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# Growth Hormone Secretion and Circulating Insulin-Like Growth Factor-I (IGF-I) and IGF Binding Protein-3 Concentrations in Children With Sickle Cell Disease

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**Impaired growth involving both height and weight accompanying sickle cell disease (SCD) poses diagnostic and therapeutic problems. We undertook this study to test the hypothesis that this impaired growth is associated with abnormalities of the growth hormone (GH)/insulin-like growth factor-I (IGF-I)/IGF binding protein-3 (IGFBP-3)axis in 21 children with SCD and that SCD is associated with GH resistance. Nine of 21 children with SCD had a defective GH response to both clonidine and glucagon provocation (peak, < 10 μg/L); these children differed from the 12 others in having slower linear growth velocity (GV and GVSDS), lower circulating concentrations of IGF-I and IGFBP-3, and either partial or complete empty sellae in computed tomographic scans of the hypothalamic-pituitary area. In this group of patients with SCD, it appears that defective GH secretion and consequent low IGF-I production are the major etiological factors causing the slow growth. The two groups with SCD did not differ significantly in dietary intake, body mass index (BMI), midarm circumference, skinfold thickness, serum albumin concentration, or intestinal absorption of D-xylose. A single injection of GH produced a smaller increase in circulating IGF-I in children with SCD with or without defective GH secretion versus 10 age-matched children with idiopathic short stature (ISS) and 11 children with isolated GH deficiency (GHD), suggesting partial GH resistance in the SCD group. The presence of defective GH secretion, decreased IGF-I synthesis, and partial resistance to GH in short children with SCD suggests that treatment with IGF-I may be superior to GH therapy for improving growth.**


GROWTH AND MATURATIONAL DELAY are striking features of sickle cell disease (SCD).[1] After 6 months of life, affected children have impaired growth involving both height and weight.[2-4] Many factors have been implicated in the etiology of growth impairment in children with SCD. These include chronic anemic hypoxia, increased energy expenditure due to high erythropoietic turnover and cardiac work,[5] nutritional deficiencies including zinc, folic acid, and vitamin A,[6-8] disturbed calcium metabolism,[9] repeated infections due to defective immune functions,[10-11] and dysfunction of the endocrine glands.[12]

The basal circulating concentrations of different hormones have been studied by different groups,[12-14] with no consensus for defining the endocrine abnormalities of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis and their possible contribution to growth impairment in these children.

Recently, we have reported a high incidence of defective clonidine-induced GH secretion and low circulating IGF-I concentrations in children with SCD and short stature.[15] IGF-I is a GH-dependent polypeptide that has a threefold function as a mediator of the growth-promoting action of GH, as a potent mitogenic factor, and as a metabolic regulator with insulin-like activity.[16-18] Alteration of IGF-I regulation may provide an attractive explanation for SCD-associated growth impairment.

The predominant IGF binding protein (IGFBP) in the blood is IGFBP-3, which forms a large 150-kd ternary complex. The serum level of this complex determines the total concentration of circulating IGF-I and regulates its growth-promoting potential.[19-25] Current opinion favors GH as the major regulator of IGFBP-3 and IGF-I levels in humans.[26] In vivo and in vitro experiments indicate relatively poor control of IGFBP-3 concentrations by IGF-I.[27-30] In addition, serum levels of IGF-I and IGFBP-3 are positively related to nutritional status.[27,31-33] No study to date has examined the different components of the GH/IGF-I/IGFBP system in children with SCD.

Treatment of SCD children with marked growth retardation using human GH may also be compromised by an associated GH resistance due to hepatic iron overload, malnutrition, or

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repeated infections.[34,35] The IGF-I generation test provides valuable information on IGF-I sensitivity.[36]

We undertook the present study to test the hypothesis that (1) SCD is associated with abnormalities of the GH/IGF-I/IGFBP axis and (2) SCD is associated with GH resistance. The first issue was addressed by measuring the GH response to clonidine and glucagon and the circulating concentrations of IGF-I and IGFBP-3 in 21 children with SCD, and the second issue was tested using IGF-I generation tests. The results were compared with those for children with idiopathic short stature ([ISS] n = 10) and isolated GH deficiency ([GHD] n = 11).

