Hormonal Profile among Children with Short Stature

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Abstract:

Linear growth occurs in 3 phases. During fetal and early infant life, growth is largely regulated by nutrition, during childhood by growth hormone (GH) and during puberty by GH and sex steroids. Short stature may be the normal expression of genetic potential, in which case the growth rate is normal at least at the 25th percentile, or it may be the result of a condition causing growth failure with a growth rate below the appropriate growth velocity for age.

Short stature has been shown to have far reaching effects on psychological well being including poor academic achievement, behavioral problems, morbidity related to the underlying cause and increased risk for reduced bone mass.

One hundred fifty-nine patients divided into 4 groups were studied. Group I (Pituitary dwarf) consisted of 26 patients (16 males and 10 females) aged 4-12 years. Group II (Congenital hypothyroidism) included 23 patients (14 males and 9 females) aged 2-12 years. Group III (Down’s syndrome) consisted of 10 patients (5 males and 5 females) aged 3-12 years. A hundred apparently healthy children (50 males and 50 females) aged 2.5 – 12 years were considered as (Control group) group IV. All children were examined thoroughly, anthropometric measurements (14 items) were evaluated according to percentiles and Z-score diagrams.

Bone age was determined by plain X-ray left wrist. Hormonal study was done including T3, T4, TSH, overnight urinary growth hormone (GH) and creatinine. Serum growth hormone (insulin-induced hypoglycemia test) and insulin like growth factor-1 (IGF-1) were measured for the pituitary dwarf group. The height, sitting height and arm span measurements showed a marked decrease below normal mean Z-score (more than -2SD) in the three studied groups of patients.

Hormonal profile: There was a significant decrease in serum levels of both T3 and T4 in congenital hypothyroidism and insignificant change in the other two groups. 3 patients from Down’s syndrome group reached a hypothyroidal level of T3, T4, and TSH. Generally urinary growth hormone showed a significant decrease in the three studied groups of patients. Pituitary dwarf group showed a significant decrease in both serum and urinary growth hormones and also serum IGF-1 with a positive correlation between serum growth hormone and both urinary growth hormone and serum IGF-1.

Conclusion: Height, sitting height and arm span are simple and accurate measurements for early detection and follow up of the short child. Assessment of the thyroid hormonal profile is essential as early as possible in all children with short stature with and without clinical stigmata of hypothyroidism. Determination of urinary growth hormone is as accurate as serum GH, moreover it is easier. Measurement of serum IGF-1 is an important era in diagnosis of short stature.

Introduction:

Growth is a complex process and represents an integration of the genetic potential, appropriately functioning endocrine system and nutritional status. A disorder of any of these levels results in short stature.1 Short stature is defined in a short child if his/her height is below the 3rd percentile approximately (-1.9) standard deviations or (-2) on the Z-score for his/her community.2 Short stature ranges from normal variants like familial and constitutional growth delay (CGD) to pathological conditions like endocrine, genetic and systemic disorders. Fortunately, the commoner causes can be suggested by basic tools like anthropometric measurements and bone age.3 Growth hormone deficiency (GHD), hypothyroidism and Down’s syndrome (DS) are common causes of pathologic short stature.4 Growth hormone and thyroid hormones are especially important for cell multiplication and bone mineral metabolism.5 Secretion of GH by the pituitary is stimulated by GH releasing hormone (GHRH), GH releasing peptides (GHRPs), a recently discovered peptide hormone named Ghrelin,6 and multiple neurotransmitters and neuropeptides.7 When GH pulses are secreted into
the systemic circulation, IGF-1 is released. All the anabolic actions of GH are mediated through IGF. Thyroid hormone is absolutely necessary for normal growth. Evaluation of thyroid hormone levels in all children with slow growth is advised because of the possibility of subtle signs and the euthyroid sick syndrome.

The aim of this study was to re-evaluate the hormonal profile of our short children in relation to dermatoglyphic and anthropometric measurements to highlight their relative accuracy and reliability in a trial to develop a simple method of community based program for assessment of short stature.

**Subject and Methods:**

One hundred fifty-nine children were included after taking informed written consents from their guardians. The present work was conducted in 2 parts: Part (I) is a study of the hormonal profile among children with short stature. Part (II) is a study of their genetic profile.

In the present study on the hormonal profile, criteria of diagnosis of patients were based on history, clinical examination, anthropometric measurements and mid-parental height, radiological bone age calculation, IQ assessment and hormonal assay.

