

# Clinical Utility of Insulin-Like Growth Factor-I (IGF-I) and IGF Binding Protein-3 Levels in the Diagnosis of GH Deficiency (GHD) During Childhood

YUKIHIRO HASEGAWA, TOMONOBU HASEGAWA\*, MAKOTO ANZO,  
TAIJI ASO, AND YUTAKA TSUCHIYA\*

*Division of Endocrinology and Metabolism, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo 204, and*

*\* Department of Pediatrics, Keio University School of Medicine, Tokyo 160, Japan*

**Abstract.** Diagnosis of GH deficiency (GHD) has been done traditionally by the combination of auxological data and the results of GH provocation tests. Recently, limitations of GH provocation tests have been advocated. Thus, three extreme subgroups (G-1; normal, G-2; severe GHD, G-3; short children with normal GH secretion) were selected in order to show that insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) levels reflect GH secretion. In G-1 (n=52), all had normal IGF parameters. In G-2 (n=27), all had low IGF parameters. In G-3 (n=28), all except for one patient had normal IGF parameters. Taken together with the assumption that GH secretion status is continuous from zero to normal (or to acromegalic), the data on IGF parameters in the three subgroups indicate that they are functional tests for GH secretion. IGF-I and IGFBP-3, together with free IGF-I and acid-labile subunit, may replace GH provocation tests in the diagnosis of GH deficiency during childhood; these functional tests for GH secretion, which show minimal intradaily variation, are more physiological and cost-effective than GH provocation test.

**Key words:** Insulin-like growth factor-I (IGF-I), IGF binding protein-3, GH secretion, GH deficiency  
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INSULIN-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) levels are known to be GH-dependent. IGF-I and IGFBP-3 measurements are thought to be one of the best screening parameters in the diagnosis of GH deficiency (GHD) during childhood.

Diagnosis of GHD has been done traditionally by the combination of auxological data and the results of GH provocation tests. In order to verify the clinical utility of IGF parameters (IGF-I and IGFBP-3), comparison of these parameters with the results of GH provocation tests has been done. Because limitations of GH provocation tests have

recently been advocated [2], in addition to the comparison of these IGF parameters with the results of GH provocation tests, three extreme subgroups (normal, severe GHD, and short with normal GH secretion) were selected in order to show that IGF-I and IGFBP-3 reflect GH secretion.

## Materials and Methods

### Subjects

The first group of the subjects was patients with GHD: 1) complete GHD (CGHD, n=59): all the GH peaks of GH provocation tests were less than 5 ng/ml (Eiken immunoradiometric assay; IRMA), 2) partial GHD (PGHD, n=49): the maximum GH peak of GH provocation tests was 5 to 10 ng/ml.

Correspondence to: Dr. Yukihiro HASEGAWA, Division of Endocrinology and Metabolism, Tokyo Metropolitan Kiyose Children's Hospital, 1-3-1 Umezono, Kiyose, Tokyo 204, Japan

Given the limitations of GH provocation tests, the second group of subjects was selected among the children who had visited our hospital due to short stature for these three years (in 1992–1994;  $n=156$ ), in addition to normal reference subgroup (G-1 as will be explained below). This second group of subjects consisted of three subgroups (G-1, G-2, and G-3) as are schematically shown in Fig. 1. G-1 was a subgroup of normal children ( $n=52$ ; 3–8 years); their height was greater than minus two standard deviation score for each age [3]. G-2 was a subgroup of severe GHD ( $n=27$ ; 1–12 years); they were GHD patients with an abnormality in the GH gene or Pit-1 gene, with abnormalities on magnetic resonance image such as invisible stalk, or with other deficiencies of anterior pituitary hormones. Group-3 was a subgroup of short children ( $Ht < -2.5$  SDS [3]) with normal GH secretion ( $n=28$ ; 3–12 years); they had at least one GH peak of more than 20 ng/ml. Because a subgroup with unequivocally normal GH secretion should have been selected, not the usual criterion of 10 ng/ml but the criterion of 20 ng/ml was used to define this subgroup.

### Methods

The usual GH provocation tests were arginine and insulin tolerance tests. Among children who had at least one GH peak of more than 10 ng/ml, the percentage of discordance between GH peaks in GH provocation tests in terms of below and above 10 ng/ml (the percentage where one GH peak in these two provocation tests was less than 10 ng/ml and one of the other GH peaks was more than 10 ng/ml) was 19, 25 % for the arginine test, and insulin test, respectively [4]. IGF-I and IGFBP-3 levels were measured as previously described [5]. The 5th percentile for each age was used as the cutoff value for low IGF-I and IGFBP-3 for each age.

### Results

The percentage of patients with CGHD and PGHD who had low IGF-I levels (less than the 5th percentile for each age) was 88% and 39%, respectively [5]. Similarly, the percentage of patients with CGHD and PGHD who had low IGFBP-3 levels (less than the 5th percentile for each age) was 92%

and 39%, respectively [5]. In Fig. 2, data for IGFBP-3 in CGHD are shown.

