


Correlation between Insulin-Like Growth Factor I and Skeletal Maturity Indicators

Global Pediatric Health
Volume 8: 1–6
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2333794X211011305
journals.sagepub.com/home/gph


Julia Carelli, DDS, MSc^{1,2}, Camila Mattos, MSc¹,
Nathaly D. Morais, DDS, MSc¹ , Rafaela Scariot, DDS, MSc, PhD¹,
João Armando Brancher, DDS, MSc, PhD¹,
Flares Baratto-Filho, DDS, MSc, PhD^{1,2},
Erika Calvano Kuchler, DDS, MSc, PhD¹ ,
and Alexandre Moro, DDS, MSc, PhD¹ 

Abstract

Objective: The purpose of this study was to evaluate the correlation between the growth maturity indicators in orthodontic patients. **Design:** This cross-sectional study was performed on 37 orthodontic patients (17 males and 20 females). An anamnesis, clinical and image examination, and blood sample collection were performed. The inclusion criteria were non-syndromic Class II patients of both gender, age ranging between 10 to 16 years. The lateral cephalometric radiographs were evaluated using 6-stage cervical vertebrae maturation (CVM) technique. The hand-wrist radiographs were staged using the 11-stage skeletal maturation indicator (SMI) technique. Blood was collected in the same week of the images to quantify IGF-I levels in serum. Data were tested for normality by Shapiro–Wilk test. The Pearson test was used to determine the correlation strength between the variables (alpha of 5%). **Results:** A strong correlation was observed only between SMI stages and CVM stages in the total sample ($r=0.864$; $p<0.0001$) and according to the gender ($r=0.793$; $p<0.0001$ for females; and $r=0.753$; $p<0.0001$ for males). IGF-I was only moderately correlated with SMI stages and CVM stages. **Conclusion:** Hand-wrist and cervical vertebral stages were strongly correlated among them, however, IGF-I was only moderately correlated with both skeletal maturity indicators.

Keywords

skeletal maturity, growth spurt, IGF1, orthodontic

Received January 18, 2021. Received revised April 20, 2021. Accepted for publication March 29, 2021.

Introduction

Determination of skeletal maturity of craniofacial complex is an essential part of treatment planning in orthodontic treatment. Skeletal maturity occurs after the adolescent growth spurt.^{1–5} Thus, assessment of maturation level and growth potential are used as a diagnostic tool to evaluate different clinical conditions and to define orthodontic treatment time. Several biologic indicators have been proposed to identify skeletal maturity, such as chronological age,⁶ dental development,⁷ skeletal maturation indicator (SMI) in hand wrist radiograph, cervical vertebrae maturation index (CVMI) in lateral cephalometric radiograph and increase in stature height.⁴

Skeletal growth can be predicted via CVMI and SMI, but it comes at an expense of radiation exposure to the patient,^{3,5,6,8} however CVMI has the advantage of not exposure an additional radiation in orthodontic treatment patients, once this analysis is performed in cephalometric radiographs.^{3,5} Hand wrist radiograph

¹Positivo University, Curitiba, Paraná, Brazil

²Univille - Universidade de Joinville, Joinville, Santa Catarina, Brazil

Corresponding Author:

Alexandre Moro, School of Health Science, Positivo University, Rua Cel Dulcideo, 1558, Água Verde, Curitiba, Paraná 80250-100, Brazil.

Email: alexandremoro@uol.com.br



is an easy and popular method, in which the ossification of the hand is clearly considered to represent the maturation of the skeletal system.^{6,9} During the past decades, CVMI have got increasing interest to assess individual skeletal maturity. In this method the modifications in shape and size of the cervical vertebrae are analyzed.^{3,5}

Biochemical markers have been emerging as new tools of biologic maturity assessment to identify the skeletal maturity. They are collected from some fluids such as urine, saliva or blood and have the advantage of avoid radiographic radiation exposure and overcoming the subjectivity of radiographs exams.⁵ Insulin-like growth factor 1 (IGF-1) is a growth hormone-dependent peptide that stimulates growth.¹⁰ IGF-1 is a well-characterized basic peptide secreted by the liver and circulated in the blood, which has mitogenic functions, insulin-like and growth-regulating.¹¹ Some studies have suggested that IGF-1 levels has a good correlation with radiographic techniques to determine skeletal maturity.¹² Therefore, the aim of this study was to evaluate the correlation between the growth maturity indicators in orthodontic patients, and evaluate if serum levels of IGF-1 have a good correlation with CVM and SMI in a Brazilian population.

