Influence of Body Mass Index on Growth Hormone Responses to Classic Provocative Tests in Children with Short Stature

by

Hae Sang Lee

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

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Hae Sang Lee

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Supervised by

Jin Soon Hwang, M.D., Ph.D.

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

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This certifies that the dissertation
of Gill Dong Hong is approved.

SUPERVISORY COMMITTEE

Jin Soon Hwang

Ki Soo Pai

Jo Won Jung

The Graduate School, Ajou University
December, 23rd, 2010

-Abstract-

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Objective: Growth hormone (GH) secretion is regulated by physiological parameters. Obesity is associated with diminished spontaneous and stimulated GH secretion. The aim of this study was to assess the influence of BMI on growth hormone response to provocative testing in children with short stature.

Materials and methods: Clinical data was collected retrospectively by chart review from the Pediatric Endocrine Unit at Ajou University Hospital. A total of 187 subjects with short stature who completed a GH stimulation testing between 2003 and 2009 were included in the study.

Results: The study population included 123 (65.8%) males and 64 (34.2%) females with a mean age of 8.5 ± 2.9 years. Of the 187 subjects, 66 (35.3%) had GH deficiency (serum peak GH <10 ng/ml), while 121 (64.7%) were categorized as having idiopathic short stature (serum peak GH ≥ 10 ng/ml). In a stepwise multivariate analysis, BMI was a significantly independent predictor of peak GH. Elevated BMI was negatively associated with peak plasma GH levels.

Conclusion: Higher BMI is associated with lower GH secretion. BMI should be measured and GH results appropriately interpreted for all subject undergoing GH stimulation testing.

Key words: Body mass index, Growth hormone, Short stature

TABLE OF CONTESTS

ABSTRACT----------i

TABLE OF CONTENTS----------ii

LIST OF FIGURES----------iii

LIST OF TABLES----------iv

I. INTRODUCTION----------1

II. MATERIALS AND METHODS----------2

A. SUBJECTS----------2

B. STUDY DESIGN----------2

C. LABORATORY MEASUREMENTS----------3

D. STATISTICAL ANALYSIS----------4

III. RESULTS----------5

A. SUBJECTS CHARACTERISTICS ----------5

B. COMPARISON OF GH RESPONSES OF INSULIN VS. DOPAMINE AND CLONIDINE----------5

C. DETERMINANTS OF PEAK GROWTH HORMONE RESPONSE TO PHARMACOLOGICAL TESTS----------6

D. RELIABILITY OF TESTS----------6

IV. DISCUSSION----------12

V. CONCLUSION----------15

REFERENCES----------16

국문요약----------21

LIST OF FIGURES

Fig. 1. Mean peak GH responses to various provocative stimuli in all subjects----------9

Fig. 2. Correlation between the results of the test with first and second evaluation----------10

LIST OF TABLES

Table 1. Clinical and laboratory characteristics of the subjects----------6

Table 2. Multivariate analysis of factors associated with peak growth hormone values--------7

Table 3. Peak growth hormone concentrations during the first and second test with clonidine, insulin, and dopamine----------8

I. INTRODUCTION

The diagnosis of growth hormone (GH) deficiency during childhood is classically based on the results of two stimulating tests performed using different stimuli. Growth hormone stimulation tests are burdened by methodological and interpretative limitations. The reliability of pharmacological tests used for GH secretion evaluation have been repeatedly questioned given the lack of normal age-related reference values, the use of different pharmacological stimuli and different laboratory methods for the measurement of circulating GH (Carel, et al., 1997;Hilczer, et al., 2006a;Mazzola, et al., 2008;Vestergaard, et al., 1997). Growth hormone secretion is regulated by multiple physiologic factors, including age, onset of puberty, nutritional status and body weight (Ho, et al., 1987;Iranmanesh, et al., 1991;Qu, et al., 2005). In adults, several reports have shown that obesity is associated with diminished spontaneous and stimulated GH secretion (Micmacher, et al., 2009;Qu, et al., 2005;Tzanela, et al., 2010;Van Dam, et al., 2002). There are only a few studies on GH response in obese children and adolescents (Misra, et al., 2008;Stanley, et al., 2009). Body mass index (BMI) is currently not considered a factor when determining current peak GH cut-off points used in the diagnosis of GH deficiency. We analyzed the effect of body mass index on the results of GH stimulation testing, studied the relative potencies of clonidine, insulin, and levodopa, as well as analyzed the reproducibility of growth hormone stimulation test in children with short stature.

