The Usefulness of Serum Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) for Evaluation of Children with Short Stature

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Abstract

The diagnostic value of serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) was studied in 24 growth hormone deficient (GHD) and 36 normal variant short stature (NVSS) children. The serum IGF-1 and IGFBP-3 concentrations were markedly below the 5th centile for chronological age in all 24 GHD children, but were in the low normal range for age in most of the NVSS children. The concentrations of IGF-1 and IGFBP-3 significantly correlated with peak GH concentration, height age, and bone age. To account for the age- and sex-dependency, IGF-1 and IGFBP-3 levels were transformed to standard deviation score (SDS). Using the -2 SDS as a cut-off level to differentiate between GHD and NVSS, the diagnostic value of IGF, as well as IGFBP-3, showed sensitivity 100 per cent, specificity 66.7 per cent, and accuracy 80 per cent. The combined use of IGF-1 and IGFBP-3 < -2 SDS improved the diagnostic value with sensitivity 100 per cent, specificity 77.8 per cent, and accuracy 86.7 per cent. We concluded that the serum cencentrations of IGF-1 and IGFBP-3 could reflect endogenous GH secretion and could be used as a screening evaluation of GH status in short children.

Key word : Growth Hormone, Insulin-like Growth Factor-1 (IGF-1), Insulin-like Growth Factor Binding Protein-3 (IGFBP-3), Short Stature

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Short stature as defined by height below the third centile for age is a common problem in pediatric practice. Evaluation for growth hormone deficiency (GHD) in those short children is important for definite diagnosis as well as its therapeutic consequences. The measurement of random growth hormone (GH) concentration is of little value due to its short half-life of 15 minutes and the typical pulsatile secretion which usually has low cencentration during the daytime. Conventionally, the gold standard for diagnosis of GHD requires 2 different provocative tests demonstrating a peak serum GH level less than 10 mIU/L (ng/ml)[1-3]. However, all provocative tests are non-physiologic, time-consuming, costly, and carry some risks or adverse reactions[4]. An alternative method for GH evaluation is 12-hour nocturnal or 24-hour serial blood sampling which although more physiologic and has fewer adverse reactions, requires hospitalization of the patient and more frequent blood sampling.

Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) are GH - dependent peptides that mediate the growth promoting actions of GH[5-7]. Both peptides are mainly synthesized by the liver and circulate in the plasma in a complex form of IGF-IGFBP complex which results in a long half-life of 15-20 hours and a minor circadian variation. Thus, the serum levels of IGF-1 and IGFBP-3 reflect the endogenous GH secretion and are accepted to be very useful as a screening evaluation of GH status[5-7]. Recently, we presented the normative data of serum IGF-1 and IGFBP-3 concentrations in Thai children and adolescents according to age, sex, and stage of puberty[8]. In this study, we measured the serum IGF-1, IGFBP-3 concentrations in patients with and without GHD. The objective of this study was to evaluate the diagnostic value of serum IGF-1, IGFBP-3 in relation to the outcome of GH provocative tests.

SUBJECTS AND METHOD

Sixty patients, aged between 5-20 years, with standing height below the third centile for chronological age were included. All patients were followed-up for at least 12 months to evaluate their height velocity. The screening procedure, including complete blood count, serum chemistry, thyroid function test, urinalysis, and bone age based on Greulich and Pyle[9] were done before performing the GH provocative tests which were clonidine and insulin tolerance tests. In our clinic, oral premarin 0.3-0.625 mg was used for priming 2 nights before the GH provocative tests[10]. GH levels were measured using radioimmunoassay (RIA). The diagnosis of growth hormone deficiency (GHD) was made on the basis of standing height less than the third centile for age, height velocity less than 4 cm per year, and a maximal GH response less than 10 mIU/L in 2 GH provocative tests. Normal variant short stature (NVSS) was diagnosed in children with short stature and height velocity at least 4 cm per year and a maximal GH response of more than 10 mIU/L[11]. The clinical characteristics of patients with GHD (n = 24) and NVSS (n = 36) are summarized in Table 1. To account for sex- and age-dependency, the height and weight of the patients were calculated to standard deviation score (SDS) by using the actual measurement minus the mean, then divided by the standard deviation (SD)[2]. The mean and SD of growth parameters were based on the normative data for Thai children[12].

