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Correlation of Serum Insulin-Like Growth Factor-1 and Hand Wrist Radiographs as Skeletal Maturity Indicators: An ex-vivo Study

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Abstract

Introduction: Conventional Hand and Wrist radiographs, have certain drawbacks of exposing orthodontic patients to unnecessary radiation hazards and subjectivity to errors. Serum insulin-like growth factor 1 (IGF-1) levels have been reported to increase until the pubertal peak in literature. The present study aims to assess the relationship between serum IGF-1 and skeletal maturity indicators Materials and Methods: Lateral cephalograms of 60 patients were assigned SMI stage according to Fishman's classification system. The serum IGF-1 levels of the patients were also evaluated. Correlation between the serum IGF-1 levels, age of the patient, and their SMI stage was analyzed. Results: Pearson's coefficient of correlation revealed a non-significant weak positive correlation (p=0.69; >0.05) between age and IGF-1 levels, and a non-significant weak negative correlation (p =0.52; >0.05) between SMI stages and IGF-1 levels. Results of the ANOVA test indicated that there was no significant difference between mean IGF-1 levels across the different age groups and eleven SMI groups. However, there was a significant difference noted in the mean IGF-1 levels and the restructured SMI categories and groups. Conclusion: The moderate correlation between age and serum IGF-1 fluctuations during puberty underscores the hormone's pivotal role in adolescent growth. This positions serum IGF-1 as a potentially specific and reliable marker for assessing mandibular growth modifications, offering a radiation-free alternative to conventional radiographic methods.

Keywords: *Cephalometry, Skeletal Maturity Assessment; Orthodontics; Pubertal Growth Spurt*

1. Introduction

Pubertal growth spurt plays a critical role in orthodontics, and its accurate assessment is essential for the successful implementation of orthodontic treatment plans. Determining the precise timing of pubertal growth spurt is a crucial aspect of orthodontic treatment planning, as it directly impacts the success of growth modification procedures.[1] Over the years, these methods have transitioned from relying on chronological age, physiological maturity indicators, and sexual maturity indicators to adopting more dependable skeletal maturity indicators (SMI).[2] Nevertheless, concerns regarding radiation exposure and the potential for errors have prompted a quest for innovative and radiation-free alternatives. Traditionally, both the medical and dental fields have relied on ossification events in the Hand and Wrist to estimate pubertal stages, considering it a reliable method.[3] However, the conventional approach, involving Hand and Wrist radiographs, poses the significant drawback of exposing orthodontic patients to unnecessary radiation hazards.[4] In addition to this radiation concern, the method may be susceptible to methodological and interpretation errors, highlighting the need for alternative, safer, and more accurate techniques for evaluating pubertal growth.[4,5] In light of the limitations associated with skeletal maturity indicators, this research explores a novel and non-invasive approach to understanding pubertal growth spurt dynamics. Insulin-like growth factor-1 (IGF-1) is a mediator for growth hormone that plays an essential role in both local and systemic regulation of prenatal and postnatal longitudinal bone growth. The existing body of literature has

indicated a distinct association between serum IGF-1 levels and puberty.[6] Specifically, serum IGF-1 levels tend to increase until the pubertal peak and subsequently decline. This intriguing correlation has led us to explore whether serum IGF-1 levels can serve as a reliable, non-invasive, and patient-friendly proxy for assessing the timing of pubertal growth spurt in orthodontic patients. This study, therefore, seeks to bridge the gap between traditional skeletal maturity indicators and a more radiation-free and potentially precise method for evaluating pubertal growth. By investigating the correlation between serum IGF-1 levels and skeletal maturational events, we aim to contribute to the ongoing efforts to enhance orthodontic treatment planning and minimize unnecessary radiation exposure in dental practice. The primary objective was to assess the relationship between serum IGF-1 and skeletal maturity indicators, as well as to establish a reference range for serum IGF-1 values during the pre-puberty, puberty, and post-puberty stages.