II. MATERIALS AND METHODS

A.Subjects

Clinical data was collected retrospectively by chart review from the Pediatric Endocrine Unit at Ajou University Hospital. A total of 187 pediatric patients with short stature who completed GH stimulation testing between 2003 and 2009 were included in the study. The patients' heights were all less than -2 standard deviation (SD) below average, together with a decreased height velocity and delayed bone age. Study subjects underwent GH stimulation testing with a combination of at least two of the following: clonidine, L-dopa, insulin. Central nervous system neoplasm, multiple pituitary hormone deficiencies, and known Turner syndrome patients were excluded. Children receiving medications that may affect endogenous GH secretion, including oral or inhaled corticosteroids, antipsychotic medications, and ondansetron, were also excluded. GH deficiency patients had a GH peak <10 ng/ml on provocation with a combination of at least two separate stimulation trials (2000). Idiopathic short stature (ISS) was defined as a height less than -2 SD with a serum GH peak ≥ 10 ng/ml with stimulation.

B. Study design

After an overnight fast, an indwelling catheter was inserted into a cubital vein that was kept patent by slow saline infusion, and blood was sampled at the time of catheter insertion. All the stimulating tests were performed in the morning hours with one-day time interval

between the two tests. Three different stimulation test protocols were used to assess GH secretion. Clonidin (150 μg/m^2) and dopamine (Sinemet®, 10mg carbidopa/100mg levo-dopa, 150-175 mg/m^2) was administered orally at time 0. Blood was drawn at the time of administration of clonidine and dopamine to obtain the baseline GH values, and at 30, 60, 90, and 120 min thereafter. Insulin (0.1 IU/kg) was administered by an intravenous bolus at time 0 to induce a fall in the blood glucose level to 40 mg/dl or less Blood was drawn before testing (0 min) to obtain the baseline GH values and at 30, 60, 90, and 120 min after administration of the test. Experienced physicians or nurses were present throughout the procedure. From review of clinic charts and electronic medical records, height, weight, IGF-1, IGF-binding protein(IGFBP)-3, pubertal status, thyroid function, type of GH stimulation test, and peak GH levels after stimulation were collected. Pubertal status (Tanner stage for breast development [F] or genital development [M]) was assessed and documented by one pediatric endocrinologist. Bone age was measured using the method described by Greulich and Pyle (Greulich & Pyle, 1959). Body mass index was calculated, and BMI and height SD score were calculated using the 2007 Korean National Growth Charts (Moon, et al., 2008). Of the 121 ISS subjects, 48 subjects underwent reevaluation GH stimulation test reevaluation. During that time, none of the patients received GH therapy or entered puberty.

C. Laboratory Measurements

Serum GH levels were measured by immunoradiometric assay (BioSource, Nivelles, Belgium). Serum IGF-1 levels were measured using immunoradiometric assay (NEXT IRMA CT BC 1110, Biocede Hycel, France). Serum IGFBP-3 levels were also measured by

immunoradiometric assay (IRMA IGFBP-3, Immunotech, France).

D. Statistical analysis

Statistical analysis was performed using SPSS version 14.0 (SAS Institute, Chicago, USA). Univariate analyses were performed using Pearson correlation coefficient for continuous variables and Student's *t* test for categorical variables. Factors significantly associated with peak GH in the univariate analysis were then used to construct a multivariate regression model in several stages. Statistical significance was defined as $P < 0.05$. Results are described as mean ± SD unless otherwise stated.