Table 1. Characteristics of patients with GHD and NVSS.

	GHD (n = 24) M/F = 11/13		NVSS (n = 36) M/F = 28/8		
	Mean ± SD	Range	Mean ± SD	Range	p value
Age	12.2 ± 5.1	5-20	11.5 ± 3.4	6-18	0.24
Ht SDS	-3.85 ± 1.73	(-7.54)-(-2.04)	-2.33 ± 0.47	(-4.77)-(-1.95)	< 0.01
Wt SDS	-1.98 ± 1.52	(-5.02)-(+1.22)	-1.73 ± 0.96	-4.1-(+0.55)	0.57
BMI	17.4 ± 3.33	14.4-23.2	17.2 ± 2.72	13.7-24.4	0.72
Maximal GH level	3.27 ± 2.56	0-7.4	17.37 ± 5.01	10.7-31.1	< 0.001
Bone age	8.6 ± 4.5	2-14	8.7 ± 3.4	3.4-18	0.62
Height age	8.2 ± 4.0	1.5-13.5	8.9 ± 2.6	4-14.0	0.39

The serum sample for IGF-1 and IGFBP-3 measurements were obtained 2-4 weeks before the GH provocative test to avoid the probable stimulating effect of premarin priming. The serum was separated and stored at -20°C until the time of analysis. The levels of IGF-1 and IGFBP-3 were determined by immunoradiometric assay (IRMA) using DSL-5600 and DSL-6600 kits, respectively (Diagnostic System Laboratories, Texas, USA). The details of assay analysis were previously described (8). The interassay variations of IGF-1 and IGFBP-3 were 7.18 per cent and 5.33 per cent, and the intraassay variations were 4.86 per cent and 3.2 per cent, respectively. The concentrations of IGF-1 and IGFBP-3 were plotted against the normative curves for males and females, then calculated to SDS to account for the age- and sex-dependency.

RESULTS

All 24 patients with GHD had the IGF-1 and IGFBP-3 concentrations below the 5th centile for chronological age, whereas, most of the patients with NVSS had the IGF-1 and IGFBP-3 concentrations in the lower normal range for age (Fig. 1). The concentrations of IGF-1, as well as IGFBP-3 correlated significantly with the peak GH concen-

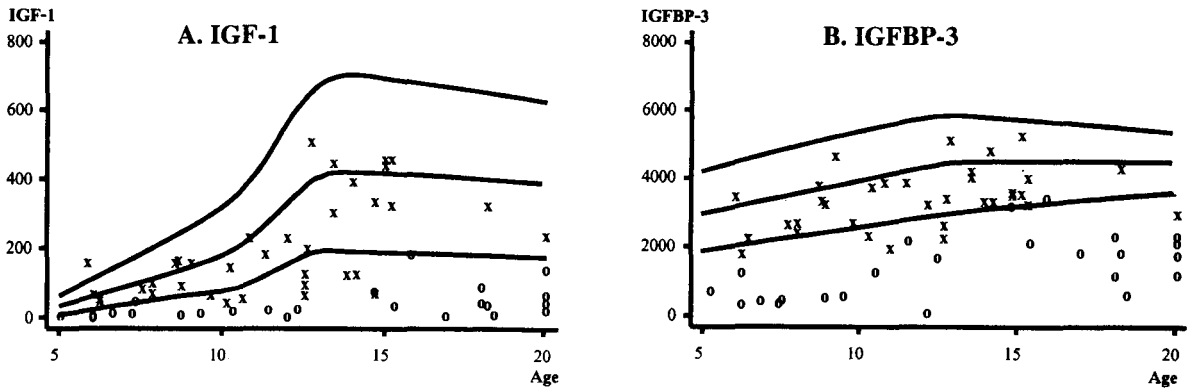


Fig. 1. The concentrations of IGF-1 (A) and IGFBP-3 (B) in short children with GHD (o) and NVSS (x) plotted with the centile curves of normal children.