2. Materials And Methods

The present ex-vivo study comprised 60 patients visiting the institutional Department of Orthodontics and Dentofacial Orthopedics. Only clinically healthy patients within the age range of 8 to 22 years were included after duly obtaining their informed consent. Individuals with a history of blood dyscrasias or bone disorders were excluded from the study. The study protocol was approved by the institutional ethical review board. Hand-wrist radiographs of the subjects were obtained and assessed by a single operator using the 11-stage Skeletal Maturity Assessment (SMA) system developed by Fishman.[7] By strictly adhering to aseptic precautions, 2 ml of venous blood was drawn by disposable syringes and collected in plain tubes. It was ensured that the blood collection was performed between 8:00 AM and 3:00 PM on the same day of radiography. The collected tubes were promptly placed in dry ice and transported to a cold storage facility within 4 hours of collection. The serum was separated from the blood, and deep refrigeration at temperatures ranging from -2 to -40 degrees Celsius was maintained. The entire collection process was completed within 7 days, and samples were transferred to the laboratory in dry ice for subsequent analysis of IGF-1 levels.

The analysis was performed using 25 µL of the pretreated serum sample (1- in 10 dilution with IGF-1 pretreatment solution by means of chemiluminescent immunometric assay (Immulite 1000 system). To assess the relationship between serum IGF-1 levels and Skeletal Maturity Indicators (SMI), the study categorized the subjects into eleven groups, each corresponding to one of the eleven SMI stages. For the purpose of comparison of values found in this study with the other study, the 11 SMIs were restructured into 6 groups according to the growth percentage method given by Fishman (1982) as follows – Prepubertal (SMI 1,2); Prepubertal acceleration (SMI 3,4); Peak mandibular velocity (SMI 5,6), Post peak mandibular velocity (SMI 7,8), Deceleration (SMI 9,10) and Post pubertal (SMI 11).[8] The SMI groups were also restructured into three categories according to Fishman's classification - Prepubertal Group (SMI 1, 2, 3, 4), Pubertal Group (SMI 5, 6, 7) and Post-Pubertal Group (SMI 8, 9, 10, 11).[9] Descriptive statistics were employed to calculate the mean IGF-1 levels for each age group and the different SMI categories. To assess whether there were statistically significant differences in mean serum IGF-1 levels across different age groups and SMI categories, ANOVA test was conducted.

3. Results and Discussion

The mean IGF-1 levels across subjects of different age are depicted in Figure 1 and those among different SMI groups (Fishman’s classification) are depicted in Figure 2. Pearson's coefficient of correlation revealed a non-significant weak positive correlation ($p=0.69$; >0.05) between age and IGF-1 levels, and a non-significant weak negative correlation ($p =0.52$; >0.05) between SMI stages and IGF-1 levels. Results of the ANOVA test indicated that there was no significant difference between mean IGF-1 levels across the different age groups and eleven SMI groups. However, there was a significant difference noted in the mean IGF-1 levels and the restructured SMI categories and groups.

