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Diagnosis of Growth Hormone Deficiency: the role of Growth Hormone (GH), Insulin-Like Growth Factor (IGF-I) and IGF-Binding Protein (IGFBP-3)

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ABSTRACT

Despite dramatic changes in the treatment of growth hormone (GH) deficiency from cadaveric pituitary growth hormone to recombinant human growth hormone, the diagnosis of idiopathic growth hormone deficiency remains a challenge for the clinician. The uncertainties in the cut-off values to describe growth hormone deficiency and reference data for growth hormone secretion in normally growing children, differences in growth hormone assays over the time, problems in reproducibility of growth hormone test results all contribute to this vagueness. However, diagnosing growth hormone deficiency is important to identify children who will benefit most from the GH treatment. GH dependent peptides, insulin-like growth factor I (IGF-I) and insulin-like growth factor-binding protein 3, (IGFBP-3) are good markers of growth hormone status and are useful in diagnosing GH deficiency as well as monitoring efficacy of growth hormone treatment. An overview of problems in the diagnosis of GH deficiency and the role of IGF-I and IGFBP-3 in the diagnosis of GH deficiency is provided in this paper.

Conflict of interest: None declared

SUPPLEMENT

Since numerous reasons other than GH deficiency can cause growth retardation, the diagnosis of GH deficiency in a child with short stature should never be based solely on auxological or solely on biochemical-hormonal criteria. The diagnosis should be reached by a critical evaluation of all the relevant data brought together. In fact, even the normal limits for GH response to stimulation tests for endogenous GH secretion have not yet been fully standardised and this response is known to be influenced by factors like age, sex, pubertal stage and body mass index. Problems with the diagnosis of growth hormone deficency based on GH measurements alone are as follows:

1. The established approach to the diagnosis of GH deficiency is based on the assumption that GH deficient children have a lower GH response to stimulation compared to that of normally growing children. However, many studies have shown that the maximal response in normal children can remain below 10, 7 or even under 5 µg/L. Differences in methods used for measurement of GH in biological materials, interlaboratory differences in cutoff values for normal ranges arising from differences in methodology, difficulties inherent in the use of physio-

logical stimulation tests as well as the multiplicity of agents used for pharmacological stimulation and the non-standardised use of sex steroids prior to the testing, all contribute to the present inadequacies of the diagnostic criteria.(1, 2, 3, 4)

2. Even if we all agree on a cut-off value, reproducibility of GH response on GH stimulation testing is poor. A significantly large proportion of the so-called GH deficient patients demonstrate normal response to GH re-testing after the completion of the treatment. In 25-44% of the individuals with the diagnosis of GH deficiency during childhood found to have normal GH levels on spontaneous GH secretion during sleep or on pharmacological testing when retested at adulthood.(5, 6)
3. Another area of imprecision comes from the question of conditions where the normalcy of GH secretion is evaluated (spontaneous vs stimulated). Although the best approach is considered to be the assessment of the spontaneous GH release, the difficulties associated with technicalities and the standardisation of the results in this method as well as the costs, have restricted its application to research procedures only.(7, 8)
4. GH estimation in the body fluids is presently carried out by a variety of methods made available with commercial kits. These methods include radioimmunoassay (RIA) which utilizes polyclonal antibodies or enzyme-linked immunoabsorbant assay, immunoradiometric assay and ligand immunofunctional assay, all of which utilise monoclonal antibodies. A GH standard of 2 IU/mg, derived from hypophyseal tissue and made available by the 'National Hormone and Pituitary Program' (USA), used in the earlier stages of laboratory measurement of GH was later replaced by another standard of 2.6 IU/mg, also of hypophysial origin and coded as IRP 80/505. In 1998, WHO recommended the use of recombinant 22-kDa hGH (human GH), coded 88/624, of 3 IU/mg strength, and inclusion of this standard material in the kits presented to the market by the industry.(1, 2)

Although these new assays have provided sensitivity, speed, cost reduction and the facility of automisation, they have also brought the endocrinologist face to face with a number of problems. The use of polyclonal antibodies enabled the detection of all immunogenic epitopes of GH in the circulation, while the more recent assay kits with monoclonal antibodies, which do not recognise all components of GH in the circulation, give lower results for GH levels and necessitate the establishment of new and lower cut-off (threshold) values. For example, the previously accepted threshold of 5-7 µg/L should now become <5 µg/L. However, exactly the opposite has been recommended and the threshold has been raised to 10 µg/L. We believe this is an error and should be corrected. The new assays should be assessed on samples from normally growing children to establish the appropriate threshold levels.