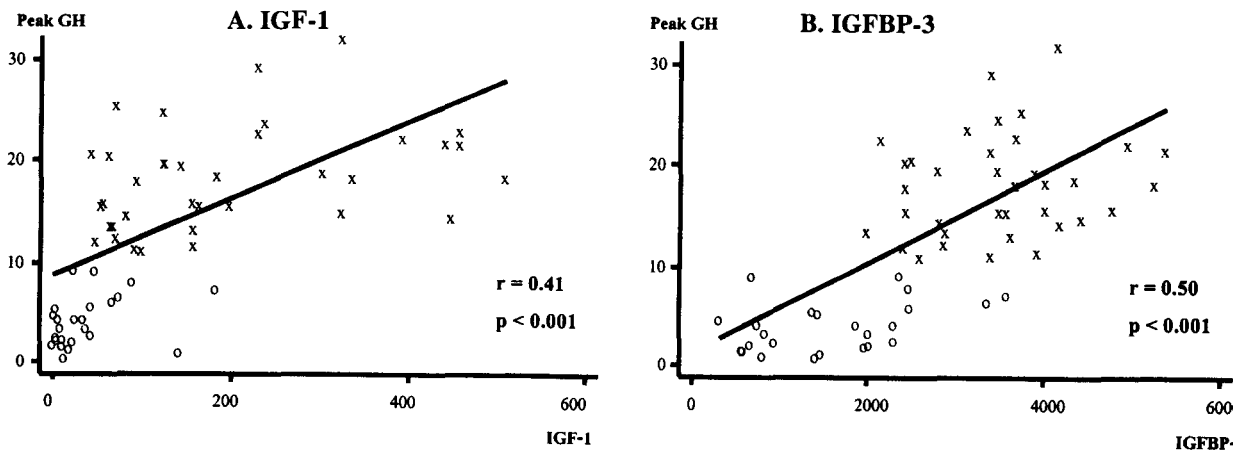


Fig. 2. The correlation of peak GH levels and IGF-1 (A), IGFBP-3 (B) concentrations in GHD (o) and NVSS (x) patients.

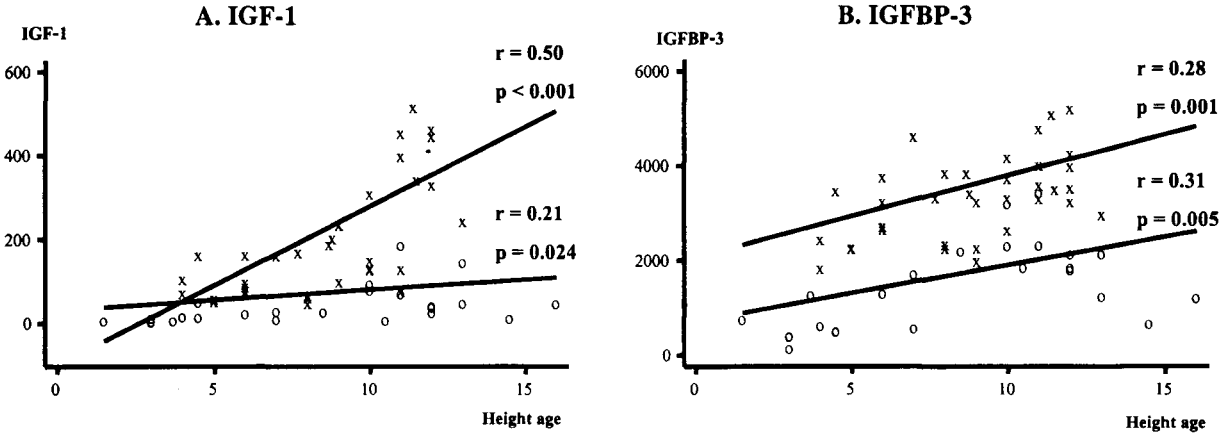


Fig. 3. The correlation of height age and IGF-1 (A), IGFBP-3 (B) concentrations in GHD (o) and NVSS (x) patients.

