

NOTE

Acid-Labile Subunit in Growth Hormone Excess and Deficiency in Adults: Evaluation of Its Diagnostic Value in Comparison with Insulin-Like Growth Factor (IGF)-I and IGF-Binding Protein-3

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Abstract. In serum, insulin-like growth factors (IGFs) are primarily present as a ~150 kDa ternary protein complex, which consists of IGFs, IGF binding protein-3 (IGFBP-3), and acid-labile subunit (ALS). Like IGF-I and IGFBP-3, serum levels of ALS depend on growth hormone (GH). To date, the diagnostic relevance of ALS in adult GH deficiency (GHD) has remained uncertain. To clarify the clinical utility of ALS measurement in adults, we measured serum ALS levels in patients with adult GHD or acromegaly. We also measured the levels of serum IGF-I and IGFBP-3 in these patients to compare the utility of ALS with IGF-I and IGFBP-3 as a marker of GH secretion. Serum ALS was measured by radioimmunoassay (RIA) kit, and serum IGF-I and IGFBP-3 were measured by immunoradiometric assay (IRMA) kits in 56 patients with adult GHD (adult-onset (AO)/child-onset (CO), 13/43) and 43 patients with acromegaly. Serum ALS levels were less than 5th percentile in 40 of 56 (71%) patients with adult GHD (32/43 (74%) for CO and 8/13 (62%) for AO), and more than 95th percentile in 38 of 43 (88%) patients with acromegaly, respectively. Serum IGF-I levels were less than -1.96 SD in 43 of 56 (77%) patients with adult GHD (35/43 (81%) for CO and 8/13 (62%) for AO) and more than $+1.96$ SD in 42 of 43 (98%) patients with acromegaly, respectively. Serum IGFBP-3 levels were less than -1.96 SD in 51 of 56 (91%) patients with adult GHD (42/43 (98%) for CO and 9/13 (69%) for AO) and more than $+1.96$ SD in 31 of 43 (72%) patients with acromegaly, respectively. These data suggested that measurement of ALS offers no advantage over measurements of serum IGF-I and IGFBP-3. Furthermore, our results indicate that serum IGFBP-3 is the most suitable marker of GH secretion for adult GHD, especially CO, while IGF-I may be the most useful in acromegaly.

Key words: Acid-labile subunit, IGF-I, IGFBP-3, Adult GH deficiency, Acromegaly

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ADULTS with growth hormone deficiency (GHD) have altered body composition, osteopenia, an abnormal lipid profile, increased cardiovascular disease, and reduced quality of life [1, 2]. For these patients, the benefit of GH replacement therapy has been recently demonstrated [1]. In order to select

patients for such treatment, requires being able to accurately determine whether they are deficient in GH. One mediator of GH action in serum is insulin-like growth factor I (IGF-I), which is present as a ~150 kDa ternary protein complex consisting of IGF-I, IGF binding protein 3 (IGFBP-3), and a serum protein known as acid-labile subunit (ALS) [3]. All three components depend on GH secretory status and show only slight daily variations [3–5]. To date, measurements of IGF-I and IGFBP-3 have been proposed as good diagnostic markers of GHD, particularly in children of short stature [6, 7]. However, the utility of ALS, IGF-I, and IGFBP-3 as

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screening markers for the diagnosis of adult GHD remains controversial. In the present study, we investigated serum levels of these three proteins in adult GHD and acromegaly. We then evaluated the clinical utility of each protein as a marker of GH secretory status in disorders of GH secretion.