Various pharmacological agents are being used for GH stimulation tests. The sensitivity of these tests is low.(4) The results obtained with these pharmacological agents on healthy children of normal or subnormal height, using 7 µg/L and 10 µg/L as the lower limits of normal are shown in Table 1. The figures indicate the proportion of healthy children which show values under these cut-off limits. When the lower limit for GH deficiency is taken as 7.5 µg/L, the sensitivity is calculated as 73%, the specificity 83%, and the positive predictive value is 50%.

Stimulation of GH secretion with sex steroids: The physiological decrease in GH secretion just before puberty causes difficulty in differentiating this physiological event from GH deficiency. Therefore, exogenous sex steroids has been recommended to be used as a priming tool prior to the stimulation tests.(9) Priming with sex steroids can be done at age 10 in prepubertal girls and at age 12 in prepubertal boys. The use of ethynyl oestradiol can be recommended in both sexes at a single dose of 20-40 µg/day, given the night before

Table 1: GH response to pharmacological stimulation in healthy children of normal and subnormal height, calculated with 7 µg/L and <10 µg/L as cut-off limits.[4]

Pharmacological agent	Max (min)	Mean (range)	<7 µg/L	<10 µg/L
Pyridostigmin	60	13.5 (2.5-35)	15%	36%
Insulin	90	13.2 (2.7-46)	23.7%	49.1%
Arginine	45	16.7 (4.4-45.5)	12.6%	32.9%
Clonidine	60	13.1 (4.5-56.5)	10.1%	23.2%
L-Dopa	45	13 (1.9-40)	23.6%	%36.4%
Glucagon	120	16.9 (1.9-49.5)	10%	35%
GHRH	30	28.8 (2.7-102)	8.9%	14.9%
Pyridostigmin+GHRH	30	47 (19-106)	0	0
Arginine+GHRH	45	61 (19-120)	0	0

GHRH: GH releasing hormone ; Max: maximum

the test. An alternative approach would be to administer 20 µg/day × 3 days ethynyl oestradiol in girls, and 100 mg i.m. testosterone enanthate in boys in one dose three days before the test. However, a consensus has not been reached regarding the use of exogenous sex steroids or the age at which they should be given. More data especially on final height is needed to clarify whether priming is helpful in differentiating those children who are not "really GH deficient" and therefore will not benefit from GH treatment.

WHICH PATIENTS SHOLUD BE TESTED?

For the clinical diagnosis of GH deficiency, after the elimination of skeletal dysplasias, genetic diseases such as Turner syndrome, other endocrinopathies, any chronic or systemic condition that might explain shortness or growth retardation, the history, physical findings and auxological data given below can be taken as signs of GH deficiency.(1)

Clinical findings suggestive of GH deficiency

Presence of (1) a family history of GH deficiency or of close consanguinity between the parents; (2) a history of perinatal trauma or of hypoglycemia, prolonged jaundice, micropenis in the newborn period; (3) anomalies such as the midline defects; (4) a history of cranial irradiation, intracranial lesions, head trauma, central nervous system infections and multiple hypophyseal hormone deficiency, have been agreed upon to be suggestive of GH deficiency.

Auxological findings suggestive of GH deficiency

Auxological findings accepted by the Growth Hormone Society (GHS) and the European Society of Paediatric Endocrinology (ESPE) as suggestive of a diagnosis of GH deficiency and which need to be confirmed by further investigation include:

1. Extreme shortness (height for age < -3 SD) without an explanatory reason
2. Medium shortness (height for age between -2 SD and -3 SD) with
   a) a growth velocity less than 25th percentile or, in children > 2 years of age, a decrease of > 0.5 SDS in height noted after one year of follow-up
   b) a predicted height value lower than the target height by 1.5 SD (approximately 9-10 cm)
3. Without shortness of stature, a slow growth velocity of (< 2 SD or < 5 p) over 1 year or of < 1.5 SD over two years.

