

Original Article

Correlation between Serum IGF-1, IGFBP-3 Levels, and Hand-Wrist Radiographs in Determining Skeletal Maturity

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Abstract

The aim of this study was to assess the correlation between serum levels of insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and hand-wrist radiographs using a skeletal maturity indicator (SMI) and the middle phalanx of the third finger (MP3). Hand-wrist radiographs and blood samples from 205 patients aged 7 - 17 years were retrospectively analyzed by two dentists using the SMI stages, MP3 stages, and serum IGF-1 and IGFBP-3 levels. Serum IGF-1 levels were highest at the SMI 6 - 8 and MP3 - G stage and lowest at the SMI 1 - 3 and MP3 - F stage ($p < 0.0001$). Serum IGFBP-3 levels were highest at the SMI 9 - 10 and MP3 - I stage and lowest at the SMI 1 - 3 and MP3 - FG stage ($p = 0.010, 0.030$). As a result of Pearson correlation analysis, a relatively high correlation was found between skeletal maturity using the SMI and MP3 stages and serum IGF-1 levels ($r = 0.698, 0.622, p < 0.0001$). According to the results of this study, serum IGF-1 levels can be used as an auxiliary measure to evaluate the skeletal maturity of children and adolescents in dentistry. The range from the mean serum IGF-1 level of 472 $\mu\text{g/L}$ in SMI 6 stage to the mean IGF-1 level of 510.63 $\mu\text{g/L}$ in MP3 G stage could be considered as the peak height velocity in clinical practice. [J Korean Acad Pediatr Dent 2023;50(3):334-346]

Keywords

Insulin-like growth factor-1, Insulin-like growth factor binding protein-3, Hand-wrist radiographs, Skeletal maturity indicators

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Introduction

Assessing the skeletal maturity and remaining growth potential of a patient is crucial for planning orthodontic treatment and providing effective care. This is especially important for children and adolescents because adjusting their remain-

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ing growth can improve their facial profiles and affect treatment methods such as the types and duration of devices and the need for extractions[1-3].

Various indicators have been studied to evaluate growth and development, including chronological age, physical growth, dental maturity, sexual maturity, and skeletal maturity. However, due to individual variability, chronological age, physical growth, sexual maturity, and dental maturity are not suitable predictive tools for accurately assessing the peak growth spurt during puberty[4-6].

Owing to the limitations of other methods, the analysis of skeletal maturity using hand-wrist radiographs is mainly used to predict the peak growth spurt during puberty[7]. There are several methods for evaluating skeletal maturity using hand-wrist radiographs; however, the 11 - stages skeletal maturity indicator (SMI)[8] and the middle phalanx of the third finger (MP3) 5 stages[9] are widely used because of their relative simplicity.

Meanwhile, biochemical markers related to growth regulation, such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding protein (IGFBP-3), are being actively studied for their diagnostic utility in predicting bone maturity.

GH stimulates the production of IGF-1 in the liver, which promotes bone growth, and increased GH levels play an important role in the growth rate during puberty[10,11]. Since GH is secreted pulsatilely by the pituitary gland, a single measurement of GH level is not meaningful[12,13].

Serum IGF-1 and IGFBP-3 levels are good diagnostic indicators for determining GH status. Unlike GH, their levels remain stable throughout the day and have a longer half-life than GH. Serum IGF-1, which is produced in response to GH, is not secreted in significant amounts at birth, but gradually increases as humans grow. IGF-1 accelerates the growth, differentiation, and synthesis of the extracellular matrix in osteoblasts and chondrocytes[14,15].

Circulating serum IGF-1 binds to IGFBP-3, which is directly associated with cell membrane molecules, and plays an important role in regulating bone cell differen-

tiation. IGFBP-3 levels are regulated by GH and can serve as additional indicators of GH secretion[16,17].

To date, several studies comparing IGF-1 levels with lateral cephalograms or hand-wrist radiographs have been reported, but the sample sizes were small and the studies were conducted in different ethnic groups[18-20]. To date, no studies have been conducted on serum IGF-1 and IGFBP-3 with radiographic skeletal maturity in Korean children and adolescents. In particular, studies evaluating serum IGFBP-3 levels with skeletal maturity are limited[21] and there have been no comparative studies on the correlation between serum IGF-1 and IGFBP-3 levels and SMI and MP3 stages, to our knowledge.