## SUBJECTS AND METHODS

Twenty-one prepubertal children with SCD were the subjects of this study. They were randomly selected, using random tables, from 58 children with SCD and short stature (height, 10th percentile for age and sex). The 58 children were all the patients with SCD and stature less than the 10th percentile selected from a cohort of 156 children with SCD regularly attending the hematology outpatient clinic of the Royal Hospital in Muscat, Oman. According to peak GH responses to two provocation tests (with clonidine and glucagon), they were divided into two subgroups. Nine of them (group 1) had a low peak GH response on at least two provocation tests (<7 μg/L), and the other 12 children (group 2) had a normal GH response to stimulation (>7 μg/L). All have been on folic acid supplementation and vaccinated against pneumococci. None of them had a history of intrauterine growth retardation or any other systemic or endocrine disease, dysmorphic trait, or central nervous system irradiation. Ten age-matched children with idiopathic short stature (ISS) (height standard deviation score [HtSDS] < −2 and normal GH response to provocation) and 11 children with isolated GHD (GH peak response < 5 μg/L on at least 2 provocation tests) served as controls. Informed consent was obtained from all the parents and, when appropriate, from the children before inclusion in the study.

All of the children were examined thoroughly, with special emphasis on the nutritional data. Auxanological measurements included weight, height, head circumference, midarm circumference, and scapular, triceps, and abdominal skinfold thickness. Harpenden calipers were used. The data recorded were the average of three sequential measurements determined by the same observer (A.T.S.). HtSDS was calculated according to the formula, HtSDS = (X1 − X2)/SD, where X2 and SD are the age-matched population mean height and SD, respectively, and X1 is the subject height.

Height growth velocity (GV) in centimeters per year was calculated for the previous 2 years. Normal population data were from Tanner et al.[37] Body mass index (BMI) was calculated according to the formula, BMI = weight (kg)/height $(m)^2$. Bone age was determined according to the Greulich and Pyle atlas.[38]

Children were admitted to the Royal Hospital in Muscat, Oman, for the period of investigation. The initial nutritional evaluation, both qualitative and quantitative, was performed by the dietitian using the recall method, and the patients received a high-protein (2 g/kg/d) diet for 7 days before hormonal evaluation. After an overnight fast (8 hours), venous blood samples were obtained between 8 and 9 AM for determination of complete blood cell count, serum albumin, bilirubin, alanine aminotransferase (ALT), bone-specific alkaline phosphatase (ALP), calcium, phosphorus, and bicarbonate concentrations. The serum was separated from the formed elements by centrifugation and kept frozen at −20°C until analyzed for IGF-I, IGFBP-3, cortisol, free thyroxine ($fT_4$), and thyrotropin (TSH) by radioimmunoassay. The subjects received a single injection of recombinant human GH 0.1 mg/kg subcutaneously. Serum IGF-I and IGFBP-3 levels were remeasured 24 hours after the injection.[36]

Human GH and IGF-I levels were measured by radioimmunometric assay using reagents purchased from Nichols Institute (San Juan Capistrano, CA). Intraassay coefficients of variation (CVs) were 5.6% and 6.8%, respectively, and interassay CVs were 7.8% and 8.3%, respectively, in the range of GH and IGF-I values detected. IGFBP-3 concentration was measured by radioimmunoassay at SCL Bioscience Services using reagents supplied by Mediagnost. The assay sensitivity was 0.06 μg/mL, with intraassay and interassay CVs of 5.2% and 8.6%, respectively.

Results are expressed as the mean ± SD and analyzed by ANOVA to compare analyte concentrations among groups. A paired Student *t* test was used to compare data in the same group before and after GH injection. Correlations between variables of interest were examined by linear regression analysis and, when appropriate, multiple regression analysis.

## RESULTS

Children with SCD and ISS had normal circulating concentrations of albumin, calcium, phosphate, ALP, ALT, and bicarbonate. Serum levels of $fT_4$, TSH, and 8 AM cortisol did not differ among the two groups. Bilirubin (unconjugated) concentrations were higher and hemoglobin and hematocrit values were lower in the SCD group versus the ISS group. The peak D-xylose concentration after ingestion of 5 g D-xylose did not differ between the two groups.