Estimation of target height

There are two equations which can be used for this calculation:

1. Target Height for Boys = (Mother's Height+Father's Height)/2+6.5
   Target Height for Girls = (Mother's Height+Father's Height)/2–6.5
2. Midparental Height SDS = (Mother's Height SDS+Father's Height SDS)/1.6

DIAGNOSIS OF GH DEFICIENCY IN THE NEWBORN

In both preterm and term newborns, GH levels in the first days of life are >20 µg/L.[10-11] IGF-I values, are relatively low, but it has been shown that in infancy, IGF-I values lower than -2 SD for age are suggestive of GH deficiency. In newborns with micropenis, hypoglycemia, birth trauma or a family history of GH deficiency, a value of 20 µg/L or below by routine GH estimation (using polyclonal antibodies) can be accepted as indicative of GH deficiency.

IGF-I AND IGFBP-3 IN GH DEFICIENCY

Changes in the levels of growth factors with age

In healthy children serum IGF-I and IGFBP-3 levels well reflect the endogenous 24-hour GH secretion. These levels have been recognised as useful clinical parameters since they show very little diurnal change and remain stable.(12, 13, 14, 15, 16, 17, 18, 19)

Insulin and IGF-I are the two main factors responsible for growth in the early postnatal period. Studies have shown that birth weight, placental weight and gestational age correlate positively with the cord blood IGF-I levels. In preterms, cord blood IGF-I, IGFBP-3 and the acid-labile subunit (ALS) levels are lower than in term newborns.(10, 20, 21)

In the early neonatal period, serum IGF-I levels are closely associated with nutritional state. This association weakens but remains through childhood and adulthood. The levels fall during periods of inadequate nutrition and rise with reversion to normal nutrition.(22)

The fundamental factors influencing growth are nutrition during the infancy period, primarily GH and also other hormones during childhood, and in addition to these, sex steroids during the pubertal period. In late infancy and early childhood, serum IGF-I and IGFBP-3 levels become GH dependent.

The relatively low serum IGF-I and IGFBP-3 levels at birth start increasing during childhood and reach maximal levels in adolescence and fall thereafter to prepubertal levels in adulthood.(23)

During childhood IGF-I levels increase slowly and show each year a parallelism with the growth rate of the following year.(23, 24) Longitudinal studies have shown that serum IGF-levels maintain this parallelism until the attainment of the maximal growth velocity. Thereafter, despite the fall in postpubertal growth rate, IGF-I levels have been observed to remain high. Therefore, the correlation between the IGF-I levels and the growth rate is marked only in prepubertal children.(25, 26)

In both sexes, the increase in sex steroids during puberty results in higher GH secretion. Alongside with this increase in GH secretion, an increase in GH sensitivity also contributes to the increase in IGF-I and IGFBP-3 levels.(13) Peak IGF-I and IGFBP-3 levels are reached approximately 2 years after the attainment of peak height velocity.(27, 28)

Although serum IGF-I and IGFBP-3 determinations are very useful in evaluating growth disorders, a reliable normative data is needed for optimal benefit of these diagnostic tools. Since IGF-I levels vary with age, sex and puberty, a large sample is needed to determine normative values. There are differences in reported reference values for normal ranges due to differences in populations studied and differences in assay methods used. Values obtained in a study using the immunoradiometric assay (IRMA) method (DSL assay kits) carried out on healthy school children in Istanbul in order to determine the reference range for IGF-I levels in Turkey are presented in Tables 2-7 and Figures 2-5 below. These data have made possible the calculation of IGF-I SDS and IGFBP-3 SDS values.(28, 29)

Table 2: Change in serum mean, standard deviation (SD) and standard deviation score (SDS) IGF-I levels in healthy girls with age.

		IGF-I(*)		IGF-I				
				SD			SD	
Age	N	Mean	SD	-1	1	Mean	-2	2
4	17	11.7	3.2	75	220	140	30	330
5	6	13.8	3.7	110	280	180	50	400
6	17	15.3	2.1	140	340	225	70	480
7	28	15.8	3.9	170	390	270	90	545
8	41	17.2	3.8	210	455	320	120	620
9	30	18.5	3.4	260	520	370	160	680
10	33	20.3	3.7	320	580	430	220	740
11	46	23.1	3.2	380	630	500	280	780
12	32	24.0	1.6	440	670	545	340	805
13	39	24.1	1.9	470	690	580	380	820
14	31	24.5	2.1	485	705	590	390	830
15	24	24.1	2.8	480	700	585	385	830
16	28	24.1	2.7	465	680	580	375	805
17	7	23.0	1.7	455	640	545	360	750

**Square-root transformation has been utilised to normalise the data*

Table 3: Change in serum mean, standard deviation (SD) and standard deviation score (SDS) IGF-I levels in healthy boys with age.