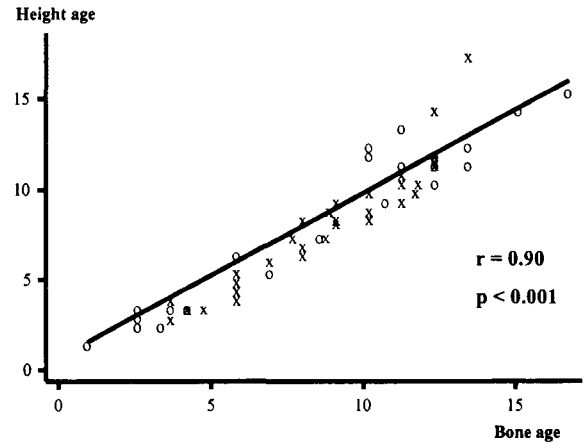


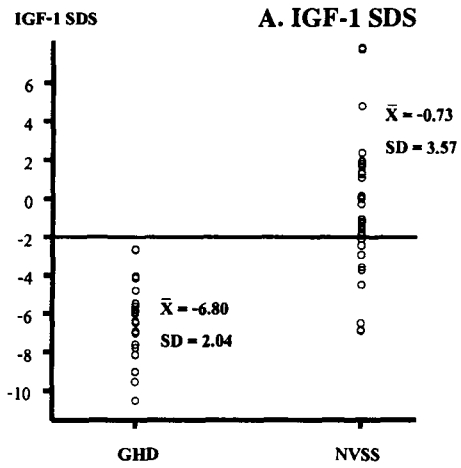
Fig. 4. The correlation of height age and bone age in GHD (o) and NVSS (x) patients.

tration (r = 0.41 and r = 0.50, both p < 0.001) (Fig. 2). The IGF-1 and IGFBP-3 concentrations also correlated significantly with height age in GHD patients (r = 0.21, p = 0.024 and r = 0.31, p = 0.005, respectively), as well as in NVSS patients (r = 0.50, p < 0.001 and r = 0.28, p = 0.001, respectively) (Fig. 3). In both GHD and NVSS patients, the height age correlated very well with the bone age (r = 0.9; p < 0.001) (Fig. 4). The GHD patients had a slight advance, whereas, the NVSS patients had a slight delay in bone age compared to height age, however, without statistical significance. The concentrations of IGF-1, IGFBP-3 corrected for height age and bone age were still below 5th centile in all patients with GHD, but were close to the 50th centile in 24 of 26 (92.3%) patients with NVSS.

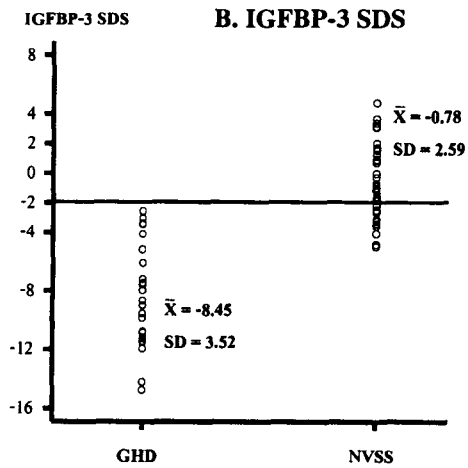
For the diagnostic value of serum IGF-1 and IGFBP-3 concentrations in differentiating the patients with GHD from NVSS, we used the -2 SDS as the cut-off level. The concentrations of IGF-1 as well as IGFBP-3 were below -2 SDS in all patients with GHD, and were above -2 SDS in 24 out of 36 patients with NVSS, resulting in diagnostic value of sensitivity 100 per cent, specificity 66.7 per cent, positive predictive value 66.7 per cent, negative predictive value 100 per cent, and accuracy 80 per cent in each of the parameters (Fig. 5). The combined use of IGF-1 and IGFBP-3 below -2 SDS improved the diagnostic value with the sensitivity 100 per cent, specificity up to 77.8 per cent, positive predictive value 75 per cent, negative predictive value 100 per cent, and accuracy up to 86.7 per cent (Fig. 6).

DISCUSSION

Our results showed that the concentrations of IGF-1 and IGFBP-3 were below the 5th centile for age in all GHD patients, and were in the low normal range for age in most of the NVSS patients. After being corrected for height age or bone age, the concentrations of IGF-1 and IGFBP-3