Methods

Sample Recruitment

Ethical approval was obtained from the research ethical committee of the Positivo University (CAAE: 02613418.5.0000.0093; number of approval: 3.036.106). The informed consent was signed by legal guardians and the patients previous to be included in the study.

The study consisted of a consecutive sample of 37 individuals (17 males and 20 females) from the patients seeking for orthodontic treatment at the Department of Orthodontics of Positivo University, Curitiba, Brazil. The age of the study subjects ranged from 10 to 16.3 years. An anamnesis, clinical and image examination and blood sample were performed and all patients were enrolled in the Orthodontic treatment.

The inclusion criteria were patients of both genders, age ranging between 10 to 16 years, Class II molar relationship with at least half-cusp in both sides, convex facial profile suggestive of retrognathia, and pronounced overjet (greater than 4 mm). Patients subjected to previous orthodontic treatment, suffering from illness, syndromes, oral cleft, those with tooth agenesis, or history of any serious trauma or injury to the face, as well as and those with history of abnormal bone growth were excluded from the study.

All individuals were submitted to Cone-Beam Computed Tomography (CBCT) before the orthodontic treatment.

CBCT scans were performed following the same protocol, with standard head positioning (Frankfurt horizontal plane), scanning time of 17.8 seconds, a field of view of 170 /170 mm, 120 kVp, 8-mA exposure, and patient in maximum intercuspation. An i-CAT (Imaging Sciences International, Hatfield, PA, USA), model 9140, was used. The CBCT images were exported as DICOM (Digital Imaging and Communication in Medicine) files with a voxel size of 0.3 mm.

Hand wrist radiographs were obtained with the hand placed over the film in a clenched-fist positioned and using a CC Proline Panoramic Cephalometric X-ray unit (Planmeca, Finland) and Kodak film with exposure settings of 3.2 to 16 mA, 57 to 90 kVp potential difference, 0.2 second exposure time, and a 5 central symmetric collimator.

CBCT scans and hand-wrist radiographs of each patient were taken on the same day.

The hand-wrist radiographs were staged by using the 11-SMI-stage, technique described by Fishman (1982). Based on Fishman's mandibular growth-increment data, the stages were regrouped into 5 stages: pre-pubertal (SMIs 1-3), acceleration (SMIs 4-5), high facial growth velocity (SMIs 6-8), deceleration (SMIs 9-10), and post-pubertal (SMI 11).¹³ All evaluations were done by an operator and checked for accuracy by a second investigator.

In the present study, the CVM method, according to McNamara and Franchi⁴ including 6 stages has been applied. A qualitative cervical vertebral maturation assessment, based on head and neck images visualized on the InVivo 5.0 software (Anatomage Inc., San Jose, CA, USA) was performed for each patient. This method allows the analyze the vertebral body shape and the cervical vertebrae CS2, CS3 and CS4 on lower border concavity. The stages were regrouped into 3 stages: pre-pubertal (CS1-2), pubertal (CS3-4), and post-pubertal (CS5-6). All evaluations were done by an operator and checked for accuracy by a second investigator.

For each patient were collected 5 mL of blood on the week of the radiographs. The samples of blood were centrifuged to separate the serum from blood.

Measurements of IGF-I levels were made using human IGF-1 ELISA kits. The kit uses an in-vitro sandwich enzyme linked immunosorbent assay for the quantitative measurements of IGF-1 in serum, plasma, cell culture supernatants. The kit has a coefficient of variation for intra-assay reproducibility of less than 10%. We constructed the standard calibration curves for the ranges corresponding to serum and urine IGF-1 values.