		IGF-I(*)		IGF-I				
				SD			SD	
Age	N	Mean	SD	-1	1	Mean	-2	2
4	20	10.0	3.2	50	180	100	15	270
5	7	11.2	3.4	70	220	130	30	325
6	19	13.9	3.2	100	260	170	45	380
7	25	14.5	3.2	120	300	200	60	420
8	28	15.7	2.3	140	340	230	70	480
9	39	15.4	4.0	160	380	260	80	540
10	41	16.6	3.1	190	440	300	100	610
11	37	18.5	4.3	230	510	350	130	700
12	31	19.6	4.7	280	580	415	180	780
13	38	22.9	2.5	340	640	480	240	830
14	48	24.1	3.2	405	700	540	290	880
15	41	25.1	2.9	450	740	580	330	910
16	26	25.0	2.8	470	750	600	350	910
17	28	23.7	2.8	475	740	600	355	890

**Square-root transformation has been utilised to normalise the data*

THE DIAGNOSTIC SIGNIFICANCE OF IGF-I AND IGFBP-3

In the diagnosis of GH deficiency

The conditions which affect the GH-IGF axis and the relative changes of serum GH, IGF-I ve IGFBP-3 levels are given in Table 8.

Low IGF-I levels in GH deficiency have been shown in many studies. While IGF-I levels were found to be lower than -2 SD

Table 4: Change in serum mean, standard deviation (SD) and standard deviation score (SDS) of IGFBP-3 levels in healthy girls with age.

		IGFBP-3		IGFBP-3				
				SD			SD	
Age	N	Mean	SD	-1	1	Mean	-2	2
4	14	4291	457	3650	5000	4300	2950	5650
5	6	4635	1157	3750	5350	4550	2950	6150
6	16	4654	806	3900	5600	4750	3050	6400
7	25	4917	793	4100	5750	4950	3250	6600
8	37	5150	860	4300	5950	5100	3450	6750
9	31	5062	758	4500	6150	5300	3700	6950
10	33	5505	821	4700	6350	5500	3950	7200
11	45	5763	793	4900	6450	5700	4150	7250
12	30	5916	659	5050	6550	5800	4300	7350
13	37	6047	778	5100	6600	5850	4350	7350
14	30	5580	779	5050	6550	5800	4350	7300
15	29	5863	822	5000	6400	5700	4350	7100
16	28	5455	523	4900	6150	5550	4350	6800
17	11	5346	539	4800	5900	5350	4350	6400

Table 5: Change in serum mean, standard deviation (SD) and standard deviation score (SDS) IGFBP-3 levels in healthy boys with age.

		IGFBP-3		IGFBP-3				
				SD			SD	
Age	N	Mean	SD	-1	1	Mean	-2	2
4	20	4040	755	3550	4700	4100	2950	5300
5	8	4557	315	3600	4900	4250	2950	5600
6	16	4208	870	3650	5150	4400	2900	5900
7	22	4417	886	3700	5350	4550	2900	6200
8	26	4547	927	3850	5600	4750	3000	6500
9	34	4971	805	4100	5850	4950	3200	6750
10	39	5141	927	4350	6100	5225	3400	7000
11	37	5578	910	4550	6350	5450	3650	7200
12	29	5631	925	4700	6450	5600	3850	7350
13	36	5932	686	4800	6550	5700	4000	7350
14	44	5617	807	4900	6450	5650	4050	7300
15	35	5566	952	4750	6350	5575	4000	7150
16	26	5294	623	4650	6200	5490	3950	6950
17	29	5348	745	4550	6000	5450	3850	6700

of the mean value for respective age in 82% of patients with GH deficiency, these values were found to be within normal limits in 68% of short children with no GH deficiency.(30) In 203 boys of low stature, Juul et al.(31) have found that IGF- I values of -2 SD below the mean had a positive predictive value of 57%. In children younger than 10 years, IGF-I estimation is more useful than estimation of GH in pointing to subnormality in GH stimulation tests (Figure 13). An IGF-I value of -2.5 SD gives the optimal limit for discriminating GH deficiency from idiopathic low stature.(31)

Table 6: Calculation of IGF-I z-score (SDS) according to the Tanner scoring.