The purpose of this study was to investigate the correlation between serum IGF-1, IGFBP-3, and hand-wrist radiographs using SMI and MP3 stages in the skeletal maturity assessment of children and adolescents and to evaluate the diagnostic usefulness of serum IGF-1 and IGFBP-3.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Ajou University Hospital (IRB File No.: AJOU-IRB-DB-2023-011) prior to the research.

1. Study subjects

This study included the patients (n = 744), aged 7 to 17, who visited both the Dentistry and Pediatrics departments of Ajou University Hospital from January 2018 to December 2022. Patients with medical problems were initially excluded. Also, patients with incomplete blood test results and those with poor quality of radiographs were excluded. Finally, 205 patients were included in this study (Fig. 1).

2. Study Design

Patients' sex, age, and medical history were investigated using their medical records. Radiographs of the hand and wrist were taken with a Shimadzu BR-120T (Shi-

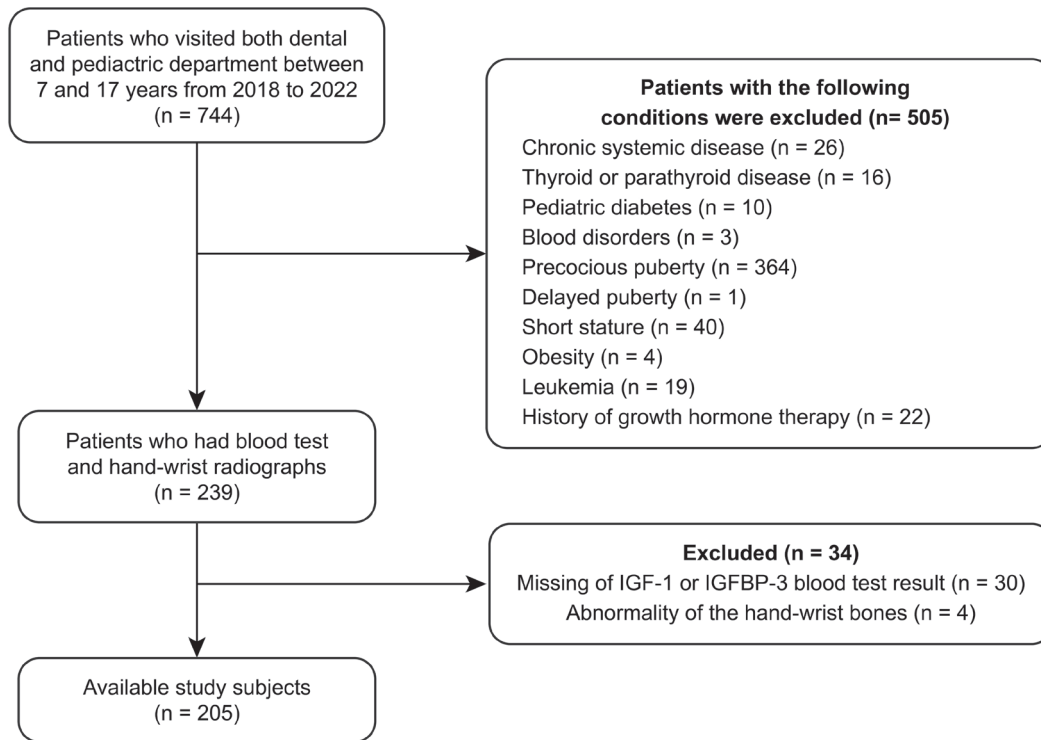


Fig. 1. Flow chart of study subjects selection. Among a total of 744 patients, 539 were excluded according to the exclusion criteria in the boxes on the right, and 205 were selected as study subjects.

madzu Corporation, Kyoto, Japan) using the following conditions: 42 kVP, 3 mA, scan time, 0.05 sec for patients under 10 years of age and 45 kVP, 3 mA, scan time, 0.05 sec for patients aged 10 years or older; the left hand was imaged. Images were interpreted using the Infinitt PACS (Infinitt Co., Seoul, Korea).

1) Assessment of the Hand-Wrist Bone

Two dentists independently evaluated all hand-wrist radiographs using the SMI stages proposed by Fishman[8] with an interval of two weeks between each interpretation. Based on the relative mandibular growth rate[8], the 11 stages of the SMI were divided into five groups. SMI stages 1 - 3 were categorized as Group I pre-puberty, stages 4 - 5 as Group II acceleration, stages 6 - 8 as Group III peak height velocity, stages 9 - 10 as Group IV deceleration, and stage 11 as Group V post-puberty.