III. RESULTS

A. Subject characteristics

The study population included 123 (65.8%) males and 64 (34.2%) females with a mean age of 8.5 ± 2.9 years. Of the 187 subjects, 66 (35.3%) were GH deficient (serum peak GH <10 ng/ml) and 121 (64.7%) were ISS (serum peak GH ≥ 10 ng/ml). The majority of children were prepubertal (n=173, 92.4%) and 14 children (7.4%) were pubertal (Tanner II~V). The clinical and biochemical characteristics of the patients are summarized in Table 1. There were no significant differences in the baseline characteristics, except for BMI, BMI SDS, IGF-1, and peak GH hormone. BMI was significantly higher in children with GH deficiency (16.3 ± 2.1 vs. 15.5 ± 1.6, *P*=0.012).

B. Comparison of GH responses of Insulin vs. L-dopa and Clonidine

Total of 470 tests were performed. Of the 470 stimulation tests, insulin, clonidine, and dopamine were used in 190 (40.4%), 146 (31%), and 132 (28.1%) tests respectively. The mean GH peak in the test with insulin was 9.8 ± 8.1 ng/ml, being significantly lower than GH peak in both the test with clonidine (12.9 ± 8.0 ng/ml) and dopamine (13.4 ± 10.2 ng/ml) (*P*=0.002). These differences in the provocative tests remained after adjusting for gender, age, and BMI. There was no significant difference in the test with clonidine and dopamine (Fig. 1).

C. Determinants of peak GH response to pharmacological tests

In stepwise multivariate regression analysis including age, gender, weight, height, BMI, IGF-1, IGF-BP3, and type of pharmacological stimulus as independent variables tested in the model and peak GH as the dependent variable, BMI, IGF-1 and type of pharmacological stimulus were noted to be significant independent predictors for peak GH (Table 2). BMI and stimulation test by insulin were inversely and IGF-1 was positively associated with peak plasma GH.

D. Reliability of tests

Reliability was calculated for 48 patients with ISS who had underdone the GH stimulation test twice. A GH response ≥10 ng/ml after retesting was found in 39 (81.3%) patients and a GH response <10 ng/ml was found in 9 (18.7%) patients. Peak GH concentrations during the first and second test with clonidine, insulin, and dopamine are shown in Table 3. Intraclass correlation coefficients (r) are presented in Fig. 2. In all type of stimulus, r was inferior to 0.2 and no significant correlation was found in the peak GH values of repeat GH stimulation tests (P>0.05). However, IGF-I and IGFBP-3 were more reproducible values during repeat testing (Fig. 2).

Table 1. Clinical and laboratory characteristics of the subjects

	Total (n=187)	Idiopathic short stature (n=121)	Growth hormone deficiency (n=66)	P-value
Sex(M/F)	123/64	78/43	45/21	
Age(year)	8.5±2.9	8.6±2.9	8.3±2.9	0.573
Height(cm)	115.8±14.3	116.2±14.1	114.9±14.8	0.527
Height SDS	-2.4±0.5	-2.3±0.5	-2.4±0.5	0.670
Weight(kg)	21.6±6.5	21.3±6	22.1±7.3	0.454
Weight SDS	-2±1	-2.1±1	-1.8±1.1	0.075
BMI(kg/cm^2)	15.8±1.8	15.5±1.6	16.3±2.1	0.012
BMI SDS	-0.7±1.1	-0.9±1	-0.5±1.1	0.014
Bone age(year)	6.9±2.7	7±2.7	6.8±2.7	0.643
Bone age SDS	-1.9±0.9	-1.9±1	-1.8±0.9	0.713
Peak GH(ng/ml)	16.6±10.1	21.3±9.5	8±3.2	0.000
IGF-1(ng/ml)	188.3±118.7	202.7±128.2	165.5±98.6	0.005
IGFBP-3(mg/L)	2.7±0.6	2.7±0.6	2.7±0.5	0.982

Table 2. Multivariate analysis of factors associated with peak growth hormone values (n=187, r^2=0.340, *P*<0.001)