All short children included were below the 3rd percentile for height. Family history of growth pattern and direct measurement of the parents and calculation of the midparental height were crucial to determine the genetic potential for growth in the child which is reflected in the heights of his parents and relatives. The sex-adjusted midparental height (MPH) was estimated as follows:

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\text{MPH range for boys (cm)} = \frac{(\text{Mother's height} + 13) + \text{Father's height} + 8}{2}
\]

\[
\text{MPH range for girls (cm)} = \frac{(\text{Mother's height} + 13) + \text{Father's height} - 8}{2}
\]

The studied children were classified into: Group I (Pituitary dwarf): Twenty-six patients (16 males and 10 females) aged 4-12 years (mean 9.5±2.9 years). Group II (Congenital hypothyroidism): Twenty-three patients (14 males and 9 females) aged 2-12 years (mean 8.5±2.2 years). Group III (Down's syndrome): Twenty-three patients (14 males and 9 females) aged 4-12 years (mean 9.5±2.9 years). Group IV (Control group): Twenty-six patients (16 males and 10 females) aged 3-12 years (mean 8.5±2.2 years).

- Careful history taking including personal data, prenatal, natal and post natal, obstetric and family history.
- A detailed family pedigree.
- Thorough clinical examination and anthropometric measurements (14 items). Height, sitting height and arm span, (using a wall mounted wooden meter stick), head width, head breadth, head circumference, biacromion distance, bitrochanteric distance, bi-iliac distance, chest width, chest breadth, chest circumference and internipple distance, (using a standard non stretch type measure) and weight. All the above measurements for both patients and control children were subjected to percentile curves including the DS specific growth charts and z-scores.

The z-score is the system adopted by Sempé, in recording the anthropometric measurements. He used the mean (± 2 SD) to be sure that the anthropometric measurements are at the center of spectrum of scattering around the mean. The true population mean is likely to lie within the range (± 1.96 SD) on either side of the mean (fig. 1). The 3rd percentile which is the lowest line given in the usual standard charts is at (-1.9) or (-2) SD.

- Bone age: X-ray for the left wrist was done for all patients. Bone age was calculated by the use of Tanner-Whitehouse second classification (TW2).
- Laboratory investigations:
  - Routine investigations (urine analysis, CBC, renal and hepatic functions and ESR) to exclude other causes of pathologic short stature.
  - Serum T3, T4 and TSH levels by immunoassay methods (using T3-HRPEIA and T4-HRPEIA kits and ELISA kits from Randox Co. respectively).
  - Urinary growth hormone (by immunoradiometric assay), based on the collection of 12 hours over night urine. Normal level of growth hormone in urine is (0.6-10) ng/ml.
  - Urinary creatinine level using a kit from Randox Co. depending on the kinetic method. Normal range is 8.8-13.3 mmol/24 hours.
  - Serum growth hormone (by immunoradiometric assay). Under precautions, patients of the pituitary dwarf group were injected by I.V. insulin 0.1 unit/kg as a provocative test. The same GH-IRMA kit was used for assessment of urinary and serum growth hormones. Normal level of growth hormone in serum is (0.6-10) ng/ml, and the level should be increased 10 times after one and half hour of the provocative stimulation. The insulin induced hypoglycemia test for GH stimulation probably remains the most reliable test and is still considered the gold standard. However; glucose stimulation tests rely on arbitrary cut off values,
have poor reproducibility, are uncomfortable, expensive, carry some risk and response varies with age as well as sexual development. Growth hormone stimulates the liver to produce IGF-1, which in turn stimulates the long bones to grow in length.

Results & Discussion:

| Table I: Demographic data for the three studied groups of patients |
|-------------------|-------------------|-------------------|-------------------|
| Variable          | Group I (Pituitary dwarf) (n = 26) | Group II (Congenital hypothyroidism) (n = 23) | Group III (Down’s syndrome) (n = 10) |
| Sex               | Male 16 | Female 10 | Male 14 | Female 9 | Male 5 | Female 5 |
| Age (years)       | Mean ± SD | 9.5 ± 2.9 | 8.5 ± 2.2 | 10.5 ± 2.8 |
| Consanguinity     | +ve 12 | -ve 14 | +ve 18 | -ve 5 | +ve 4 | -ve 6 |
| Other affected members | +ve 6 | -ve 20 | +ve 3 | -ve 20 | +ve 0 | -ve 10 |
| Mental status     | Normal | M.R | M.R | M.R |