Table 1 shows auxanological and hormonal data for children with SCD, GHD, and ISS. The HtSDS was significantly lower in children with ISS and GHD versus children with SCD. Linear

**Table 1. Auxanological and Hormonal Data of the Three Groups**

| Group | Age (yr) | BMI (kg/m²) | IGF-I-B (ng/mL) | IGF-I-A (ng/mL) | IGF-I-D (ng/mL) | IGFBP-B (mg/L) | IGFBP-A (mg/L) | IGFBP-D (mg/L) | Peak GH (μg/L) | HtSDS | GV (cm/yr) | GVSDS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SCD (n = 21) | | | | | | | | | | | | |
| Mean | 6.99 | 14.6 | 113 | 141* | 27.6*† | 1.86* | 2.27 | 0.33* | 7.36* | −1.34 | 4.9 | −1 |
| SD | 3.27 | 1.8 | 78 | 74 | 15.6 | 0.8 | 0.87 | 0.258 | 3.85 | 0.6 | 1.7 | 1 |
| ISS (n = 10) | | | | | | | | | | | | |
| Mean | 8.1 | 13.8 | 138 | 192 | 53.5† | 2.39 | 2.42 | 0.133 | 19.6 | −2.3* | 4.6 | −1.1 |
| SD | 1.8 | 0.6 | 43 | 39 | 17.6 | 0.37 | 0.36 | 0.071 | 2.7 | 0.3 | 0.4 | 0.5 |
| GHD (n = 11) | | | | | | | | | | | | |
| Mean | 7.3 | 15.1 | 66.1† | 146.1 | 82.3 | ND | ND | ND | 4.6† | −3.2† | 3.7† | −2.3 |
| SD | 1.8 | 1.2 | 25 | 50.7 | 42.4 | | | | 1.9 | 0.9 | 1.2 | 1.2† |

NOTE. Plasma IGF-I and IGFBP-3 were measured immediately before (B) and 24 hours after (A) GH administration (0.1 mg/kg). The suffix "-D" indicates the change in IGF-I and IGFBP-3 from basal to 24 hours.

*$P < .05$, SCD *v* ISS.

†$P < .05$, SCD *v* GHD.

GV, GVSDS, and BMI did not differ significantly among the two groups with ISS and SCD. However, GV and GVSDS were significantly decreased in children with GHD. The peak GH response to provocation was significantly lower in children with SCD versus ISS ($P < .001$). Basal circulating IGF-I concentrations were higher in children with ISS versus the other two groups. Basal circulating IGFBP-3 concentrations were significantly lower in the SCD group ($P < .05$) versus the ISS group. The IGF-I response to GH administration ([IGF-I-D], equal to the 24-hour IGF-I value minus the basal value) was significantly lower in children with SCD (27.6 ± 15.6 ng/mL) compared with children with ISS (53.5 ± 17.6 ng/mL). IGF-I increased significantly after human GH injection in the three study groups. However, the IGF-I response (IGF-I-D) was significantly higher in children with GHD and those with ISS versus children with SCD.

Table 2 presents a comparison between two groups of children with SCD: group 1 with defective GH secretion (n = 9; peak GH response to provocation, 4.2 ± 2.3 μg/L) and group 2 (n = 12) with a normal peak GH response to provocation (9.9 ± 2.4 μg/L). Age and BMI did not differ among the two groups. HtSDS and GVSDS were significantly lower in group 1. Basal circulating concentrations of IGF-I and IGFBP-3 were significantly lower in group 1 (SCD with defective GH secretion). IGF-I responses to GH administration did not differ significantly among the two groups and were significantly lower than those for children with isolated GHD.

Correlations between auxanological and hormonal data in 21 children with SCD are presented in Table 3. Basal and GH-stimulated concentrations of IGF-I and IGFBP-3 were correlated significantly with height GV and GVSDS ($P < .01$) and GH peak values. The dependence of serum IGFBP-3 on GH was evident from a significant correlation with peak GH secretion (n = 21, $r = .665$, $P < .01$) and the significant increase in IGFBP-3 after one injection of GH. IGFBP-3 concentrations correlated significantly with IGF-I levels before and after GH administration ($r = .600$, $P < .01$). Serum ferritin was inversely correlated with GV, GVSDS, and IGF-I ($r = -.35$, $-.46$, and $-.25$, respectively, $P < .05$).