Tanner Score	α (SE)	β (SE)	SD	*P*	*N*	*r*
Boys						
I	7.94 (0.997)	0.82 (0.108)	3.95	<0.0001	198	0.479
II	14.53 (4.642)	0.44 (0.381)	3.12	0.258	32	0.206
III	7.96 (6.692)	1.01 (0.507)	3.66	0.058	25	0.384
IV	25.40 (5.599)	-0.07 (0.396)	2.68	0.858	41	-0.029
V	27.08 (3.119)	-0.16 (0.197)	2.64	0.428	113	-0.075
Girls						
I	8.09 (1.101)	1.0 (0.143)	3.75	<0.0001	123	0.536
II	14.96 (4.764)	0.36 (0.464)	3.00	0.442	21	0.177
III	15.24 (4.532)	0.632 (0.410)	3.12	0.130	44	0.232
IV	20.52 (2.554)	0.290 (0.204)	2.28	0.159	67	0.174
V	25.96 (2.205)	-0.128 (0.147)	2.33	0.386	114	-0.082

Y= β x Age (year) + α
IGF-I z-score= (IGF-1 SQR –Y)/SD
E.g.: 12- year old girl; Tanner score III; IGF-I = 400 ng/mL
√IGF-I = IGF-1 SQR = 20
Y = 0.632 x 12 + 15.24 = 22.82
*IGF-I z-score= (20-22.82)/3.12= **-0.904***

Table 7: Calculation of IGFBP-3 z-score (SDS) according to Tanner scoring.

Tanner Score	α (SE)	β (SE)	SD	*P*	*N*	*r*
Boys						
I	3518 (234)	140 (25)	929	<0.0001	187	0.378
II	2710 (1100)	251 (91)	803	0.010	30	0.463
III	7083 (1354)	-97 (104)	742	0.357	26	-0.188
IV	10934 (1538)	-352 (109)	803	0.003	35	-0.489
V	6926 (939)	-93 (59)	778	0.117	108	-0.152
Girls						
I	3948 (318)	111 (40)	780	0.007	114	0.250
II	4216 (1371)	133 (132)	699	0.326	20	0.231
III	4100 (1076)	129 (97)	776	0.191	44	0.201
IV	7129 (816)	-51 (65)	801	0.429	66	-0.099
V	7540 (674)	-96 (45)	717	0.033	119	-0.196

Y= β x Age (year) + α
IGFBP-3 z-score = (IGFBP-3 –Y)/SD
E.g.: 12-year old boy; Tanner score III; IGFBP-3 = 6000 ng/mL
Y = -97 x 12 + 7083 = 5919
*IGFBP-3 z-score = (6000-5919)/742= **0.109***

Table 8: Laboratory findings in conditions affecting the GH-IGF axis

Condition	GH	IGF-I	IGFBP-3	Growth
GH deficiency	Variable	Low	Low	Decreased
GH resistance	Normal/High	Low	Low	Decreased
IGF deficiency	Variable	Low	Low/Normal	Decreased
Acromegaly	High	High	High	Increased
LGA	Variable	High	High	Increased
SGA	Low	Low	Low	Decreased

LGA: High birth weight for gestational age
SGA: Low birth weight for gestational age

Figure 2: Change in serum IGF-I levels in healthy Turkish girls with age.