Subjects and Methods

Subjects

Fifty-six patients with adult GHD (29 men and 27 women), with a mean age of 35 ± 14 yr (mean \pm SD; range, 20–76 yr) were studied. Forty-three of 56 patients had child-onset (CO) GHD (25 men and 18 women), and 13 patients had adult-onset (AO) GHD (four men and nine women). One of three tests was used to confirm that peak GH response was less than 3 ng/ml, as measured by immunoradiometric assay (IRMA): insulin-induced hypoglycemic test ($n=46$), glucagon-propranolol test ($n=2$), and arginine test ($n=1$). In the remaining seven patients we performed a GRH test, and the peak GH response was also less than 3 ng/ml. These seven patients had organic pituitary disease and two or more other pituitary hormone deficiencies in addition to GHD. The causes of CO were idiopathic ($n=28$), germinoma ($n=7$), craniopharyngioma ($n=5$), Rathke's cleft cyst ($n=1$), optic glioma ($n=1$), and tuberculosis meningitis ($n=1$). Of 28 patients with idiopathic CO GHD, 27 had a history of either breech presentation or neonatal asphyxia, or both ($n=15$). The causes of AO GHD were Sheehan's syndrome ($n=5$), non-functioning pituitary adenoma ($n=6$), germinoma ($n=1$), and prolactinoma ($n=1$). In addition to GHD, all patients had multiple pituitary hormone deficiencies in various combinations as shown in Table 1. The subjects were receiving suitable hormonal replacement therapy and in stable condition. The route of estrogen replacement was oral in female patients.

Forty-three patients with active acromegaly (18 men and 25 women), with a mean age of 53 ± 13 yr (mean \pm SD; range, 18–82 yr) were also studied. The diagnosis of acromegaly was based on clinical signs and lack of GH suppression to less than 1 ng/ml after oral glucose (75 g) loading test. The presence of a pituitary adenoma was confirmed by magnetic

Table 1. Pituitary hormone deficiency in patients with adult GHD.

Hormone deficiency	CO GHD	AO GHD
Gonadotropin	41/43 (95%)	12/13 (92%)
Corticotropin	25/43 (58%)	12/13 (92%)
Thyrotropin	35/43 (81%)	12/13 (92%)
Prolactin	5/43 (12%)	5/13 (38%)
Vasopressin	12/43 (28%)	5/13 (38%)

Number of deficient pituitary hormones	CO GHD	AO GHD
1*	0	0
2	6	1
3	12	1
4	15	7
5	8	4
6	2	0
Total	43	13

*: Isolated GH deficiency

resonance imaging and/or computerized tomography in all patients. Most patients had been newly diagnosed. However, 13 of the 43 patients were previously treated with surgery or conventional radiotherapy. The persistence of acromegaly had been proven in these patients, following the initial therapy, by oral glucose tolerance test ($n=8$), abnormal GH response for TRH administration ($n=4$), or high serum GH levels (basal GH levels more than 120 ng/ml, $n=1$).

All patients were examined at the Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical University. Informed consent for blood sampling was obtained from all patients. Blood samples were obtained for measuring serum IGF-I, IGFBP-3, and ALS. Sera were frozen at -20°C until time of assay.

Measurements of serum ALS, IGF-I, and IGFBP-3

Serum ALS was measured by radioimmunoassay (RIA) kit (Bioclone Australia, Marrickville, Australia). The intra- and inter-assay coefficients of variation of the RIA were less than 5.4 and 4.9%, respectively. Serum IGF-I and IGFBP-3 were measured by immunoradiometric assay (IRMA) kits (Daiichi Radioisotope Laboratories, Tokyo, Japan). The intra- and inter-assay coefficients of variation for

IGF-I were 2.4 and 2.6%, respectively. The intra- and inter-assay coefficients of variation for IGFBP-3 were 5.1 and 5.0%, respectively. As the serum concentrations of ALS, IGF-I, and IGFBP-3 depend on gender and age [3–5], the normal reference values for age-matched controls of the kits were used [8]. For ALS, the reference ranges of each gender and age (median, 5th and 95th percentile) used were those given in the attached document of the kit.