Variables	Estimate	SE	P value
Insulin	-4.980	0.930	<0.001
BMI	-2.062	0.439	<0.001
IGF-1	0.016	0.005	0.002

Table 3. Peak growth hormone concentrations during the first and second test with clonidine, insulin, and dopamine (n=48)

Peak GH at diagnosis(ng/ml)			Peak GH at retesting(ng/ml)			
clonidine	insulin	L-dopa	clonidine	insulin	L-dopa	Interval(month)
15.9±8	10.5±8.1	12.4±10.2	14.6±6.3	8.4±5.5	13.2±10.1	0.5±0.2

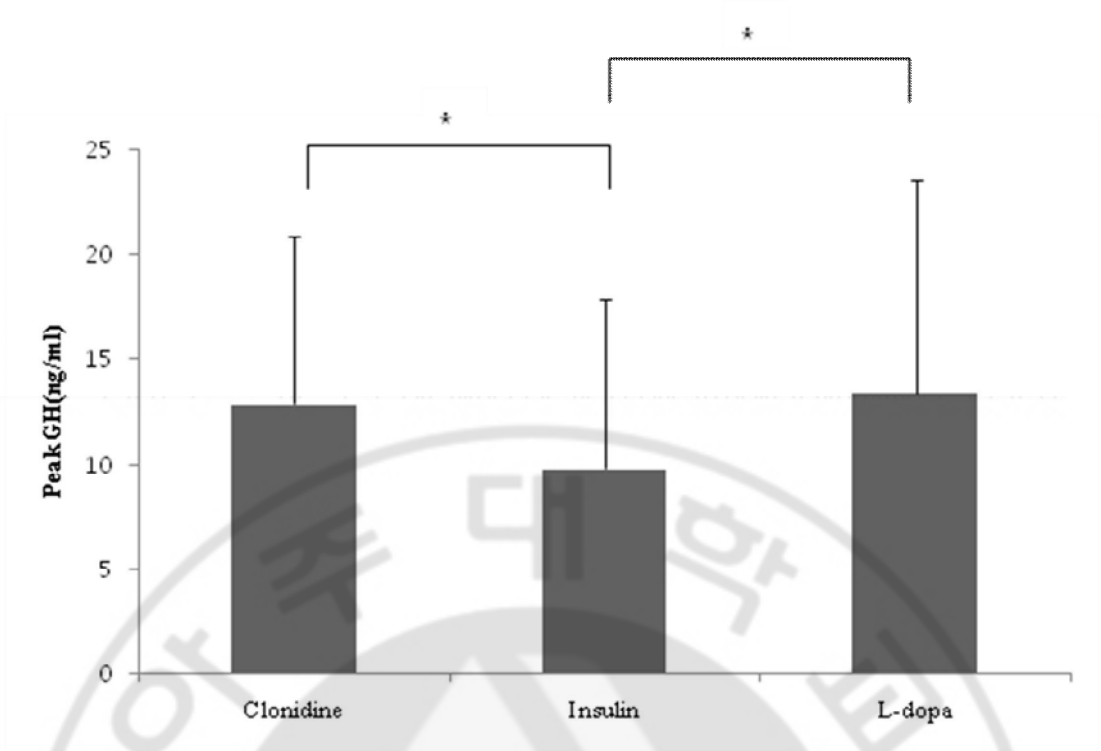

Fig. 1. Mean peak GH responses to various provocative stimuli in all subjects
***, *P*<0.005**

