4 months. No changes in dosing or treatment schedule had to be carried out due to adverse events, and no serious adverse events were encountered. However, it is to be borne in mind that this experience is reflective of the GH dose used in this study. Encouraged by the safety profile, physicians may be tempted to escalate doses to achieve greater height-promoting effects, which raises the possibility of delayed post-treatment effects of hyperinsulinaemia and/or heightened GH and IGF-I exposure on cancer risk.[24]

Ours is the first study from eastern India to systematically look at the effects of GH therapy in children with idiopathic short stature or due to various growth disorders. We are able to recruit 50 patients, which is a good starting point concerning the rarity of GH disorder in the general population. We have shown that GH therapy significantly improves the height, weight, BMI and skeletal age with time. We have also shown how laboratory parameters change with GH therapy. We have performed bone marker levels, which indicate an increase in bone remodelling. However, it suffers from the inherent limitations of any observational study. The data from the first two visits were collected in a retrospective manner making them prone to limitations in this regard. There is no control group for comparison. We have compared some of our findings with general population data for inference. Finally, the relatively short follow-up is the major limitation of this study.

Accepting these limitations, in conclusion we can say that this observational study has generated eastern India-specific data on GH therapy in different growth disorders. Despite obvious anthropometric parameter improvements, the short stature children did not attain target height and normal bone mineral density with 2-year regular treatment. Changes in laboratory parameters and bone biomarkers reflecting a positive impact on bone remodelling have been described. Larger scale studies,

preferably with longer follow-up times, are needed for further exploration of this subject.

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## Conflicts of interest

There are no conflicts of interest.

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