Statistics

All data are expressed as mean \pm SEM. Serum levels of IGF-I and IGFBP-3 are expressed as standard deviation scores (SDS) for sex and age, according to the constructed reference [8]. A chi-square test was used to compare the sensitivities of ALS, IGF-I, and IGFBP-3 between patients with CO adult GHD, AO GHD, and acromegaly. Unpaired t-tests were used to evaluate differences between IGF-I SDS and IGFBP-3 SDS in patients with CO GHD, AO GHD, and acromegaly. Significance was established at $P < 0.05$. All statistical analyses were performed using StatView 4.51 (Abacus Concepts Inc., Berkeley, CA). Sensitivity (true positive ratio) of IGF-I SDS, IGFBP-3 SDS, and ALS was defined as the

number of true positives divided by the number of all patients.

Results

In adult GHD, 40 of 56 patients (71%) had serum ALS levels less than 5th percentile. Sixteen patients with adult GHD, 11 with CO (M/F 10/1) and 5 with AO (M/F 2/3), had normal ALS levels (Fig. 1). There were no significant differences between the sensitivity of ALS for CO (74%) and AO (62%) GHD. Serum IGF-I levels were less than -1.96 SD in 43 of 56 patients (77%). Of the remaining 13 patients, eight with CO (M/F 6/2) and five with AO (M/F 2/3) had IGF-I values within the normal range (Fig. 2). Serum IGFBP-3 levels were less than -1.96 SD in 51 of 56 patients (91%) with adult GHD. Of the remaining 5 patients, one woman with CO and four patients with AO GHD (M/F 1/3) had normal IGFBP-3 concentrations (Fig. 3). The sensitivity of IGFBP-3 for adult GHD (91%) was significantly higher than that of ALS (71%) or IGF-I (77%) ($p < 0.05$ for both).

In patients with adult GHD, IGFBP-3 SDS were significantly lower (-4.75 ± 0.37 ; range, -12.15 to

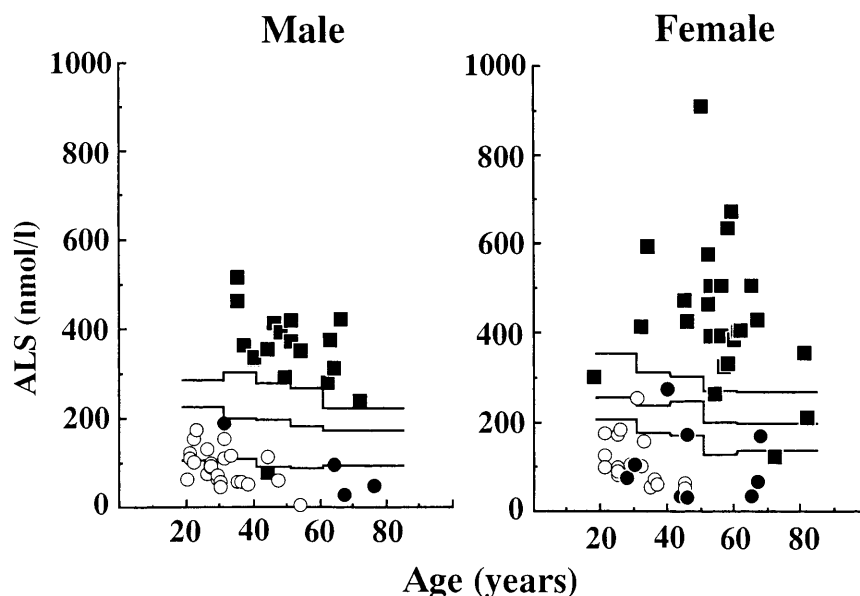


Fig. 1. Serum ALS levels in patients with CO GHD, AO GHD and acromegaly. Solid lines, median, 5th and 95th percentiles of normal values; open circle, CO GHD ($n = 43$, M/F 25/18); closed circle, AO GHD ($n = 13$, M/F 4/9); closed square, acromegaly ($n = 43$, M/F 18/25).