2) Assessment of the middle phalanx of the third finger

Two dentists independently evaluated all hand-wrist

radiographs to assess the maturation stage of the MP3 using the MP3 5 stages (F, FG, G, H, and I) proposed by Hägg and Taranger[9] with an interval of two weeks between each interpretation.

3) Serum IGF-1 and IGFBP-3 Blood Tests

Blood samples were collected to measure the serum IGF-1 and IGFBP-3 levels on the day that hand-wrist radiographs were taken. The serum samples were separated by centrifugation and stored at 2 - 8°C until testing. Serum IGF-1 and IGFBP-3 concentrations were measured using an immunoradiometric assay kit (Beckman Coulter, Brea, CA, USA).

3. Statistical Analysis

Statistical significance was assessed using SPSS 28 (IBM SPSS Inc., Armonk, NY, USA) with a significance level of $p < 0.05$. The Cohen's kappa coefficients were calculated for the evaluation of the intra- and inter-examiner reli-

ability. The Mann-Whitney U test was used to compare chronological age according to sex. The Kolmogorov-Smirnov test was used to assess normality, and one-way analysis of variance (ANOVA) was performed to compare serum IGF-1 and IGFBP-3 levels between the SMI and MP3 stages. Post hoc analysis was conducted using the Bonferroni correction. The Jonckheere-Terpstra test was used to analyze the tendency of the mean level of serum IGF-1 and IGFBP-3 according to SMI and MP3 stages. To investigate the correlation between the SMI and MP3 stages and variables, Pearson correlation coefficients, Spearman correlation, and point-biserial correlation were calculated, and Stepwise multiple regression analysis was conducted.

Results

The Cohen's kappa coefficients for intra-examiner reliability regarding SMI and MP3 stages consistently showed values greater than 0.90. And to evaluate the agreement between the investigators for the SMI and MP3 stages, Cohen's kappa coefficients were calculated and found to be 0.825 and 0.848, respectively.

1. Chronological Age Distribution According to SMI and MP3 stages

Tables 1 and 2 show the distribution of chronological age according to sex in the SMI and MP3 stages. In SMI

Table 1. Chronological age distribution according to SMI group

SMI	Sex	Number	Chronological age (Mean \pm SD)	<i>p</i> value
Group I (1 - 3)	M	66	9.77 \pm 1.42	< 0.0001
	F	34	8.29 \pm 0.94	
Group II (4 - 5)	M	16	11.69 \pm 0.70	0.010
	F	16	11.06 \pm 0.57	
Group III (6 - 8)	M	13	13.23 \pm 0.93	< 0.0001
	F	16	12.25 \pm 0.86	
Group IV (9 - 10)	M	21	14.52 \pm 0.98	0.003
	F	11	13.45 \pm 0.63	
Group V (11)	M	7	16.29 \pm 0.95	0.343
	F	5	15.60 \pm 1.14	

p value from Mann-Whitney U test.

SMI: skeletal maturity indicators; M: male; F: female.

Table 2. Chronological age distribution according to MP3 stage

MP3	Sex	Number	Chronological age (Mean \pm SD)	<i>p</i> value
Stage F	M	51	10.35 \pm 1.43	< 0.0001
	F	21	8.71 \pm 1.10	
Stage FG	M	10	11.70 \pm 0.82	0.036
	F	11	10.55 \pm 1.21	
Stage G	M	5	12.20 \pm 1.10	0.088
	F	19	11.21 \pm 0.79	
Stage H	M	13	13.54 \pm 0.66	0.004
	F	9	12.33 \pm 0.75	
Stage I	M	13	14.77 \pm 1.01	0.171
	F	2	13.50 \pm 0.71	

p value from Mann-Whitney U test.

MP3: middle phalanx of the third finger; M: male; F: female.

groups, males showed a significantly higher chronological age than females at the same stages, except at stage 11. In MP3 stages, significant differences in chronological age between males and females were observed in stages F, FG, and H.