All statistical analyses were performed using Graph Pad Prism 5.0a (Graph Pad Software Inc., San Diego, CA, USA). All continuous data were tested for normality by Shapiro–Wilk test and therefore, parametric and non-parametric tests were used to analyze the data. The Pearson correlation coefficient was used to determine the correlation strength between the variables (normal data). The strength of the positive correlations was defined according the value of the “Correlation Coefficient,” such as: 1: perfect; .7 to .9: strong; .4 to .6: moderate; .1 to .3: weak; and 0: no correlation. The statistical significance was defined by 2-tailed $P < .05$.

Results

Among the included patients, 17 (46%) were males and 20 (54%) were females. The age ranged from 10 to 16 years old.

Regarding the hand-wrist skeletal stages, 1 (2.7%) child presented SMI-1; 3 (8.1%) children presented SMI-2; 3 (8.1%) children presented SMI-3; 3 (8.1%) children presented SMI-4; 14 (37.8%) children presented SMI 7; 2 (5.4%) children presented SMI-8; 5 (13.5%) children presented SMI-9; 5 (13.5%) children presented SMI-10; and 1 (2.7%) children presented SMI-11. Regarding CVM stages, 4 (10.8%) children presented CS-1; 6 (16.2%) children presented CS-2; 4 (10.8 %) children presented CS-3; 12 (32.4%) children presented CS-4; 6 (16,2%) children presented CS-5; 5 (13.5%) children presented CS-6.

The IGF-1 levels (minimum, maximum, mean and standard deviation) according to the CVM stages and SMI stages are presented in Figure 1.

A strong correlation was observed only between SMI stages and CVM stages in the total sample and according to the gender.

The Figure 1 shows the correlation between SMI stages and CVM stages and IGF-1 levels. A moderate correlation was observed for all comparisons.

Discussion

Biologic indicator of skeletal maturity have been widely investigated by many research groups from different scientific areas,^{5,8} however, a special attention has been draw by dental researchers. In orthodontics and dentofacial orthopedics, it is evident that the timing of the treatment may be as critical as the selection of the specific treatment protocol influencing the clinical outcome. For this reason, in the present study, we decided to explore the biologic indicator correlation of skeletal maturity in a group of orthodontic Brazilian patients.

IGF-1 is synthesized and secreted in the liver following stimulation by growth hormone. In the puberty IGF-1 levels can be independent of Growth Hormone because IGF-1 production can directly be stimulated by androgens. IGF-1 levels have been related to sexual maturity, chronological age and have been shown to peak late in puberty.¹⁴ Therefore, IGF-1 can stimulate primary and secondary cartilage, also follow the mandibular growth velocity pattern, which can be proved the fact that mandibular condyle is sensitive to IGF-1 (Delatte 2003).¹⁵ IGF-1 levels can be measured in blood, urine, and saliva. In our study we used blood samples to evaluate the IGF-1 levels, however, other studies measured salivary IGF-1¹⁶ and urine IGF-1.¹⁷ We decided to evaluate only serum IGF-1, due the fact that salivary and urine IGF-1 has the disadvantage that variation of the values throughout the day can be observed.¹⁶

The identification of the mandibular skeletal maturity has a key role in orthodontics and dentofacial orthopedics. The ideal biologic indicator of mandibular skeletal maturity should present efficacy to detect the peak in mandibular growth, no additional x-ray exposure, and consistency in the interpretation.² IGF-1 could present all the characteristics of a biological indicator, and may be used as an additional tool for optimizing orthodontic treatment timing,^{8,18} therefore, in this study we decided to investigate the correlation between IGF-1 serum levels and skeletal indicators. The IGF-1 assessment would provide the orthodontist with an idea of how much growth can impact the planned treatment. Sinha et al⁵ proposed that IGF-1 assessment would provide to clinicians an idea of how much growth can be generated into planned treatment. However, in our study, only moderate correlations were observed between IGF-1 and SMI and between IGF-1 and CMV, regardless the gender.