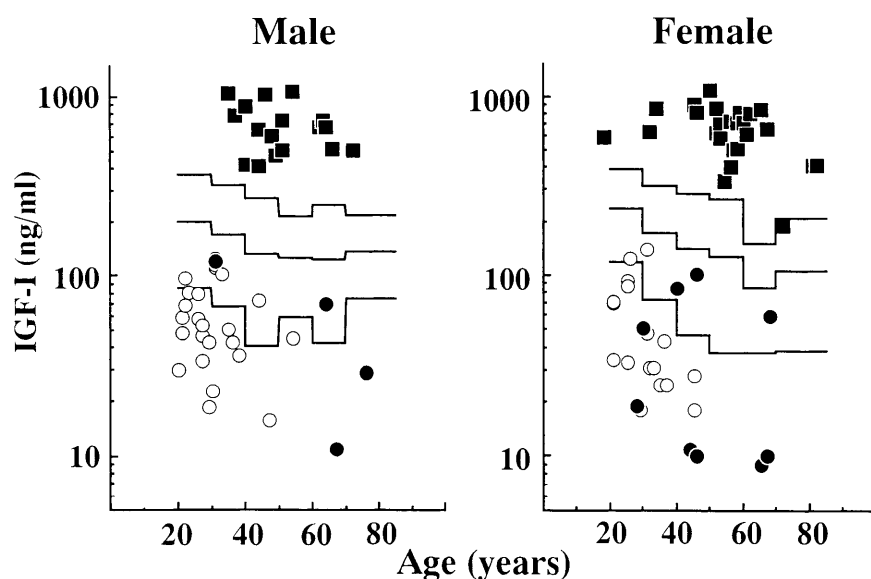


Fig. 2. Serum IGF-I levels in patients with CO GHD, AO GHD and acromegaly. Solid lines, mean \pm 1.96SD of normal values; open circle, CO GHD (n = 43, M/F 25/18); closed circle, AO GHD (n = 13, M/F 4/9); closed square, acromegaly (n = 43, M/F 18/25).

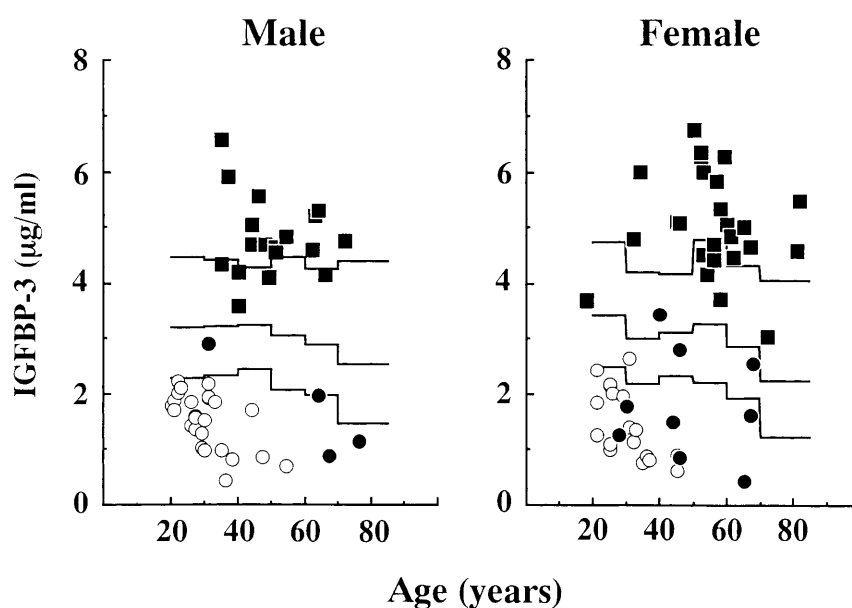


Fig. 3. Serum IGFBP-3 levels in patients with CO GHD, AO GHD and acromegaly. Solid lines, mean \pm 1.96SD of normal values; open circle, CO GHD (n = 43, M/F 25/18); closed circle, AO GHD (n = 13, M/F 4/9); closed square, acromegaly (n = 43, M/F 18/25).

0.69) than those for IGF-I (-2.68 ± 0.15 , $p < 0.0001$; range -4.92 to -0.56). When GHD patients were classified according to onset of GH deficiency, there were no significant differences between CO and AO patients in either IGFBP-3 SDS (-5.10 ± 0.39 vs.