2. Mean Serum IGF-1 and IGFBP-3 Levels Compared Between Each SMI Group

The mean serum IGF-1 level was highest in the SMI 6 - 8 group at $502.24 \pm 160.17 \mu\text{g/L}$ and lowest in the SMI

1 - 3 group at $211.17 \pm 70.08 \mu\text{g/L}$ ($p < 0.0001$). The mean serum IGFBP-3 level was highest in the SMI 9 - 10 group at $2.77 \pm 0.70 \text{ mg/L}$ and lowest in the SMI 1 - 3 group at $2.33 \pm 0.48 \text{ mg/L}$ ($p = 0.010$, Table 3).

Post hoc analysis revealed significant differences in serum IGF-1 levels between all groups, except for the pairs of SMI 4 - 5 and SMI 11 stages ($p = 0.984$), and SMI 6 - 8 and SMI 9 - 10 stages ($p = 0.863$, Fig. 2). In contrast, there was a significant difference in mean serum IGFBP-3 levels only between the SMI 1 - 3 and SMI 9 - 10 stages ($p = 0.003$, Fig. 3).

Table 3. Mean serum IGF-1 and IGFBP-3 levels compared between each SMI group

SMI	Number	Serum IGF-1 ($\mu\text{g/L}$)			Serum IGFBP-3 (mg/L)		
		Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value
Group I (1 - 3)	100	211.17	70.08		2.33	0.48	
Group II (4 - 5)	32	360.38	126.86		2.47	0.62	
Group III (6 - 8)	29	502.24	160.17	< 0.0001	2.39	0.55	0.010
Group IV (9 - 10)	32	474.19	151.34		2.77	0.70	
Group V (11)	12	340.50	78.57		2.49	0.96	
Total	205	324.26	163.35		2.44	0.60	

p value from One-way ANOVA test.

IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3; SMI: skeletal maturity indicators.

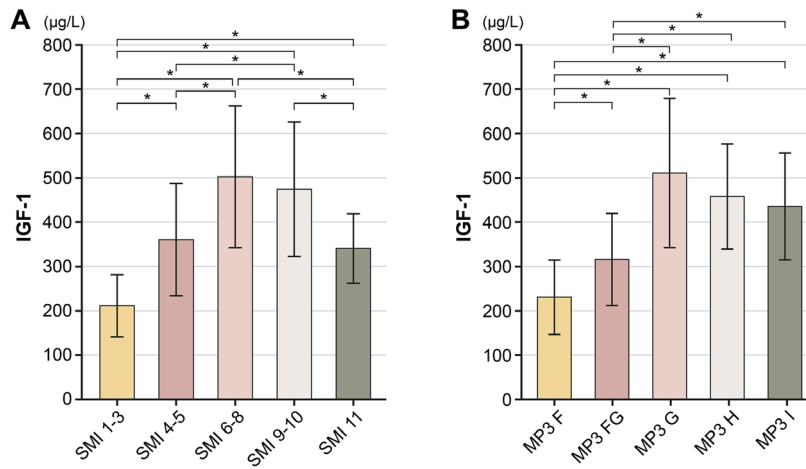


Fig. 2. Mean and Standard deviation of Serum IGF-1 levels according to SMI, MP3 stages. (A) Mean serum IGF-1 level had significant increasing trend as the SMI stages progressed to 6 - 8 ($p < 0.0001$). After reaching the peak, the Mean serum IGF-1 levels of SMI stages showed a decreasing trend ($p = 0.009$), (B) Mean serum IGF-1 levels of MP3 stages had a significant increasing trend as they progressed to stage G ($p < 0.0001$) and decreased after stage G, but they did not have a significant trend ($p = 0.134$). *p* values from Jonckheere-Terpstra test and * letters indicate pairs that showed significant differences in the post hoc analysis of One-way ANOVA test. SMI: skeletal maturational indicator; MP3: middle phalanx of the third finger; IGF-1: insulin-like growth factor-1.

3. Mean Serum IGF-1 and IGFBP-3 Levels Compared Between Each MP3 Stage

The serum IGF-1 level was highest in stage G at $510.63 \pm 168.37 \mu\text{g/L}$ and lowest in stage F at $230.51 \pm 83.80 \mu\text{g/L}$ ($p < 0.0001$). The serum IGFBP-3 level was highest in stage I at $2.86 \pm 0.81 \text{ mg/L}$ and lowest in stages FG at $2.34 \pm 0.59 \text{ mg/L}$ ($p = 0.030$, Table 4).

Post hoc analysis revealed significant differences in serum IGF-1 levels between all groups, except for the MP3 G - H ($p = 1.0$), G - I ($p = 0.427$) and H - I ($p = 1.0$) stage

pairs (Fig. 2). In contrast, there was a significant difference in the mean serum IGFBP-3 levels only between the MP3 - F and I stages ($p = 0.02$, Fig. 3).