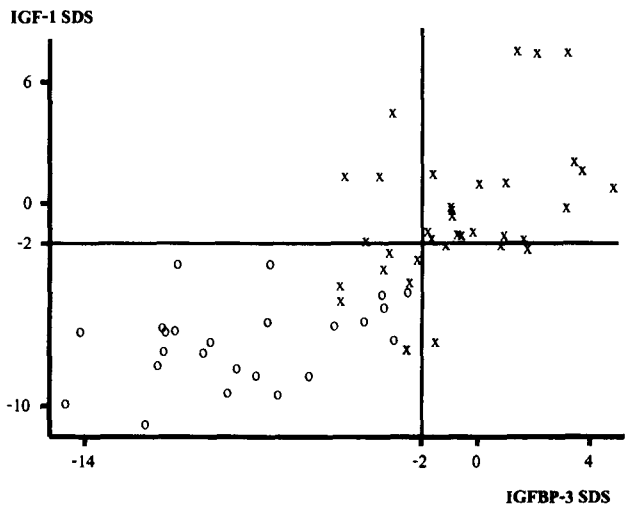


sensitivity =100%
specificity = 66.7%
positive predictive value = 66.7%
negative predictive value = 100%
accuracy = 80%



sensitivity =100%
specificity = 66.7%
positive predictive value = 66.7%
negative predictive value = 100%
accuracy = 80%

Fig. 5. The diagnostic value of IGF-1 SDS (A) and IGFBP-3 SDS (B) in GHD patients (< -2 SDS) and NVSS patients (> -2 SDS).



sensitivity =100%
specificity = 77.8%
positive predictive value = 75%
negative predictive value = 100%
accuracy = 86.7%

Fig. 6. The diagnostic value of combined use of IGF-1 SDS and IGFBP-3 SDS using -2 SDS as the cut-off level in GHD (o) and NVSS (x) patients.

were still very low in GHD patients, but were within normal ranges in almost all patients with NVSS. Using the -2 SDS as a cut-off level to differentiate between GHD and NVSS, the diagnostic value of IGF-1 as well as IGFBP-3 showed sensitivity 100 per cent, specificity 66.7, and accuracy 80 per cent. The combined use of IGF-1 and IGFBP-3 SDS below -2 SDS improved the diagnostic value with sensitivity 100 per cent, specificity up to 77.8 per cent, and accuracy up to 86.7 per cent. All this evidence supported that IGF-1 and IGFBP-3 reflected the GH status and could be used as a screening parameter for GH evaluation in short children. Therefore, short statured children whose IGF-1 and IGFBP-3 levels were clearly within the normal range for chronological age or whose IGF-1 and IGFBP-3 levels were in the relative low range for chronological age but in the normal range after correction for height age or bone age should be excluded for GHD. On the contrary, short children whose IGF-1 and IGFBP-3 were very low for chronological age and still very low after correction for height age or bone age were very much likely to be GHD.

The benefit of using IGF-1 and IGFBP-3 as a screening test for GH status is to avoid the harmful risk associated with GH provocative tests in normal short children. As already known, most of the pharmacological agents used for GH provocative tests have side effects such as nausea, somnolence, hypotension and hypoglycemia[4]. Insulin-induced hypoglycemia which is the most common standard GH provocative test can result in seizures. Death following the use of insulin tolerance test has been reported from either hypoglycemia itself or overly vigorous replacement of glucose[13]. In addition, all provocative tests require multiple sequential samples to be drawn at the exact time which is costly and time-consuming. Another important factor is that none of the pharmacological provocative tests satisfactorily mimic the normal pattern of pituitary GH secretion, and no single provocative test has been judged to be sufficient for the diagnosis of GHD. The alternative method is the measurement of spontaneous GH pulsatile secretion. The spontaneous GH secretion typically requires blood sampling every 20 minutes for 12-24 hours and determining GH level in at least 36-72 samples is more expensive and time-consuming than the GH provocative test[14,15]. Moreover, the patient needs hospitalization, and acclimatization to the hospital setting may be necessary in young children[4]. The simpler and more convenient method for assessment of spontaneous GH secretion is the measurement of GH concentration in 24-hour urine. However, GH is present in urine in a very low concentration and may be influenced by renal function resulting in day to day variation in GH levels[16,17]. Therefore, a parameter that reflects the integrated GH secretion over time by a single serum sample would be ideal. The measurements of serum IGF-1 and IGFBP-3 were thought to meet these requirements, and their value for diagnosis of GHD is well recognized[5-7]. Their usefulness as a screening laboratory test can substitute the risky, costly, and time-consuming evaluation of GH provocative testing in many cases. Normal levels of IGF-1 and IGFBP-3 can exclude GHD and GH provocative test is unnecessary. Low concentrations of IGF-1 and IGFBP-3 suggest GHD and the borderline low IGF-1 or IGFBP-3 concentrations may indicate insufficient GH secretion. In these latter 2 categories, GH provocative tests are indicated for definite diagnosis.