Many factors could be involved in our findings and should be interpreted with caution. To minimize type I and II errors, future studies with a larger sample size are suggested. The classical and most widely used method for skeletal-age evaluation is the highly reliable hand-wrist bone analysis. However, some authors reported that besides the exposure of x-ray, not only SMI stages, but also CVM stages, have disadvantage of subjectivity during the interpretation.^{12,19-21} The validity of the CVM has been questioned by many authors.^{3,22,23} Due to the limitations posed by exposure to radiation, it is unclear how long each cervical stage lasts.²⁰ According to Ball³ if the treatment timing is determinant to a successful treatment outcome, the CVM method should be used with other maturity indicators. On the other hand, Perinetti et al,²² concluded that visual assessment of the

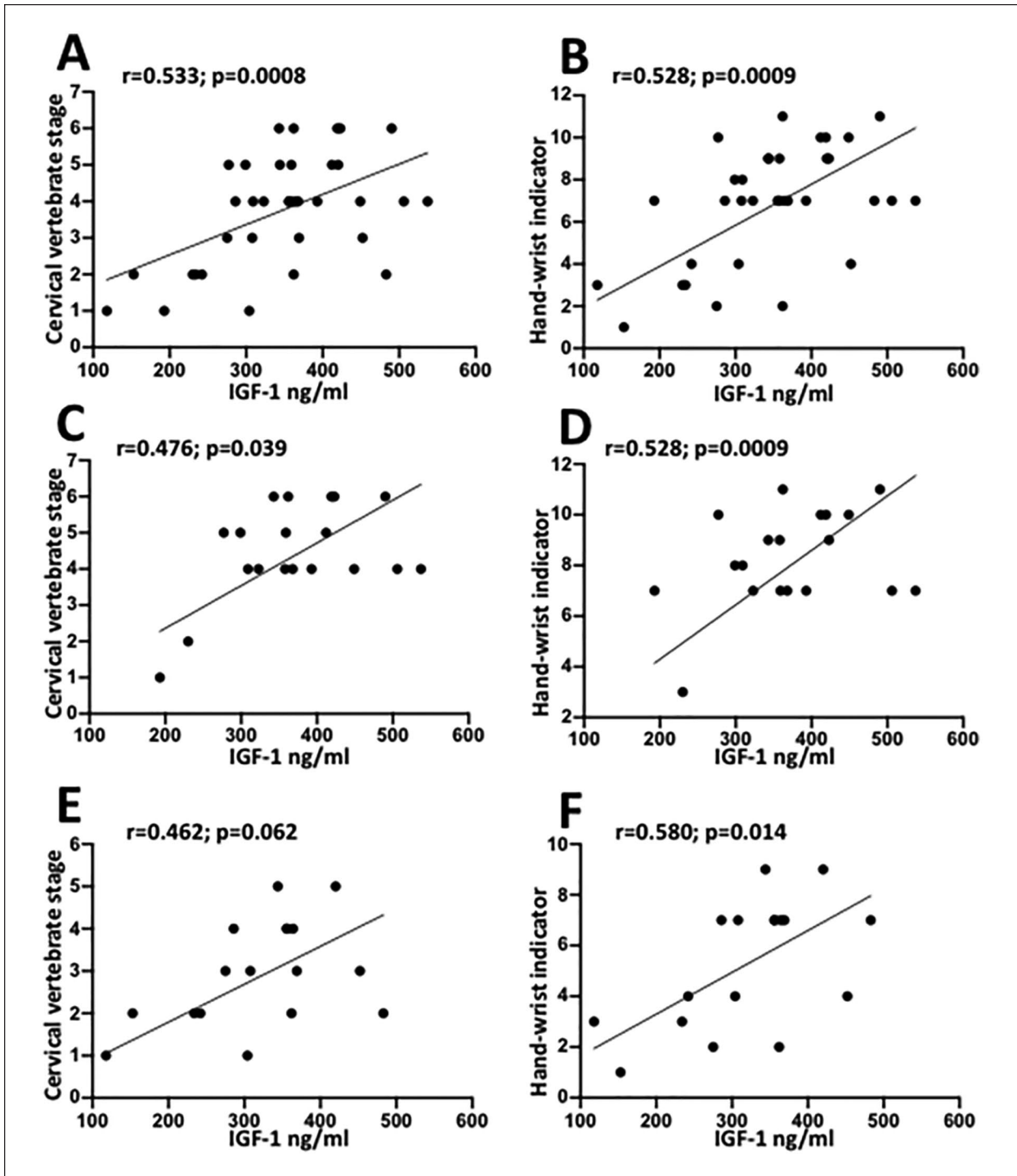


Figure 1. Correlation between SMI and CVM stages and IGF-I levels. (A) Correlation between CVM stages and IGF-I levels in general patients. [Pearson coefficient correlation $r=0.533$; $P=.0008$]. (B) Correlation between SMI and IGF-I levels in general patients. [Pearson coefficient correlation $r=0.528$; $P=.009$]. (C) Correlation between CVM stage and IGF-I levels in girls [Pearson coefficient correlation $r=0.476$; $P=.039$]. (D) Correlation between SMI and IGF-I levels in girls. [Pearson coefficient correlation $r=0.528$; $P=.009$]. (E) Correlation between CVM stage and IGF-I levels in boys [Pearson coefficient correlation $r=0.462$; $P=.062$]. (F) Correlation between SMI and IGF-I levels in boys. [Pearson coefficient correlation $r=0.580$; $P=.0140$].