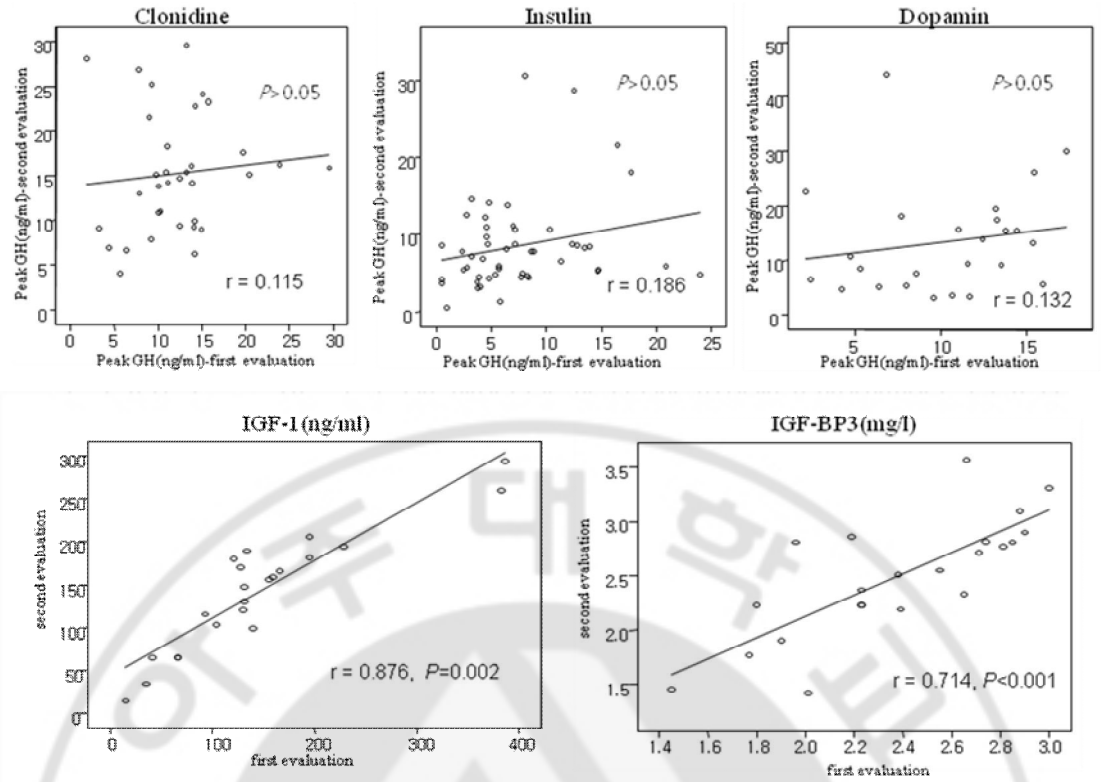

Fig. 2. Correlation between the results of the test with first and second evaluation

IV. DISCUSSION

Our study shows that increased BMI is a major negative determinant of GH response to provocative testing. In addition, clonidine and dopamine are stronger stimuli than insulin and 18.7% of patients with normal GH secretion in the first evaluation fulfilled the criteria of GH deficiency during their second assessment.

Adults with obesity are known to have abnormal basal GH secretion, with obesity having been associated with impairment in GH response to stimulation test. There have been a few studies on GH secretion in obese children. Martha et al. reported that BMI was negatively associated with several parameters of endogenous GH secretion in 46 healthy boys (Martha, et al., 1992). In another study by Albertsson-Wikland and colleagues, the GH secretion rate correlated negatively with weight for height expressed in SD scores in pubertal children (Albertsson-Wikland, et al., 1994). In a recent study, higher BMI was associated with lower GH secretion in 116 children with short stature (Stanley, et al., 2009). The pathogenesis of GH insufficiency in obesity is unclear. High-circulating free fatty acid concentration may be involved in the pathogenesis of GH insufficiency (Casanueva, et al., 1987;Maccario, et al., 1994;Pontiroli, et al., 1991). Free fatty acid reduction by acipimox, an inhibitor of lipolysis, was able to enhance spontaneous GH secretion and GH response to various stimuli (Kok, et al., 2004;Lee, et al., 1995). Also, several reports showed that leptin, a hormone produced by the adipocytes plays a significant role in GH regulation (Coutant, et al., 1998;Tannenbaum, et al., 1998). However, Ozata et al. reported that high plasma level of leptin in obesity was not associated with the inhibition of GH secretion (Ozata, et al., 2003).