4. Trend Test of Mean Serum IGF-1 and IGFBP-3 Levels According to SMI and MP3 Stage

Regarding the mean level of serum IGF-1, there was a statistically significant increasing trend as the SMI stages progressed to stage 6 - 8 and the MP3 stages progressed to G ($p < 0.001$). A decreasing trend was observed as the

Table 4. Mean serum IGF-1 and IGFBP-3 levels compared with each MP3 stage

MP3	Number	Serum IGF-1 ($\mu\text{g/L}$)		<i>p</i> value	Serum IGFBP-3 (mg/L)		
		Mean	SD		Mean	SD	<i>p</i> value
Stage F	72	230.51	83.80		2.37	0.48	
Stage FG	21	315.62	103.95		2.34	0.59	
Stage G	24	510.63	168.37	<0.0001	2.53	0.62	0.030
Stage H	22	457.77	118.60		2.47	0.49	
Stage I	15	435.33	120.75		2.86	0.81	
Total	154	338.19	159.28		2.46	0.57	

p value from One-way ANOVA test.

IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3; MP3: middle phalanx of the third finger.

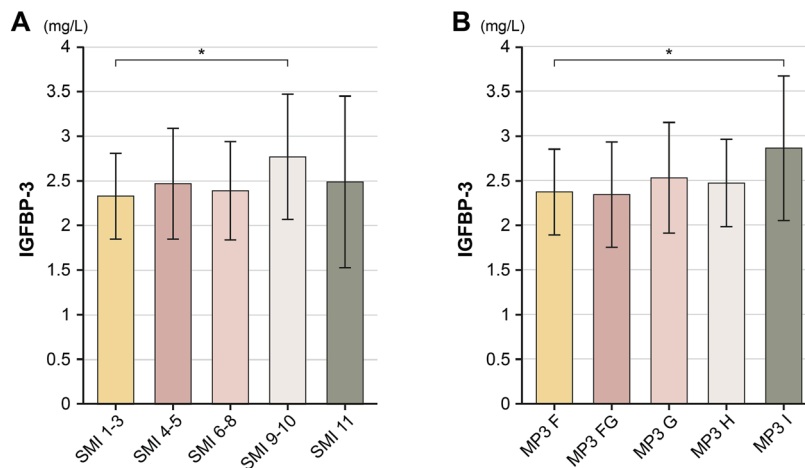


Fig. 3. Mean and Standard deviation of Serum IGFBP-3 levels according to SMI, MP3 stages. (A) Mean serum IGFBP-3 level was highest at the SMI 9 - 10 and lowest at the SMI 1 - 3. There was no significant trend from Jonckheere-Terpstra test, (B) Mean serum IGFBP-3 level was highest at the MP3 I stages and lowest at the MP3 FG stage. There was no significant trend from Jonckheere-Terpstra test and * letters indicate pairs that showed significant differences in the Bonferroni post hoc analysis of One-way ANOVA test. SMI: skeletal maturational indicator; MP3: middle phalanx of the third finger; IGFBP-3: insulin-like growth factor binding protein-3.

SMI stage advanced to stage 11 ($p = 0.009$, Fig. 2).

On the contrary, for the mean level of serum IGFBP-3, SMI stages 9 - 10 and MP3 stage I showed the highest levels, but it was challenging to find a significant trend using both radiographic analysis methods (Fig. 3).

5. Correlation between SMI, MP3 stages and Age, Sex, Serum IGF-1, IGFBP-3

There was a relatively strong positive correlation between chronological age and the SMI stage as well as between chronological age and the MP3 stage ($r = 0.842$ in SMI stage and $r = 0.741$ in MP3 stage, $p < 0.0001$). Conversely, there was no significant correlation between sex and both SMI and MP3 stages.

The correlation coefficient between the SMI and MP3 stages was 0.917 ($p < 0.001$), indicating a strong correlation. Although the SMI stage showed a slightly higher correlation coefficient than the MP3 stage with serum IGF-1 levels, both methods showed a relatively high correlation with serum IGF-1 levels ($r = 0.698$ in SMI stage

and $r = 0.622$ in MP3 stage, $p < 0.0001$). Serum IGFBP-3 levels showed a weak correlation with the SMI and MP3 stages ($r = 0.186$ in SMI stage, $p = 0.008$ and $r = 0.218$ with MP3 stage, $p = 0.007$, Table 5).