CVM stages was accurate and repeatable to an adequate level. It is important to emphasize, that in our sample, both methods, SMI and CVM stages, were strongly correlated among them in males, females and both genders, suggesting that both could be used in the clinical practice.

Several studies shown that in the CS3 and CS4 are associated with the peak growth velocities in height and mandibular growth and in these stages the growth modification can be maximized.^{3,12,24} In hand wrist radiographs the peak mandibular growth occurs in SMI7.⁹ IGF-1 levels also tend to peak late in puberty stage⁵ Juul et al 1994.²⁵ Additionally, IGF-1 levels tended to be higher in patients who were in their radiographically determined growth spurt, for both SMI and CVM techniques.⁸ However, this was not observed in our sample.

Briefly, skeletal maturity occurs after the growth spurt and the knowledge regarding this period and the correlation among the biomarkers of this period is important in many treatments, including orthodontic and orthopedics treatment.^{1-5,26}

Conclusion

Hand-wrist radiographs and cervical vertebral stages were strongly correlated among them. IGF-1 was only moderately correlated with both skeletal maturity indicators.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Nathaly D. Morais  <https://orcid.org/0000-0002-8348-3751>

Erika Calvano Kuchler  <https://orcid.org/0000-0001-5351-2526>

Alexandre Moro  <https://orcid.org/0000-0002-3127-1837>

Referências

1. Baccetti T, Franchi L. Treatment timing for Twin-block therapy. *Am J Orthod Dentofacial Orthop.* 2000;118:159-170.
2. Baccetti T, Franchi L, McNamara JA. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. *Sem Orthod.* 2005;11:119-129.