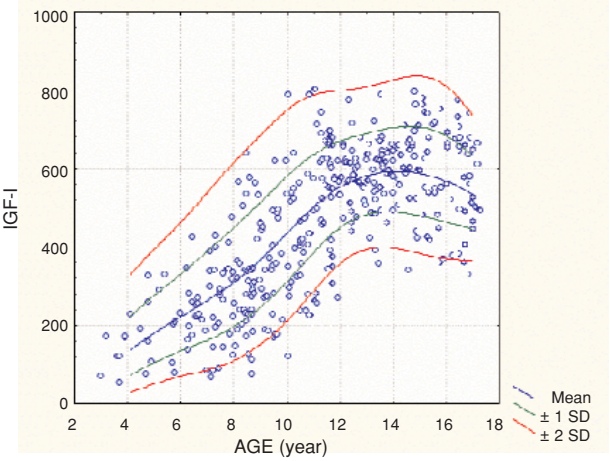


Figure 3: Change in serum IGF-I levels of healthy Turkish boys with age

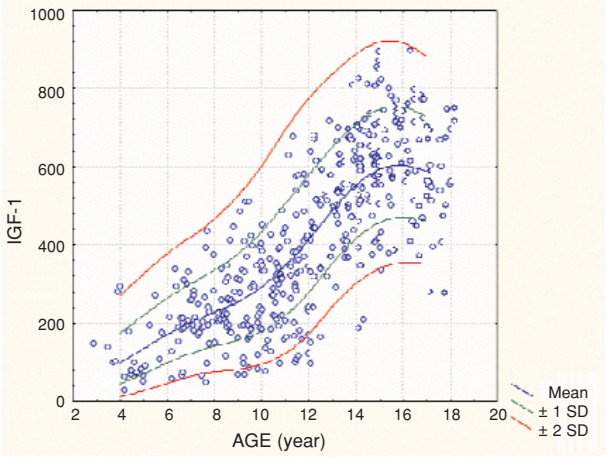


Figure 4: Change in serum IGFBP-3 levels of healthy Turkish girls with age

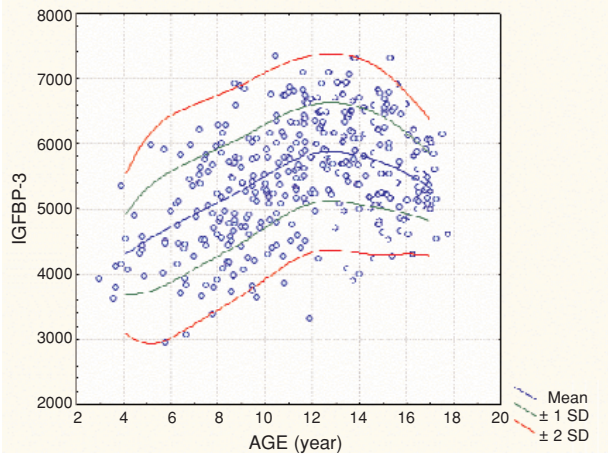
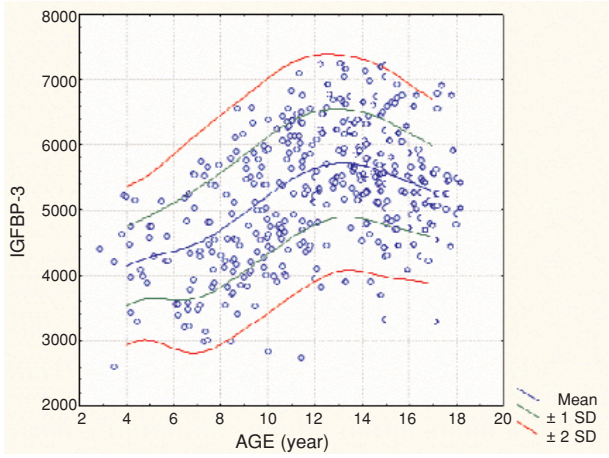