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<th>Table II: Z-score (mean &amp; SD) of anthropometric parameters for the three studied groups of patients</th>
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<td>Anthropometric parameters</td>
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<td>Sitting height</td>
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<td>Arm span</td>
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<td>Bi-acromion diameter</td>
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<td>Intermalleolar distance</td>
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<td>Weight</td>
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<th>Table III: Hormonal profile for the four studied groups</th>
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<td>Variable</td>
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<td>Serum T3 (ng/dl) Male</td>
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<td>Serum T4 (µg/dl) Male</td>
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<td>Serum TSH (mU/L) Male</td>
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<td>Urine GH (ng/ml) Male</td>
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<td>Urine creatinine (mmol/24 hrs) Male</td>
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<td>Serum GH (ng/ml) Male</td>
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<td>Serum IGF-1 (ng/ml) Male</td>
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*Highly significant.
The results of the present study are shown in tables I-III and figures 1 and 2.

Growth is a sensitive indicator for a child’s state of health, deviation from the normal range both for height and rate of growth may indicate an underlying congenital or acquired problem. Thus the early growth assessment of children is very important to the early detection of diseases in children and of the possible cause of short stature.25

Prevalence of consanguinity was high in the studied groups (46%, 79%, and 40% in groups I, II and III respectively). The high prevalence of consanguinity among Egyptian population and its effect on children were also reported by Hafez et al.26

In this study, 14 anthropometric measurements were assessed for all patients and control children. The study of anthropometric measurements is a very important and useful tool for the demonstration of the variations in the peak of growth and growth velocity during the childhood period.27

As regards these measurements, in the pituitary dwarf group, the height, sitting height and arm span showed a marked decrease in their mean z-scores (fig.2) more than −2SD (mean = −3.67±1.76, −3.09±1.73 and −3.28±1.68 respectively). Many authors reported pituitary dwarf children with decreased height, sitting height and also arm span below the normal mean (more than -2SD) which defined them as short children with normal body proportions.28,29 Z-scores of head circumference, breadth and length, chest circumference and depth and internipple distance were around the normal mean. The marked growth failure and short stature with abnormal anthropometric measurements due to GHD were repeatedly confirmed by many researches since the isolated GH was discovered to stimulate growth in children who had GHD in the 1950s.29,30

In group II (congenital hypothyroidism), the mean z-scores of the height, sitting height and arm span were markedly below (more than −2SD) the normal mean (mean = −3.52±1.28, −2.59±1.60 and −2.45±1.09 respectively). Tanner31 and Rivkees32 agreed with us; they stated that linear growth and bone maturation are markedly affected by long term hypothyroidism. Franklin et al.7 stated that thyroid hormone is essential for postnatal growth and that the inter-relationships between the thyroid and the pituitary GH-IGF axis are complex and not yet fully defined. Hypotheses include a direct effect of thyroid hormone on epiphyseal cartilage growth and a permissive effect on GH secretion.7,8 On the other hand, the mean z-scores of other parameters were around the normal mean.

In the Down’s syndrome group, the mean z-scores of the height, sitting height and arm span showed marked decrease more than −2SD (mean = −3.30±0.70, −2.63±1.63, and −2.34±0.78 respectively) and the mean z-score of the other measurements were around the normal mean. The significant decrease in height in Down’s syndrome group agrees with previous studies.5,14,33 However, Chen H, et al disagreed with us as regards the internipple distance as they reported its decrease in DS patients.33 As short stature is multifactorial in origin and according to our study, nearly all patients were of low socioeconomic status and of high prevalence rate of consanguinity indicating their possible effects on the growth of our patients, as previously suggested by Gallo et al.34 and Amigo et al.35
The hormonal profile study:
As regards the thyroid hormones (T3, T4, TSH) it was found that, when comparing these levels with the control group, there was a significant decrease in the serum levels of both T3 and T4 and increased TSH levels in the congenital hypothyroidism group. With slight decrease but statistically insignificant in the pituitary dwarf and Down's syndrome groups except in individual studies. Three Down's syndrome patients had low T3, T4 and high TSH, in agreement with results achieved by Lobe et al., who reported a similar finding in 8% of Down's syndrome patients. Also, Chen et al. found that 16-20% of DS patients had hypothyroidism, they added that their unrecognized thyroid dysfunction may further compromise CNS function in DS patients.

In the current study; generally in all our patients the urinary growth hormone showed a lower level compared to control children. Pituitary dwarf patients showed a significant decrease in both the serum growth hormone level (mean = 0.74±0.56 ng/ml and 0.67±0.29 ng/ml in males and females respectively) and the urinary growth hormone level (mean = 0.35±0.40 ng/ml in males and 0.41±0.45 ng/ml in females).