The use of two different GH stimulation tests is still considered the gold standard when

diagnosing GH deficiency. However, low reproducibility has been reported for all stimulation tests in children and adults. Loche et al. reported that 84% of GH deficiency children had normal GH secretion at reevaluation (Loche, et al., 2002). In another study, Cacciari and colleagues found that at second retesting during an interruption of childhood replacement therapy, 45.6% of GH deficiency children who normalized during first retesting, returned to the initial GH deficiency diagnosis at second retesting (Cacciari, et al., 1994). In our analysis, children with short stature who 'normalized' at first stimulation test had 'pathological' results at retesting. Another important problem constitutes different GH secretion rates in the same patient after different stimuli. Several reports showed that GH response to stimulation with clonidine was higher than that observed after other stimuli (Carel, et al., 1997;Hilczer, et al., 2006a;Zadik, et al., 1990). Our data confirm the different effects of particular stimulating agents used during the assessment of GH secretion.

Our results show that IGF-1 significantly correlated with peak GH during simulation testing, with considerable stability in repeated assessments. Serum IGF-1 concentration is fairly stable and has no circadian rhythm contrary to the labile GH serum concentration due to the pulsatile manner of GH secretion. Several reports suggested that IGF-1 is a helpful tool in the diagnostic work-up of children with short stature (Badaru & Wilson, 2004;Hilczer, et al., 2006b). However, other studies reported difficulties in diagnosing GH deficiency on the basis of IGF-1 concentrations (Boquete, et al., 2003;Ranke, et al., 2000). IGF-1 levels vary between laboratories because assays methods are not standardized. Results also are affected by malnutrition, hepatic disease, and diabetes.

A major limitation of this study is that only 3 different provocative testing methods were used. Also, this study has limitations stemming from its small sample size and retrospective

study design. Prospective, longitudinal studies in children with short stature including those with normal height would be needed to further validate and characterize the effect of BMI on GH.

V. CONCLUSION

Our results show that higher BMI is associated with lower GH secretion. BMI should be measured and GH results appropriately interpreted for all subject undergoing GH stimulation testing. Also, we question the validity of GH measurements as the arbitrary gold standard for the diagnosis of GH deficiency and alternative or complementary approaches should be developed, including IGF-1 and IGFBP3, or auxological parameters.

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-국문요약-

저신장증 소아에서 체질량 지수가 성장호르몬 자극검사에 미치는 영향

아주대학교 대학원의학과

이 해 상

(지도교수 : 황 진 순)

목적: 소아에서 성장 호르몬 결핍증을 진단하는 성장 호르몬 자극 검사는 결과가 약제간에 변동성이 많고, 약제내에서도 재현성이 낮은 점이 지적되어 왔다. 또한 비만이 성장 호르몬 자극 검사의 결과에 영향을 미친다는 보고들이 있어왔다. 본 연구에서는 성장 호르몬 자극 검사에 영향을 미치는 인자에 대해 연구하고, 성장 호르몬 자극 검사의 재현성을 알아보고자 하였다.

방법: 2003년부터 2010년까지 아주대 병원 소아청소년과에 내원한 신장이 3 퍼센타일 미만이고, 골연령이 역연령보다 1세이상 지연되어 성장 호르몬 자극 검사를 시행한 187명의 환아를 대상으로 하였다.

결과: 총 187명의 환아 중 남아가 123명 (65%), 여아가 64명 (34.2%)

였다. 이 중 66명은 성장호르몬 결핍증으로 진단되었고 121명은 특발성 저신장증으로 진단되었다. 다변량 회귀 분석을 통하여 최대 성장호르몬 수치와 연관있는 인자를 알아보았을 때 체질량지수가 통계학적으로 유의학게 최대 성장호르몬 수치를 예측할 수 있는 인자였다. 체질량지수가 증가할수록 최대 성장호르몬 수치는 감소하는 것을 알 수 있었다.

결론: 최대 성장호르몬 수치는 체질량지수가 증가할수록 감소하였다. 저신장증 환아에서 성장 호르몬 자극 검사를 시행하고 결과를 평가할 때 체질량지수를 고려하여야 한다.

핵심어: 체질량지수, 성장호르몬, 저신장