-3.58 ± 0.87 , $p = 0.08$), or IGF-I SDS (-2.70 ± 0.15 vs. -2.60 ± 0.41 , $p = 0.7$; Fig. 4).

In acromegaly, 38 of 43 patients (88%) had serum ALS levels more than 95th percentile (Fig. 1). Three patients with acromegaly had normal ALS levels, and

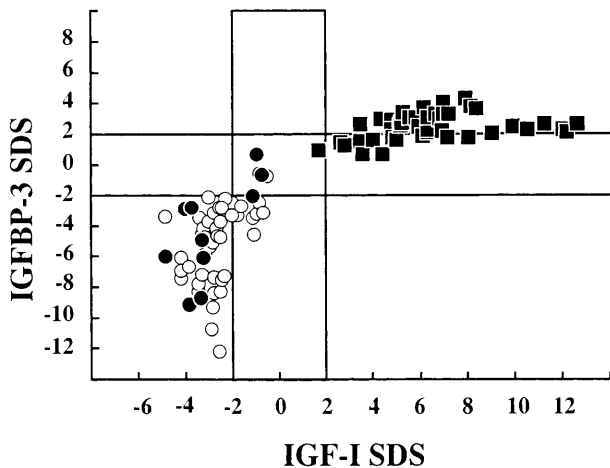


Fig. 4. IGFBP-3 SDS and IGF-I SDS in patients with CO GHD, AO GHD and acromegaly. Solid lines, mean \pm 2SD of normal values; open circle, CO GHD (n=43); closed circle, AO GHD (n=13); closed square, acromegaly (n=43).

two patients had low ALS levels. Serum IGF-I levels were more than $+1.96$ SD in 42 of 43 patients with acromegaly, but the level was normal in one woman (Fig. 2). Therefore, the sensitivity of IGF-I for acromegaly was 98%. Serum IGFBP-3 levels were more than $+1.96$ SD in 31 of 43 patients (72%). The remaining 12 patients (M/F 5/7) had normal IGFBP-3 levels (Fig. 3). In the patients with acromegaly, IGF-I SDS was significantly higher (6.47 ± 0.40 ; range, 1.65 to 12.65) than IGFBP-3 SDS (2.53 ± 0.13 ; range, 0.69 to 4.40, $p < 0.0001$; Fig. 4). The sensitivities of ALS, IGF-I, and IGFBP-3 for detecting adult GHD and acromegaly are summarized in Table 2.

Serum ALS, IGF-I, and IGFBP-3 levels were normal in five patients with adult GHD, four of whom had AO GHD.

Discussion

It has been reported that serum ALS levels are low in patients with GH deficiency, and conversely that ALS levels are significantly elevated in patients with acromegaly [5, 9–14]. In this study, we compared ALS concentrations in patients with adult GHD and acromegaly to those in age- and gender-matched populations. While we observed that the sensitivity of serum ALS in detecting GH level was higher in acromegaly than in GHD, the measurement of serum ALS offers no advantage over measuring IGF-I for acromegaly and IGFBP-3 for adult GHD. Furthermore, we saw no significant differences between the sensitivity of ALS for CO and AO GHD. Of 12 patients with persistent acromegaly who underwent surgery, ten patients had elevated serum ALS levels. This finding is in agreement with data reported by Arosio *et al.*, which showed the usefulness of serum ALS levels for postsurgical reassessment of the disease [15]. Serum ALS levels were low in two patients with acromegaly. One, a 44-year-old man, had no concomitant disease and had elevated IGF-I and IGFBP-3 levels. It is not clear why this patient had a decreased level of serum ALS. The other, a 72-year-old woman, also had IGF-I and IGFBP-3 levels within the normal range, but had a history of rectal carcinoma. In this case, chronic catabolic illness may have caused the reduced level of ALS and the normal levels of IGF-I and IGFBP-3 despite active acromegaly.