In a study done by Pirazzoli, the results obtained after overnight collection of urine compared to the results obtained by the use of pharmacological provocative tests, led him to conclude that urinary growth hormone assay is sensitive and can be used to identify subjects with severe deficiencies.

In another study done by Sarotorio, to evaluate concentration of growth hormone in both plasma and urine following a standardized exercise protocol, he found a potential role of urinary and plasma growth hormone response to this protocol and he suggested that urinary GH can be safe and acceptable first screening test for GH insufficiency.

The present study showed a positive correlation between the level of excretory urinary growth hormone and the serum level of growth hormone for the pituitary dwarf group (r = 0.73, p < 0.001).

Lehingue suggested that urinary growth hormone excretion reflects the changes in the plasma growth hormone levels during the nocturnal time of night.

In clinical practice pharmacological stimulation tests are used to identify growth hormone deficient children; however these tests do not provide information about physiological growth hormone secretion.

Fortes added that the measurement of urinary nocturnal human growth hormone is a useful, simple and non invasive method.

GH serum levels from frequent sampling may show unpredictable differences compared with those from continuous withdrawal since the half life of GH is of the order of 15 min.

Night to night variation of as much as 100% in 12 hours mean GH concentration or maximum pulse amplitude has been noted. Over night collections reflect the major episodes of secretion of GH during slow wave sleep, avoids the effects of physiological variations during the day (food, exercise and stress) and it is also more convenient.

The 24 hours secretion indices may give the best discrimination between normal and GH deficient subjects.

The estimation of endogenous GH secretion rate requires a well validated GH assay of high sensitivity and normative data from groups large enough, divided on the basis of age, gender, pubertal status, BMI and possibly other variables. Urinary excretion of GH correlates well with mean 24 hours or overnight physiological levels and therefore in the presence of normal renal function this parameter can be used as a measure of secretion rate. However, only very small amounts of GH are secreted in the urine and very sensitive GH assays are required. Losses due to adsorption to collection bottles and during concentration of urine may be considerable. Intrapersonal variability of urinary GH may be 30% or much higher. Considerable overlap exists between values in normal subjects and those in subjects with short stature. Urinary GH will reliably distinguish only those with complete GHD.

In the current study, pituitary dwarf patients had a significantly lower serum IGF-1 (mean=52.87±18.92 ng/ml) when compared to control children (mean = 154.82±11.05 ng/ml) with P-value = 0.0001. Again the correlation between serum growth hormone levels and serum IGF-1 was statistically significant (r = 0.87, p < 0.001). Scientists stated that IGF-1 and its major binding protein IGF-BP3 are a reliable reflection of GH production, if malnutrition is not a concern. They added that random GH values are of little value because of the pulsatile fashion in which it is secreted and that GH provocative tests are risky and may also yield falsely low values.

Longmire said that values below a cutoff less than −2SD for IGF-1 strongly suggest an abnormality in the GH axis.

IGF-1 is thought to mediate most of the growth promoting actions of GH. Its level in blood reflects GH status and nutrition. Serum IGF-1 concentrations show no significant diurnal rhythm or pulsatility. Reference ranges obtained from large studies using well validated and precise methods on healthy subjects of normal stature classified by age, sex and pubertal status are still needed. When the complex mechanisms of control of GH secretion are better
understood it may be possible to plan the investigations of possible GHD in a logical manner in order to locate the particular defect in each patient.  

**Conclusion & Recommendations:**

Anthropometric measurements especially, height, sitting height and arm span are simple and accurate methods for evaluation and their z-scores can be used in screening for early detection and in follow up for better management of short children. Assessment of hormonal profile of the thyroid is essential in all children with short stature because congenital hypothyroidism has profound effects on growth and development which can be prevented through early detection and management. All children with DS should be evaluated for their thyroid function. Determination of urinary growth hormone is as accurate as serum GH, moreover it is easier, it needs only the collection of overnight urine without the need for the provocation tests which may be risky. Measurement of serum IGF-1 is an important new era in diagnosis of short stature. It needs no provocation. It is assessed in a single random blood sample. It is diagnostic especially in children with idiopathic short stature despite their normal serum GH levels. Its cost is less when used in large scale screening programs. Further studies are recommended in order to establish our own national protocol for management of short stature.

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**References:**

2. Ferry JR. Medical information on short stature. Quoted from internet @ www.emedicine.com 2002.  