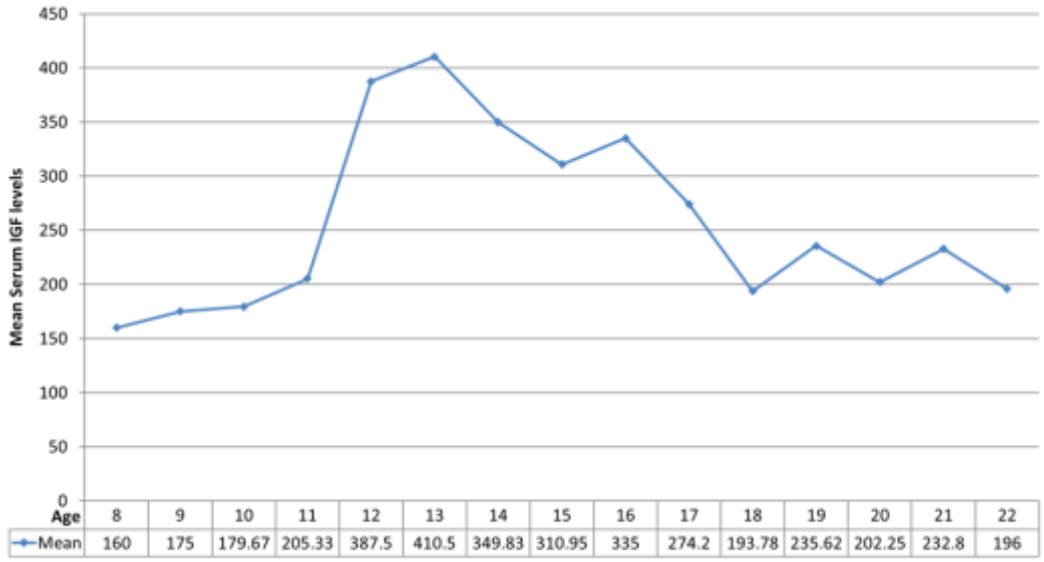

Figure 1: Mean Serum SMI levels corresponding to the age of the subjects

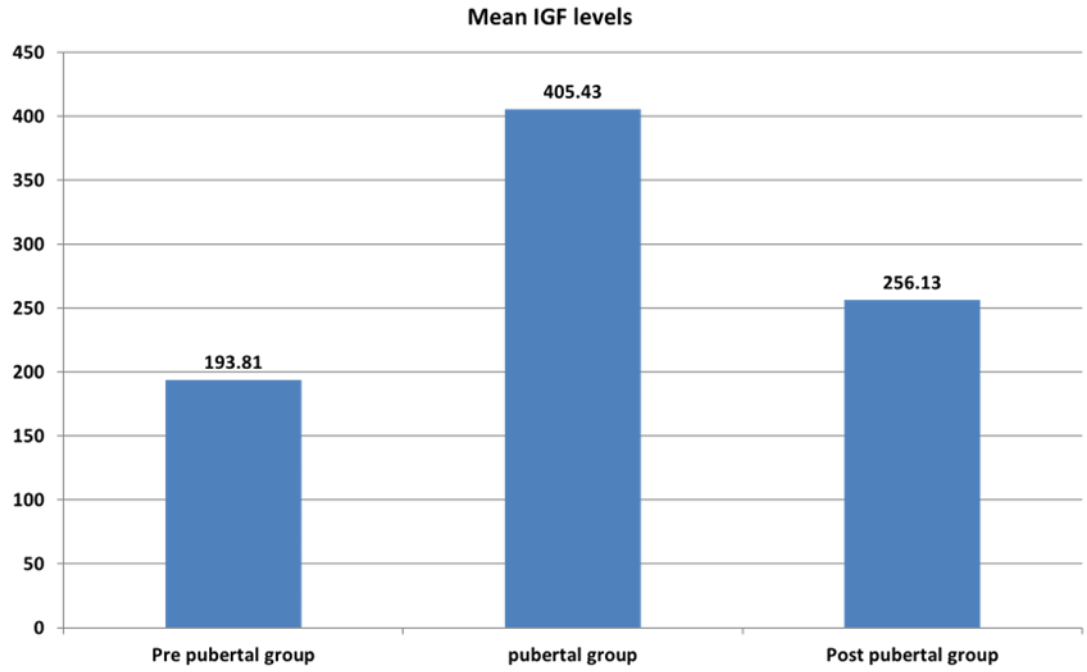

Figure 2: Mean Serum IGF-1 levels corresponding to the SMI groups (Fishman classification)

Table 1: ANOVA test between mean serum IGF-1 levels of different groups based on various parameters

ANOVA test between mean serum IGF-1 levels of different groups						
Parameters		Sum of Squares	Df	Mean Square	F	p-value
Age	Between Age Groups	267402.608	12	22283.551	1.426	.190
	Within Age Groups	703249.197	45	15627.760		
Different SMI Categories (1 to 11)	Between Groups	236239.996	8	29530.000	2.023	.063
	Within Groups	729718.712	50	14594.374		
Restructured SMI categories (Fishman Classification)	Between Groups	201164.214	2	100582.107	7.309	.001
	Within Groups	784418.476	57	13761.728		

Re-structured SMI categories (Growth percentage method) Groups 1 to 6	Between Groups	230152.144	5	46030.429	3.290	.012
	Within Groups	755430.545	54	13989.455		

LSD multiple comparisons test for different SMI categories (Fishman classification) indicated that there was a statistically significant difference between the mean serum IGF-1 levels of pre-pubertal and pubertal groups, and pubertal and post-pubertal groups. However, no significant difference was found between the serum IGF-1 levels of pre-pubertal and post-pubertal groups. The results of LSD multiple comparison test for the six re-structured SMI categories (Growth percentage method) are shown in Table 2.