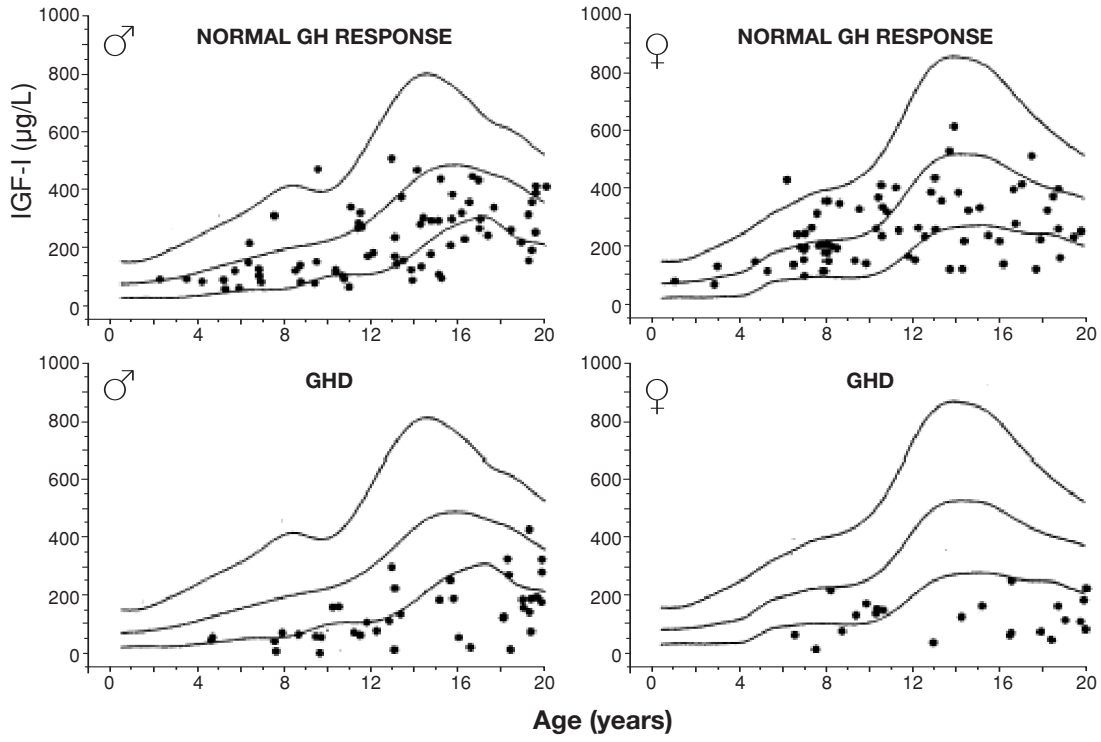
Figure 5: Change in serum IGFBP-3 levels in healthy Turkish boys with age



The diagnostic value of estimating IGF-I and IGFBP-3 changes according to the cut-off limits taken, Rikken et al.(32) have demonstrated in a study with 96 children that when a cut-off limit of -0.83 SD was taken for IGF-I, the sensitivity and the specificity of the estimations for detecting GH deficiency were 92% and 47%, respectively. If the IGF-I cut-off limit was taken as -1 SD, the percentages of GH deficiency and idiopathic low stature detected became 88 and 46, respectively. In other studies taking the IGF-I limit at -2 SD, the specificity and the sensitivity of detecting GH deficiency varied between 47% and 80% and 61% and 91%, respectively.(33, 34, 35, 36, 37, 38, 39, 40)

Blum et al. in 1990 have stated that the sensitivity and the specificity of measuring IGFBP-3 were 97% and 95%, respectively, and that estimating IGFBP-3 was more useful than measuring IGF-I for the diagnosis of GH deficiency. However, in subsequent studies these high levels of specificity and sensitivity were not demonstrable and the reported sensitivities varied between 15% and 98% and the corresponding specificities

Figure 6: Serum IGF-I values in patients presenting with low stature. The upper panel gives results of GH response to stimulation tests in children with normal GH response and the lower panel gives results on GH deficient children.[31]



varied between 50% and 98%.(42, 43, 44) After the publication of the reference curves for IGF-I and IGFBP-3 values over the age range 0 to 6 years, it was seen that the lower limits of IGF-I levels were very close to the estimated IGF-I values whereas this was not the case with IGFBP-3. Thus, theoretically IGFBP-3 has a diagnostic superiority over IGF-I for the 0 to 6-year age group and this hypothesis has been supported by other studies demonstrating the diagnostic superiority of IGFBP-3 estimations in prepubertal children as compared to those in older children.(24, 31, 33)

In most patients with GH deficiency IGF-I and IGFBP-3 levels are low and rise to normal after treatment. IGF-I and IGFBP-3 can be used in evaluation of response to treatment as well as in the follow-up of GH deficient patients, regardless of etiology. The follow up of IGF-I and IGFBP-3 levels theoretically will help to predict the growth response as well as assessing the efficacy of GH replacement and patient compliance to the treatment. In patients receiving GH replacement, positive correlations between the z-scores of IGF-I and IGFBP-3 and the increase in height have been shown. In GH replacement dose adjustment IGF-I values specific for age and sex must be taken into consideration.

In recent years, it has been argued that both from the points of view of effectiveness and long term safety, the adjustment of the GH replacement dose be made according to IGF-I and IGFBP-3 values.(45) The advantages and disadvantages of the criteria used in adjusting the GH replacement dose are shown in Table 10.

The targeted IGF-I z-scores in different stages of the replacement therapy for optimal benefits are shown in Table 11.