## DISCUSSION

There is no completely reliable test for diagnosing or excluding GHD in all short children. When used alone, none of the tests have superior diagnostic specificity or sensitivity. Measurement of GH-response peptides such as IGF-I and IGFBP-3 can add insights even when the results do not agree with GH responses to provocative stimuli. Interpretation of the tests together improves the reliability of diagnostic assessment.[39]

Nine of 21 randomly selected children with SCD (43%) had defective GH secretion in response to provocation with both clonidine and glucagon. In these children, IGF-I concentrations were comparable to those in children with isolated GHD, but were significantly lower than those in children with ISS and normal GH release. Their circulating IGFBP-3 concentrations, which reflect the integrated GH secretion over a period of days,[26,39-41] were significantly lower versus the group with normal GH secretion, but were not different from those reported by Smith et al[39] for children with GHD. The linear growth of

**Table 2. Auxanological and Hormonal Data of Children With SCD Versus Those With GHD**

| | Age (yr) | BMI (kg/m²) | IGF-I-B (ng/mL) | IGF-I-A (ng/mL) | IGF-I-D (ng/mL) | IGFBP-B (mg/L) | IGFBP-A (mg/L) | IGFBP-D (mg/L) | Peak GH (μg/L) | HtSDS (−) | GV (cm/yr) | GVSDS (−) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SCD + GHD (n = 9) | 6.6 ± 2.7 | 14.8 ± 2.2 | 46.1 ± 30.7* | 78 ± 36*† | 29.8 ± 17.1† | 1.13 ± 0.37* | 1.42 ± 0.32* | 0.30 ± 0.26 | 4.2 ± 2.3* | 1.68 ± 0.79 | 4.1 ± 1.5* | 1.55 ± 0.5* |
| SCD (n = 12) | 7.3 ± 3.4 | 14.4 ± 1.3 | 136 ± 59* | 189 ± 55 | 25.9 ± 14† | 2.4 ± 0.5* | 2.9 ± 0.5* | 0.35 ± 0.25 | 9.9 ± 2.4† | 1.1 ± 0.9 | 5.4 ± 1.5 | 1.1 ± 0.68 |
| GHD (n = 11) | 7.3 ± 1.8 | 15.1 ± 1.2 | 66.1 ± 25 | 146.1 ± 50 | 82.3 ± 42.4* | ND | ND | ND | 4.6 ± 1.9 | 3.2 ± 0.9† | 3.7 ± 1.2† | 2.3 ± 1.2† |

NOTE. Data are the mean ± SD. The suffix "-D" indicates the change in IGF-I and IGFBP-3 from basal to 24 hours.
*$P < .05$, SCD *v* SCD + GHD.
†$P < .05$, SCD groups *v* GHD.

**Table 3. Correlations Between Auxanological and Hormonal Data (r values)**

| | Peak GH (μg/L) | GV (cm/yr) | GVSDS | BMI (kg/m²) |
|---|---|---|---|---|
| IGF-I-B | .483† | .4† | .529† | −.3* |
| IGF-I-A | .436† | .476† | .538† | −.24 |
| IGF-I-D | −.505† | −.002 | −.08 | −.31* |
| IGFBP-3-B | .559† | .2 | .25* | −.27* |
| IGFBP-3-A | .716† | .25 | .35* | −.15 |
| Ferritin | −.175 | −.36* | −.46† | −.01 |
| Peak GH | 1 | .337* | .339* | .113 |

Abbreviations: B, before GH; A, after GH.
*$P < .05$.
†$P < .01$.

patients with SCD with defective GH secretion was significantly slower than that of patients with normal GH secretion. This defective GH secretion may be secondary to a hypoxic vascular insult to the hypothalamic-pituitary area during one or more of the sickling episodes and/or to pituitary atrophy as a result of iron overload. In support of this view, computed tomographic scanning of the pituitary region revealed empty sellae (partial or complete) in all nine children with SCD and GHD. Moreover, the SCD severity score, as described by El Hazmi et al,[12] was significantly higher in the SCD group with defective GH secretion versus those with normal GH secretion. Collectively, these findings suggest that acquired GHD may be a major factor in the etiology of retarded growth in some patients with SCD, especially those with severe sickling attacks.