In this study, we observed a marked decrease in serum IGFBP-3 levels in patients with adult GHD. To date, the usefulness of IGFBP-3 estimation in comparison with IGF-I in the diagnosis of adult GHD has been controversial. De Boer *et al.* reported that 93% of the young adult patients with GHD had IGFBP-3 levels below the normal range, and considered IGFBP-3 as well as IGF-I as a very discrimina-

Table 2. Sensitivities of ALS, IGF-I and IGFBP-3 for adult GHD and acromegaly.

	ALS	IGF-I	IGFBP-3
Adult GHD (< -1.96 SD)	71% (40/56)	77% (43/56)	91% (51/56)
CO GHD	74% (32/43)	81% (35/43)	98% (42/43)
AO GHD	62% (8/13)	62% (8/13)	69% (9/13)
Acromegaly ($> +1.96$ SD)	88% (38/43)	98% (42/43)	72% (31/43)

tive marker for diagnosis of GHD in adults [1, 16]. However, other studies have contradicted these findings. Thissen *et al.* reported that the sensitivity of IGFBP-3 measurement for the diagnosis of adult GHD was as much as 36%, which is much lower than the sensitivity of IGF-I [17]. Moreover, a considerable overlap was observed between patients with adult GHD and normal subjects in the circulating levels of IGFBP-3 [18, 19]. In our study, GHD patients had mean SDS that were significantly lower for IGFBP-3 than for IGF-I SDS, and eight patients with normal levels of IGF-I had low IGFBP-3 levels. Moreover, when patients were classified according to GHD onset, IGFBP-3 SDS was more frequently low in CO than in AO GHD, as previously reported [20, 21]. In our study, 98% (42/43) of CO had IGFBP-3 SDS below -1.96 , whereas only 69% (9/13) of AO patients had IGFBP-3 levels less than -1.96 SDS. So far, the underlying mechanisms for the difference in biochemical parameters between GHD acquired at childhood or that acquired as an adult have not been elucidated. In our study, the duration of GHD was longer in CO-patients than in AO-patients. But it is not clear whether the duration of GHD affects the sensitivity of IGFBP-3 synthesis to the circulating GH concentration or not. These results suggest that IGFBP-3 SDS is a more sensitive marker than IGF-I SDS for the diagnosis of CO adult GHD. It should be noted, however, that normal IGFBP-3 levels do not rule out GHD, particularly in patients with AO deficiency.

Several investigators have shown that determination of plasma IGF-I level has a more discriminative value than the level of serum IGFBP-3 for the evaluation of patients with acromegaly [22–26]. We confirmed these findings in the present study, observing that SDS were significantly higher for IGF-I than for

IGFBP-3. Moreover, only one acromegaly patient had a normal IGF-I level whereas 12 of 43 (28%) patients with active acromegaly had normal values for IGFBP-3.

ALS, IGF-I, and IGFBP-3 levels were normal in five patients with adult GHD although peak GH levels during an insulin-induced hypoglycemic test in these patients were less than 3 ng/ml by IRMA. Only one of these patients had CO GHD, the remaining four having AO of the disease. The one patient with CO GHD also had gonadotropin deficiency, three of four AO GHD patients had three pituitary hormone deficits, and the remaining AO patient had four pituitary hormone deficits in addition to the GHD. There were no differences in clinical features between the patients with normal levels of ALS, IGF-I, and IGFBP-3 and those who did not, except for the onset time of GHD.

In conclusion, serum IGFBP-3 was markedly decreased in CO GHD adults. We found IGFBP-3 to be sufficiently useful for screening CO GHD, but to have less value for AO GHD. Our results suggest that among ALS, IGF-I, and IGFBP-3, serum IGFBP-3 might be the most suitable screening marker of GH secretion for adult GHD, while IGF-I may be the most appropriate for acromegaly. The measurement of serum ALS did not offer any advantage over IGF-I for acromegaly or IGFBP-3 for adult GHD.

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