Table 9: The diagnostic sensivity and specificity of IGF-I ve IGFBP-3 estimations as compared to the results of the GH stimulation tests in children suspected with GH deficiency.

	Age group (yrs)	Stim. test	GH lower limit	Sensitivity	Specificity
IGF-I					
Rosenfeld et al.	1–18	ARG+ITT	7 ng/ml	82% (56/68)	68% (30/44)
Lee et al.	8.9±4.4	CLO, L-DOPA	7 ng/ml	81% (13/16)	53% (71/133)
Blum et al.	11.2 [0.25–34.4]	ARG, ITT	10 ng/ml	96% (127/132)	54% (70/130)
Smith et al.	0.2–18.0	ITT, ARG	1 ng/ml	86% (49/57)	70% (16/23)
Cianfarani et al.	8.1±1.8	ARG, CLO	8 mU/l	69% (11/16)	80% (8/10)
Hasegawa et al.	ND	ARG, ITT	10 ng/ml	88% (52/59)	79% (81/103)
Nunez et al.	10.7±2.4	ARG, ITT, L-DOPA	7 ng/ml	50% (8/16)	81% (60/74)
Juul and Skakkebæk	12.7 [1.1–19.9]	ARG, CLO	15 mU/l	69% (42/61)	77% (110/142)
Tillman et al.	7.9±3.4	Clinical Diagn.*		34% (20/58)	72% (78/109)
Rikken et al.	7.5±3.5	Not known	20 mU/l	61% (36/59)	78% (24/32)
Hall et al.	ND	Not known	20 mU/l	82% (18/22)	62% (29/62)
Mitchell et al.	0.9–25.4	ITT, GLU	13.5 mU/l	62% (92/148)	47% (69/147)
Bussieres et al.	4.7 [2.9–18.8]	ORN, GLU, AITT	10 ng/ml	84% (36/43)	57% (39/68)
Ranke et al.	6.8 (1.0)	AITT	10 ng/ml	75% (140/187)	50% (102/205)
IGFBP-3					
Blum et al.	11.2 [0.25–34.4]	ARG+ITT	10 ng/ml	97% (128/132)	95% (123/130)
Smith et al.	0.2–18.0	ITT, ARG	1 ng/ml	93% (53/57)	57% (13/23)
Hasegawa et al.	ND	ARG, ITT	5 ng/ml	90% (53/59)	70% (71/103)
Cianfarani et al.	8.1± 1.8	ARG, CLO	8 mU/l	50% (8/16)	90% (9/10)
Nunez et al.	10.7±2.4	ARG, ITT, L-DOPA	7 ng/ml	31% (5/16)	85% (63/74)
Juul and Skakkebæk	12.7 [1.1–19.9]	ARG, CLO	15 mU/l	61% (37/61)	85% (121/142)
Tillman et al.	7.9±3.4	Clinical Diagn.*		34% (20/58)	72% (78/109)
Rikken et al.	7.5±3.5	Not Known	20 mU/l	63% (37/59)	84% (27/32)
Mitchell et al.	0.9–25.4	ITT, GLU	13.5 mU/l	15% (22/148)	98% (147/150)
Ranke et al.[55]	6.8 (1.0)	AITT	10 ng/ml	67% (140/187)	50% (102/205)

ARG, arginin; ITT, insulin tolerance test; CLO, clonidine; L-DOPA, L-dopamine; GLU, glucagon; ORN, ornithine; AITT, arginine and ITT combination;
** According to the clinical diagnosis (organic hypopituitarism or stalk lesion seen at MRI)*

Table 10: Advantages and disadvantages of criteria used in GH replacement therapy.

	Standard dose	On body weight basis	On IGF level	On growth rate basis
Advantage	Simple Tried in adults	Easy Tried	Optimal growth Safe	Most important criterion Economical Noninvasive
Disadvantage	Variable results	Disregards individual GH sensitivity	Requires laboratory facilities	Safety? Requires a minimum time of 6 months for evaluation

Table 11: The targeted IGF-I z-score values for optimal benefits from treatment

Growth phase	Catch-up growth	Continuity of growth	Puberty	Transition to adulthood
Aim of Treatment	Maximum height correction	Maintenance of height SDS	Optimising final height	Body composition
Targeted IGF-I Z score	+2 to +3 SDS	-1 to +1 SDS	+1 to +2SDS If short +2 to 3 SDS	0 to +1 SDS

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