Table 2

(I) Fishman groups	(J) Fishman groups	Mean Difference (I-J)	Std. Error	p-value	Interpretation
1	2	-37.95000	68.28727	.581	Non-Significant
	3	-239.56667*	71.62030	.002	Significant
	4	-213.83333*	83.63449	.013	Significant
	5	-86.40196	56.16480	.130	Non-Significant
	6	-71.27536	54.22004	.194	Non-Significant
2	1	37.95000	68.28727	.581	Non-Significant
	3	-201.61667*	71.62030	.007	Significant
	4	-175.88333*	83.63449	.040	Significant
	5	-48.45196	56.16480	.392	Non-Significant
	6	-33.32536	54.22004	.541	Non-Significant
3	1	239.56667*	71.62030	.002	Significant
	2	201.61667*	71.62030	.007	Significant
	4	25.73333	86.37733	.767	Non-Significant
	5	153.16471*	60.17308	.014	Significant
	6	168.29130*	58.36204	.006	Significant
4	1	213.83333*	83.63449	.013	Significant
	2	175.88333*	83.63449	.040	Significant
	3	-25.73333	86.37733	.767	Non-Significant
	5	127.43137	74.06795	.091	Non-Significant
	6	142.55797	72.60433	.055	Non-Significant
5	1	86.40196	56.16480	.130	Non-Significant
	2	48.45196	56.16480	.392	Non-Significant
	3	-153.16471*	60.17308	.014	Significant
	4	-127.43137	74.06795	.091	Non-Significant
	6	15.12660	37.83049	.691	Non-Significant
6	1	71.27536	54.22004	.194	Non-Significant
	2	33.32536	54.22004	.541	Non-Significant
	3	-168.29130*	58.36204	.006	Significant
	4	-142.55797	72.60433	.055	Non-Significant
	5	-15.12660	37.83049	.691	Non-Significant

Conventional methods of assessing pubertal spurt have included skeletal maturity indicators like ossification events occurring in the hand and wrist and the morphology of cervical vertebrae.[2,3] Due to the additional radiation exposure associated with a hand-wrist radiograph and the lack of reliability of the cervical vertebrae maturation method, a need for a better maturity indicator was sensed.[10] Of the many methods of staging hand and wrist radiographs, the 11-staged skeletal maturity assessment system suggested by Fishman was chosen since it has more maturational stages as compared to CVM.[7,12] It is validated by a good number of longitudinal and cross-sectional studies. Its correlation with stature height and craniofacial growth velocities has been established. More importantly, the staging of this method is based on growth percentage and growth velocity. Studies have shown such methods to be more reliable than other methods available for staging hand-wrist radiographs.[12] The present ex-vivo study sought to investigate the relationship between serum IGF-1 levels and SMI in a cohort of 60 patients aged 8 to 22 years. The study aimed to shed light on the potential associations between IGF-1 levels and the various stages of skeletal development, as well as age groups, which

could have implications for orthodontic and dentofacial orthopedic treatment planning. Therefore, the inclusion of clinically healthy patients within the age range of 8 to 22 years is essential because this encompasses the period of active growth and skeletal development. The age range for inclusion was determined to ensure that subjects represented the beginning, peak, or end of the puberty stage. The exclusion of individuals with blood dyscrasias or bone disorders is logical as these conditions could confound the relationship between IGF-1 levels and skeletal maturity. Drawing blood from the venous system is a standard method for obtaining serum samples for hormone analysis. The choice of the vein is arbitrary and does not significantly impact the results. Collecting blood between the specified time is essential because IGF-1 levels exhibit diurnal variation, with peak levels in the morning.[13] Maintaining aseptic precautions, transporting samples in dry ice, and deep refrigeration are necessary steps to prevent sample contamination and degradation, and ensure the accuracy of IGF-1 measurements. The descriptive statistics revealed that the mean IGF-1 levels across different age groups and the eleven SMI categories did not display any significant trends. This was supported by Pearson's correlation analysis, which showed non-significant weak positive correlations between age and IGF-1 levels and non-significant weak negative correlations between SMI stages and IGF-1 levels. These findings suggest that age and the specific stage of skeletal maturity may not have a substantial impact on IGF-1 levels. The lack of significant differences in mean IGF-1 levels across age groups and SMI categories underscores that IGF-1 levels are subject to substantial individual variation.[14] It highlights the importance of considering multiple factors, including age and skeletal maturity, when assessing IGF-1 levels in orthodontic and dentofacial orthopedic contexts. For instance, IGF-1 levels may not correlate significantly with age because IGF-1 production is influenced by various factors, including genetics, nutrition, and hormonal regulation. Age alone may not capture the complexity of these influences.[15]