3. Ball G, Woodside D, Thompson B, Hunter WS, Posluns J. Relationship between cervical vertebral maturation and mandibular growth. *Am J Orthod Dentofacial Orthop.* 2011;139:455-461.
4. McNamara JA, Franchi L. The cervical vertebral maturation method: a user's guide. *Angle Orthod.* 2018;88:133-143.
5. Sinha M, Tripathi T, Rai P, Gupta SK. Serum and urine insulin-like growth factor-1 as biochemical growth maturity indicators. *Am J Orthod Dentofacial Orthop.* 2016;150:1020-1027.
6. Suri S, Prasad C, Tompson B, Lou W. Longitudinal comparison of skeletal age determined by the Greulich and Pyle method and chronologic age in normally growing children, and clinical interpretations for orthodontics. *Am J Orthod Dentofacial Orthop.* 2013;143:50-60.
7. Sachan K, Sharma PV, Tandon P. A correlative study of dental age and skeletal maturation. *Indian J Dent Res.* 2011;22:882.
8. Gupta S, Jain S, Deoskar A. Determining skeletal maturation using insulin-like growth factor I (IGF-I) test. *Prog Orthod.* 2012;13:288-295.
9. Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. *Angle Orthod.* 1982;52:88-112.
10. Sorensen K, Aksglaede L, Petersen JH, Andersson AM, Juul A. Serum IGF1 and insulin levels in girls with normal and precocious puberty. *Eur. J. Endocrinol.* 2012;166:903-910.
11. Zhang X, Yi J, Li Y. Effects of nutrition and hormones on functional appliance treatment outcome in patients with skeletal Class II malocclusion. *J World Fed Orthod.* 2020;9:8-11.
12. Masoud M, Masoud I, Kent RL Jr, Gowharji N, Cohen LE. Assessing skeletal maturity by using blood spot insulin-like growth factor I (IGF-I) testing. *Am J Orthod Dentofacial Orthop.* 2008;134:209-216.
13. Masoud MI, Masoud I, Kent Jr RL, Gowharji N, Hassan AH, Cohen LE. Relationship between blood-spot insulin-like growth factor 1 levels and hand-wrist assessment of skeletal maturity. *Am J Orthod Dentofacial Orthop.* 2009;136:59-64.
14. Kanbur-Oksuz N, Derman O, Kinik E. Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. *Turk J Pediatr.* 2004;46:315-321.
15. Delatte M, Von den Hoff JW, Maltha JC, Kuijpers-Jagtman AM. Growth stimulation of mandibular condyles and femoral heads of newborn rats by IGF-I. *Arch Oral Biol.* 2004;49(3):165-175.
16. Ryan J, Mantle T, Costigan DC. A normal population study of human salivary insulin-like growth factor 1 (IGF 1) concentrations from birth through puberty. *J Clin Endocrinol Metab.* 1992;74:774-778.
17. Hizuca N, Takano K, Tanaka I, et al. Demonstration of insulin-like growth factor I in human urine. *J Clin Endocrinol Metab.* 1987;64:1309-1312.
18. Jain S, Jain S, Deoskar A, Prasad V. Serum IGF-1 levels as a clinical tool for optimizing orthodontic treatment timing. *Prog Orthod.* 2013;14:46.

19. Lupu S, Totir N. The optimization of the electrochemical preparation of pedot-prussian blue hybrid electrode material and application in electrochemical sensors. *Collect Czech Chem.* 2010;75:835-851.
20. Masoud MI, Marghalani HY, Masoud IM, Gowharji NF. Prospective longitudinal evaluation of the relationship between changes in mandibular length and blood-spot IGF-1 measurements. *Am J Orthod Dentofacial Orthop.* 2012;141:694-704.
21. Mitani H, Sato K, Sugawara J. Growth of mandibular prognathism after pubertal growth peak. *Am J Orthod Dentofacial Orthop.* 1993;104:330-336.
22. Perinetti G, Caprioglio A, Contardo L. Visual assessment of the cervical vertebral maturation stages a study of diagnostic accuracy and repeatability. *Angle Orthod.* 2014;84:951-956.
23. Zhao XG, Lin J, Jiang JH, Wang Q, Ng SH. Validity and reliability of a method for assessment of cervical vertebral maturation. *Angle Orthod.* 2012;82:229-234.
24. Wong RW, Alkhal HA, Rabie ABM. Use of cervical vertebral maturation to determine skeletal age. *Am J Orthod Dentofacial Orthop.* 2009;136:484.
25. Juul A. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab.* 1994;78(3):744-752.
26. Ferring V, Pancherz H. Divine proportions in the growing face. *Am J Orthod Dentofacial Orthop.* 2008;134:472-479.