Interpretation of IGF-1 and IGFBP-3 concentration has a number of significant limitations. IGF-1 concentrations are markedly age-dependent. The levels are low in children younger than 5 years of age making it difficult to discriminate between normal and GHD children in this age group. In addition, the various factors can affect the IGF-1 and IGFBP-3 concentration such as undernutrition, chronic illness, hypothyroidism, renal failure, hepatic failure, and diabetes mellitus[18-20]. Therefore, all these conditions have to be evaluated before measuring IGF-1 and IGFBP-3 concentrations. In our study, the IGF-1 and IGFBP-3 levels in 8 children with NVSS were below -2 SDS which was probably due to undernutrition since 4 of them had a BMI less than 16 or < -1 SDS for age.

In summary, we concluded that serum IGF-1 and IGFBP-3 concentrations reflect endogenous GH secretion and can be used as a screening evaluation of GH status in short children. Subnormal serum IGF-1 and IGFBP-3 concentrations predict a subnormal GH response to provocative testing in patients suspected of having GHD, and the normal levels of IGF-1 and IGFBP-3 exclude GHD with sensitivity 100 per cent, specificity 77.8 per cent, and accuracy 86.7 per cent.

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ประโยชน์ของระดับ serum insulin-like growth factor-1 (IGF-1) และ insulin-like growth factor binding protein-3 (IGFBP-3) ในการประเมินเด็กตัวเตี้ย

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ได้ทำการศึกษาประโยชน์ของระดับ insulin-like growth factor-1 (IGF-1) และ insulin-like growth factor binding protein-3 (IGFBP-3) ในการวินิจฉัยผู้ป่วยเด็กตัวเตี้ยจากภาวะขาดฮอร์โมนการเจริญเติบโต 24 ราย และผู้ป่วยตัวเตี้ยปกติ 36 ราย พบว่าผู้ป่วยตัวเตี้ยจากภาวะขาดฮอร์โมนการเจริญเติบโตทุกรายมีระดับ IGF-1 และ IGFBP-3 ต่ำอย่างชัดเจน ในขณะที่ส่วนมากของผู้ป่วยตัวเตี้ยปกติมีระดับ IGF-1 และ IGFBP-3 อยู่ในเกณฑ์ปกติที่ค่อนข้างต่ำ ระดับ IGF-1 และ IGFBP-3 มีความสัมพันธ์กับระดับสูงสุดของ growth hormone (GH) อายุ ความสูง และอายุกระดูก อย่างมีนัยสำคัญทางสถิติ

ในรายงานนี้ ระดับ IGF-1 และ IGFBP-3 ได้ถูกคำนวณเป็นค่า standard deviation score (SDS) เพื่อตัดปัญหาความแตกต่างของอายุและเพศ ค่าที่ -2 SDS ได้ถูกนำมาใช้เป็นระดับที่ใช้ในการแยกระหว่างภาวะขาดฮอร์โมนการเจริญเติบโตและภาวะตัวเตี้ยปกติ พบว่าทั้ง IGF-1 และ IGFBP-3 ต่างมีความไวร้อยละ 100 ความจำเพาะร้อยละ 66.7 และความแม่นยำร้อยละ 80 เมื่อนำทั้ง IGF-1 และ IGFBP-3 ที่ระดับต่ำกว่า -2 SDS มาใช้ พบว่ามีความไวร้อยละ 100 ความจำเพาะเพิ่มขึ้นเป็นร้อยละ 77.8 และความแม่นยำเพิ่มขึ้นเป็นร้อยละ 86.7 ผลการวิจัยสรุปว่าระดับ serum IGF-1 และ IGFBP-3 บ่งบอกถึงภาวะการหลั่งของ GH ในผู้ป่วย และสามารถนำมาใช้ในการคัดกรองผู้ป่วยตัวเตี้ยที่มีภาวะขาด GH ได้

คำสำคัญ : เด็กตัวเตี้ย, ฮอร์โมนการเจริญเติบโต, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3)

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