Based on this, stepwise multiple regression analysis was conducted to predict the SMI and MP3 stages (Table 6, 7). In this model, age and IGF-1 level were found to have significant associations with SMI and MP3 stages ($p < 0.0001$). The age showed the highest associations with SMI and MP3 stages and the older the age, the higher the stages ($\beta = 0.749$ in SMI model and $\beta = 0.599$ in MP3 model). Serum IGF-1 had a relatively lower impact compared to age, and its influence was greater in the MP3 stage compared to the SMI stage ($\beta = 0.19$ in SMI model and $\beta = 0.29$ in MP3 model). Serum IGFBP-3 did not show a significant association in either of the two models ($p = 0.927$ in SMI model and $p = 0.128$ in MP3 model). The adjusted R-squared value for the SMI prediction model was 0.752, indicating an explanatory power of 75.2%. The MP3 prediction model had an adjusted R-squared value of 0.648, indicating an explanatory power of 64.8%.

Table 5. Correlation coefficients between SMI, MP3 stages and variables

	SMI		MP3	
	coefficient (r)	p value	coefficient (r)	p value
Age ^a	0.842	< 0.0001	0.741	< 0.0001
Sex ^b	0.079	0.262	0.104	0.199
IGF-1 ^c	0.698	< 0.0001	0.622	< 0.0001
IGFBP-3 ^c	0.186	0.008	0.218	0.007

^a: Spearman correlation; ^b: Point-biserial correlation; ^c: Pearson correlation coefficient (2-tailed).

SMI: skeletal maturity indicators; MP3: middle phalanx of the third finger; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein.

Table 6. Stepwise multiple regression analysis of SMI Group

Variables	B	Standard error	β	t value	p value	adj. R^2
(constant)	-2.825	0.27		-10.458	< 0.0001	
Age	0.403	0.023	0.749	17.676	< 0.0001	0.752
IGF-1	0.002	0.001	0.190	4.410	< 0.0001	
IGFBP-3	-0.007	0.081	-0.003	-0.092	0.927	

Stepwise multiple regression analysis.

SMI: skeletal maturity indicators.

B: unstandardized regression coefficients; β : standardized regression coefficients; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3.

Table 7. Stepwise multiple regression analysis of MP3 stage

Variables	B	Standard error	β	t value	p value	adj.R ²
(constant)	-3.78	0.464		-8.143	< 0.0001	
Age	0.421	0.04	0.599	10.582	< 0.0001	0.648
IGF-1	0.003	0.001	0.290	5.072	< 0.0001	
IGFBP-3	0.187	0.122	0.075	1.529	0.128	

Stepwise multiple regression analysis.

MP3: middle phalanx of the third finger.

B: unstandardized regression coefficients; β : standardized regression coefficients; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3.

Discussion

Accurate assessment of individual growth and development is essential for selecting the appropriate treatment timing and establishing long-term treatment plans for growing patients[22,23].

Several studies have reported on the stage of peak height velocity in SMI and MP3 classification. Hägg and Taranger[9] considered SMI stage 6 as the maximum growth period and according to studies on Koreans, Kim et al.[24] reported that males are most commonly found in SMI stages 5 - 7 and females in stages 6 - 7, whereas Lee and Mah[25] reported that males are found in SMI stages 4 - 5 and the MP3 FG - G stage and females in SMI stages 3 - 4 and the MP3 F - FG stage. To improve the accuracy of growth prediction, it is recommended that additional morphological, biological, and genetic indicators be evaluated[26,27].

Serum IGF-1 and IGFBP-3, which are stable indicators of GH status, are used as one of the indicators[28-30]. Loche et al.[14] reported a correlation between increased serum IGF-1 levels and the pubertal growth spurt. Juul et al.[31] reported that the serum IGFBP-3 levels increase in children and reach a peak during puberty; however, the correlation between serum IGFBP-3 and skeletal maturity remains controversial.

According to this study, the chronological age of females consistently appeared to be younger than that of males, with a mean difference of 0.97 in SMI group and 1.25 years in MP3 stages. This is consistent with previous studies showing that females exhibit faster skeletal

maturity than males[8,25,26,32]. The chronological age range corresponding to stage G was found to be positioned between the SMI 4 - 5 and SMI 6 - 8 groups.