The ratio of subjects in the three subgroups (G-1, 2 and 3) who had normal IGF-I and IGFBP-3 concentrations (more than the 5th percentile for each age) are shown in Table 1. In G-1, all had normal IGF parameters. In Group-2, all had low IGF parameters. In G-3, all except one patient had normal IGF parameters.

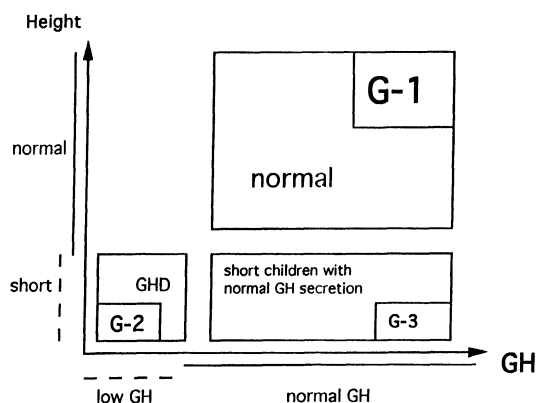


Fig. 1. Schematic explanation for the subgroups of G-1, G-2 and G-3.

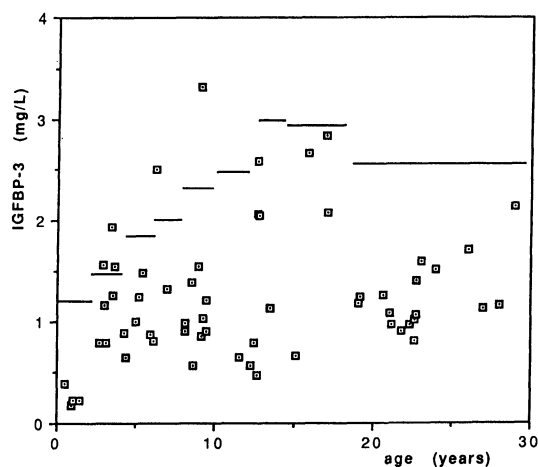


Fig. 2. IGFBP-3 levels of CGHD. The bars in this figure show the 5th percentile for each age (the authors rewrote the figure in the reference 5 with author's permission).

Table 1. Ratios of the subjects who had IGF-I and IGFBP-3 above the percentile for each age

G-1 (normal height)	52/52
G-2 (severe GHD)	0/27
G-3 (short with normal GH)	27/28

## Discussion

The diagnosis of GHD has been done by a combination of auxological criteria and laboratory data. Among laboratory data, the results of GH provocation tests have been considered to be a gold standard, but recently questions about the utility of GH provocation tests have been put forward: (a) various assays for GH are used in different hospitals, (b) almost no normal values have been presented except for a report by Martin *et al.* [5], and the usual criterion of GH peak of 10 ng/ml is totally arbitrary, (c) the tests are not reproducible, (d) they do have false positive and false negative, (e) some children with normal GH reserve based on results of GH provocation tests have low IGF-I and low IGFBP-3, and grow well with conventional GH treatment, similarly to patients with GHD.

Because of these limitations of GH provocation tests, simple comparison of IGF-I and IGFBP-3 measurements with results of GH provocation tests is therefore not enough to establish the clinical utility of IGF parameters in the diagnosis of GHD. The result obtained with IGF parameters in CGHD indicate that these parameters are one of the best indicators for screening GHD. The results obtained with IGF parameters in PGHD are probably due to the limitations of GH provocation tests.

Because of the limitations of GH provocation tests, we formed three subgroups of subjects (G-1, 2, and 3), to try to see whether these IGF parameters reflect GH secretion. Taken together with the

assumption that GH secretion is continuous from zero to normal (acromegalic), the data on IGF parameters in the three subgroups may indicate that they are functional tests for GH secretion.

Other functional tests for GH secretion are free IGF-I levels and acid-labile subunit (ALS) levels. By using a newly developed immunoradiometric assay for free IGF-I [7, 8], the levels of 12 patients in G-2 was less than the 5th percentile for each age without any exceptions (data not shown). Similarly, by means of the immunoblot technique, ALS was shown to be highly GH-dependent: ALS levels of patients with severe GHD during childhood (n=6) were unequivocally lower than those of normal children at the similar ages (data not shown).

These functional tests for GH secretion such as IGF-I and IGFBP-3 may replace GH provocation tests in the diagnosis of GHD during childhood; 1) there are several functional tests such as free IGF-I [8], total IGF-I, IGFBP-3, ALS [9], 2) these functional tests generally show minimal intradaily variations, 3) these functional tests are more physiological and cost-effective than GH provocation tests, 4) there are some examples of functional tests in other endocrine diseases, for example, diagnosis of insulin-dependent diabetes mellitus can be done by measuring blood sugar levels without checking insulin levels.

In summary, (1) IGF-I and IGFBP-3 reflect the GH secretion status and they are functional tests for GH secretion, (2) these functional tests may replace GH provocation tests in the diagnosis of GHD during childhood.

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