It is unclear which of the alterations of the GH/IGF-I/IGFBP axis found in children with SCD are of greater clinical significance. Although the influence of SCD on adult height is controversial, most data indicate a negative effect of SCD on linear growth.[1-4,6] In our study, the mean HtSDS for all patients with SCD ($n = 21$, $-1.34 \pm 0.6$) was in the lower range of normal. SCD patients with defective GH secretion had a significantly lower HtSDS and GV versus those with normal GH release. Moreover, we found a good correlation between GVSDS and IGF-I (before and after GH injection) and a strong correlation between the peak GH response to provocation and IGF-I and IGFBP-3. These findings suggest that circulating IGF-I and IGFBP-3, as in normal children, are the major determinants of linear growth in children with SCD, and both are regulated by the GH status of the child. On the other hand, the degree of GH resistance as measured by the change in IGF-I concentration after GH injection (IGF-I-D) was not correlated with linear growth parameters (HtSDS, GV, and GVSDS, $r = -.26, -.002$ and .083, respectively) in these children. This may denote that GHD plays a more significant role than GH resistance in the etiology of impaired linear growth in these children.

In children with SCD, growth impairment includes both height and weight.[2-4] Treatment with human GH has been shown to improve nitrogen balance and linear growth in a variety of growth disorders.[42] The detection of defective GH secretion in about 40% of slowly growing children with SCD suggests a beneficial growth-promoting effect of GH therapy in these patients. The IGF-I generation test has been used to assess IGF-I responsiveness to GH in children with short stature.[36] In this study, a single subcutaneous injection of GH has been used to investigate the physiological changes of IGF-I/IGFBP-3 in children with SCD to test the hypothesis that SCD is associated with GH resistance. Subjects with SCD with or without defective GH secretion had significantly lower IGF-I responses to a single injection of GH versus children with ISS and those with isolated GHD, suggesting partial GH resistance. This might attenuate the anabolic effects of GH therapy in these children.[34,35] The IGF-I response (IGF-I-D) correlated negatively with the BMI ($r = -.31$, $P < .01$), suggesting that in children with SCD, increasing wasting may be associated with progressive GH resistance. The significant negative correlation between the IGF-I response to GH injection and the peak GH response to provocation ($r = -.505$, $P < .01$) suggests that IGF-I production is better in children with defective GH secretion. However, the IGF-I response was nonsignificantly higher in children with SCD and GHD versus those with normal GH secretion.

Malnutrition can be excluded as an important cause of abnormalities of the GH/IGF-I axis in children with SCD because of the following: (1) BMI, subcutaneous fat thickness, midarm circumference, and serum albumin concentration were not different among the study groups (SCD, SCD + GHD, and ISS); (2) analysis of the nutritional history showed adequate qualitative and quantitative intake of nutrients as compared with 20 normal age-matched children; (3) the D-xylose test was normal in all children with SCD and those with ISS; and (4) in malnutrition, basal GH concentrations are usually high, unlike the case in our children with SCD (mean ± SD, $1.8 \pm 0.25$ μg/L; range, 0.5 to 3.5).[43]

The normal serum levels of creatinine, bicarbonate, calcium, phosphorus, and ALP exclude any significant contribution of renal dysfunction and/or disturbed calcium homeostasis in the etiology of growth impairment or endocrine abnormalities in these children. Normal serum concentrations of albumin, ALP, and ALT with a normal albumin to globulin ratio and prothrombin time in children with SCD make it unlikely that impaired hepatocellular synthetic function is a cause of the low IGF-I production in these patients.

The serum ferritin concentration, as an indicator of body iron stores, was negatively correlated with the height GV ($r = -.35$, $P < .01$), GVSDS ($r = -.464$, $P < .01$), and circulating concentration of IGF-I ($r = -.255$, $P < .05$). This suggests that hepatic/parenchymal iron overload may impair IGF-I synthesis and subsequently slow linear growth in children with SCD.

In summary, children with SCD have significantly lower IGF-I production in response to GH injection versus children with ISS and GHD, suggesting partial GH resistance. Some children with SCD and delayed growth may have GHD. Parenchymal iron overload, a potentially treatable factor, may contribute to the etiology of impaired hepatic IGF-I synthesis and/or defective GH secretion by the pituitary gland. Because of the presence of partial GH resistance, treatment with recombinant IGF-I may be more successful than treatment with GH.

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