Masoud et al.[19] reported that the highest serum IGF-1 level was 359.06 ± 112.5 $\mu\text{g/L}$ at SMI 6 - 8 and the lowest was 185.5 ± 59.9 $\mu\text{g/L}$ at SMI 1 - 3 stages. In a study by Phogat et al.[18], the highest concentration was 328.43 $\mu\text{g/L}$ at SMI stages 7 - 8 and the lowest was 172 $\mu\text{g/L}$ at SMI stages 1 - 2. Consistent with previous studies, in this study, the mean serum IGF-1 level among the SMI groups showed a statistically significant difference with the highest levels observed at SMI stages 6 - 8 and the lowest at SMI stages 1 - 3.

Muddaiah et al.[33] reported that serum IGF-1 level was highest at MP3 G stage with 359.06 $\mu\text{g/L}$ values and lowest at F stage with 184 $\mu\text{g/L}$. Gupta et al.[20] reported that the serum IGF-1 levels showed a gradual increase from the MP3 - F stage to the highest concentration at the MP3 - G stage, up to 397 $\mu\text{g/L}$, and then decreased at the MP3 - H and I stages to 263 $\mu\text{g/L}$, which is consistent with the results of this study.

While the previous studies and the present study align in terms of the stage and trend where the maximum value of serum IGF-1 occurs, there were differences in the measured mean levels of serum IGF-1. The differences in concentration may be attributed to the limited sample size in previous studies and racial differences among the study subjects, as well as variations in the criteria for selecting the study population. Furthermore, there is a possibility that the differences in blood testing methods could also contribute to variations in the results.

Song et al.[34] reported that in normal Korean children and adolescents, the highest serum IGF-1 levels were observed in males aged 15 - 16 years, with a maximum of 556 µg/L, and in females aged 13 - 14 years, with 554 µg/L. In this study, the SMI 6 - 8 stage showed mean serum IGF-1 levels of 502.24 µg/L and 510.63 µg/L in MP3 stage. Both studies showed maximum values above 500, but in this study, the mean level of IGF-1 reached its peak at an earlier age compared to previous research. These results suggest that improved nutrition intake has led to an accelerated growth rate in children and adolescents, resulting in an earlier onset of puberty than in the past[25].

Jain et al.[21] reported that IGFBP-3 levels could be a potential biochemical indicator for evaluating skeletal maturity. However, it was challenging to find a clear trend in serum IGFBP-3 based on SMI and MP3 stages in this study and significant results were not found in either the SMI or MP3 stages, with concentration differences between stages ranging from 0.02 mg/L to 0.43 mg/L. This could be attributed to racial or study subjects differences[35]. For serum IGFBP-3, it has been reported that the values could vary depending on the testing method or kit used, which could also be another contributing factor [36].

Unlike serum IGFBP-3, the significant trend between SMI stages 6 - 8 and SMI stage 11 suggests that as growth progresses during puberty peak growth, the serum IGF-1 levels decrease. However, there was no significant trend between the MP3 stage G and the stages H and I. Patients who transitioned from MP3 I stage to show changes in the radius, represented by R - I, R - IJ, and R - J stages, were excluded from the MP3 stage patients group in order to solely examine the relationship between changes in the middle phalanx of the third finger and the concentrations of serum IGF-1 and IGFBP-3. As a result, the decrease in serum IGF-1 concentration was relatively minor compared to SMI group, which is why it is suggested that it did not exhibit a significant decreasing trend and had differences compared to previous studies[20,33].

The final stage of skeletal maturity on a hand-wrist radiograph does not necessarily indicate the completion of growth. Mandibular growth continues, even

after the completion of skeletal maturity on the radiographs[37,38]. In this study, the pattern of serum IGF-1 levels showed a gradual decrease after peaking in SMI 6 - 8 stages, but the mean serum IGF-1 level in SMI 11 stage was significantly higher than that in SMI 1 - 3 stages. The reported Mean serum IGF-1 level of healthy adults aged 20 and above in South Korea is 184.6 ± 86.3 µg/L for males and 178.6 ± 91.8 µg/L for females[39]. These values were lower than the measurements observed in the SMI stages 1-3 of this study. Based on the IGF-1 levels, it may be difficult to determine complete growth on radiographs, even at SMI stage 11. Therefore, IGF-1 levels could be considered an auxiliary tool for predicting residual growth, even after fusion has been completed on radiographs.