One notable aspect of this study was the restructuring of SMI categories based on both Fishman's classification and the growth percentage method. The restructured SMI categories according to Fishman's classification led to the identification of significant differences in mean IGF-1 levels. Specifically, there was a significant difference in IGF-1 levels between prepubertal, pubertal, and post-pubertal groups. In corroboration without results, other studies have also found an association between serum IGF-1 levels and pubertal development. Studies have shown a remarkable rise in serum IGF-1 levels at pubertal peak as compared to prepubertal and adult values.[6,16] These findings suggest that the classification of SMI stages according to Fishman's method provides a more relevant framework for assessing the relationship between IGF-1 levels and skeletal maturity, as it identifies significant distinctions between key developmental stages. Racial variation has been seen in the serum IGF-1 levels in studies conducted in various parts of the world.[17,18] The findings of the present study notably revealed a strong link between serum IGF-1 levels and skeletal maturity, particularly in the context of mandibular growth velocity. According to the study by Fishman L (1982), the SMI 6 stage corresponds to a stage that has passed a peak in stature height.[8] Furthermore, SMI 6 and 7 are stages during which maximum mandibular growth velocity occurs. It is thus seen that the peak in serum IGF-1 levels is more closely related to the peak in mandibular growth rather than the peak in stature growth. Also, studies have also shown greater sensitivity of serum IGF-1 to the growth of condylar cartilage.[19] Findings of the present study supported by the abovementioned facts make serum IGF-1 indicator a more specific indicator of mandibular growth rather than other skeletal maturity indicators which are better indicators of overall skeletal growth rather than craniofacial growth.

In the present study, the restructured SMI categories using the growth percentage method revealed significant differences in mean IGF-1 levels between groups. This reinforces the notion that IGF-1 levels may vary with the progression of skeletal development and can be more accurately assessed when the stages are consolidated into fewer, more meaningful categories. This implies that the categorization of SMI stages is more clinically relevant and captures critical phases of growth, emphasizing the importance of precise staging. It is important to acknowledge some limitations of this study. The sample size was relatively small, and the study was conducted ex-vivo, which may not fully represent in-vivo conditions. Additionally, other factors that could affect IGF-1 levels, such as nutritional status and hormonal changes, were not explored in this study.[14,15] Future research could benefit from larger sample sizes and longitudinal designs to further investigate the relationship between IGF-1 levels and skeletal maturity. Furthermore, examining the influence of nutritional factors and hormonal changes on IGF-1 levels in a clinical setting may provide a more comprehensive understanding of this relationship. Nevertheless, it can be inferred from the results of this study that serum IGF-1 shows a rather consistent rise in accordance with skeletal maturation, till the pubertal peak followed by which there is a gradual fall in the levels of serum IGF-1 levels. If extensively used

this method can actually be economical in the long run as only the cost of initial laboratory setting is more. This method has shown a remarkable correlation with the skeletal maturity indicators found on hand and wrist radiographs and thus can be used as an alternative to these conventional methods.

4. Conclusion

In conclusion, this study unveils a nuanced connection between serum IGF-1 levels and the timing of the pubertal growth spurt, offering valuable insights for orthodontics. The moderate correlation between age and serum IGF-1 fluctuations during puberty underscores the hormone's pivotal role in adolescent growth. This positions serum IGF-1 as a potentially specific and reliable marker for assessing mandibular growth modifications, offering a radiation-free alternative to conventional radiographic methods. While promising, further exploration of its clinical applicability following evidence-based dentistry principles is needed. The potential for longitudinal studies to validate these findings and examine sex hormone influences on serum IGF-1 levels opens avenues for future research. This research emphasizes the demand for safer and more precise tools in orthodontics, aiming to enhance patient care and refine the management of pubertal growth dynamics.

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