The correlation coefficients between the SMI and MP3 and the IGFBP-3 levels were low at 0.186 and 0.218, respectively. Thus, determining skeletal maturity solely based on serum IGFBP-3 levels may be difficult. In contrast, the SMI and MP3 stages showed relatively strong positive correlations with serum IGF-1 levels ($r = 0.698$ in SMI stage and $r = 0.622$ in MP3 stage).

The multiple regression models derived from this study allow for an estimation of SMI and MP3 stages based on Age and serum IGF-1 level. However, due to the relatively greater influence of Age, it is suggested to consider the patient's age when using serum IGF-1 level as an additional tool for evaluating skeletal maturity. If the results of this study are applied clinically, it may be possible to partially replace periodic hand-wrist radiographs to determine the timing of orthodontic treatment in children and adolescents by gauging the peak growth period through changes in serum IGF-1 concentrations. Additionally, when predicting the residual bone growth after SMI stage 11, IGF-1 concentration can be utilized as an adjunctive tool.

This study had some limitations. Due to its retrospective nature, the sample size for each skeletal maturity stage was inconsistent and limited. The study participants were selected based on those who had undergone both hand-wrist radiography and blood tests on the same day, mostly for orthodontic or growth evaluation pur-

poses, which may have introduced a selection bias. Despite selecting healthy children and adolescents with no growth issues based on medical records and blood tests, it was difficult to completely exclude children with undiagnosed precocious puberty or delayed growth, which may have led to bias.

The results of this study may not represent the average values of serum IGF-1 and IGFBP-3 in Korean children and adolescents. Therefore, further nationwide sampling of serum IGF-1 and IGFBP-3 levels is needed for subsequent studies on the average values and their correlation with skeletal maturity in this cohort.

Recently, there has been an increasing interest in biomarkers, and studies analyzing skeletal maturity using salivary IGF-1 and IGFBP-3 have also been reported. As it is less invasive than blood tests and can be easily collected in dental clinics, sufficient research on the diagnostic usefulness of salivary IGF-1 and IGFBP-3 is needed[16,40].

Conclusion

Serum IGF-1 and IGFBP-3 levels correlated with skeletal maturity, as assessed by hand-wrist radiographs. Serum IGF-1 levels showed the lowest concentrations in the SMI 1 - 3 and MP3 - F groups, and the highest concentrations in the SMI 6 - 8 and MP3 - G groups gradually decreased as skeletal maturity progressed. The range from the mean serum IGF-1 level of 472 µg/L in SMI 6 stage to the mean IGF-1 level of 510.63 µg/L in MP3 - G stage could be considered as the peak height velocity in clinical practice. Measuring serum IGF-1 levels could reduce radiation exposure from periodic hand-wrist radiographs and assist in predicting the peak growth spurt and residual growth potential of the bone.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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골 성숙도 결정 시 혈청 IGF-1, IGFBP-3 농도와 수완부 방사선 사진의 상관관계

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이 연구의 목적은 Skeletal maturity indicator (SMI) 및 Middle phalanx of the third finger (MP3)와 혈청 Insulin-like growth factor-1 (IGF-1) 및 Insulin-like growth factor binding protein-3 (IGFBP-3)의 상관 관계를 통해 골격적 성숙도의 예측 지표로 사용될 수 있는지 알아보는 것이다. 2018년 1월부터 2022년 12월까지 아주대학교 치과병원 및 소아청소년과에 내원한 만 7세 이상 17세 이하 환자 205명의 의무기록을 후향적으로 분석하였다. 혈청 IGF-1 농도는 SMI 6 - 8, MP3 - G에서 가장 높았고($p < 0.0001$) 혈청 IGFBP-3 농도는 SMI 9 - 10, MP3 - I에서 가장 높았다($p = 0.010, 0.030$). SMI, MP3와 혈청 IGF-1 농도 간 비교적 높은 Pearson 상관계수를 나타냈다($r = 0.698, 0.622, p < 0.0001$). 혈청 IGF-1는 소아청소년의 골격적 성숙도를 평가하는 보조적 수단으로 활용될 수 있을 것이며 임상적으로는 472 $\mu\text{g/L}$ 에서 510.63 $\mu\text{g/L}$ 의 범위를 최대성장기로 고려할 수 있다. [J Korean Acad Pediatr Dent 2023;50(3):334-346]

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