Caspian J of Dent Res

Original Article

# The use of urinary Insulin-like Growth Factor-I (IGF-I) for determining skeletal age of participants

**Hadis Majd [1], Valiollah Arash [2]✉, Manouchehr Rahmati Kamel[3], Ali Bijani[4], MohammadAli Bayani[5]**

1. Postgraduate Student, Student Research Committee, Babol University of Medical Sciences, Babol, IR Iran. **ORCID** (0000-0003-1157-4053)
2. Associate Professor, Dental Materials Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
3. Assistant Professor, Oral Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
4. Assistant Professor, Social Departments of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
5. Assistant Professor, Clinical Research Development Unite of Rouhani Hospital, Babol University of Medical Sciences, Babol, IR Iran.

✉**Corresponding Author:** Valiollah Arash, Department of Orthodontics, Faculty of Dentistry, Babol University of Medical Sciences, Babol, IR Iran.

**Email:** vali_arash@yahoo.com **Tel:** +981132291409 **ORCID** (0000-0002-0459-3064)

**Received: 23 Oct 2019 Accepted: 9 Feb 2020**

## Abstract

**Introduction:** Biochemical markers play an important role in the growth and repair of bone and can be evaluated in different biological fluids. Therefore, the aim of this study was to evaluate the level of insulin-like growth factor-I (IGF-I) in urine as a puberty index and to compare it with cervical vertebral maturational stages (CVMSs) in lateral cephalometry.

**Materials&Methods:** In this cross-sectional study, 50 8-18-year-old patients (males and females), referred to Faculty of Dentistry with CVMS of 2 to 6 and needed orthodontic treatment as well as lateral cephalometry were selected. All of these patients were healthy. The CVMSs were recorded based on lateral cephalometric radiographs and urinary levels of IGF-I was determined using a urine-based ELISA kit. Mean IGF-I values for each CVMS were analyzed by Mann-Whitney, Kruskal-Wallis and Chi-square tests in SPSS. $P<0.05$ was statistically considered as significant level.

**Results:** In this study, the mean age of participants, ranged from 8 to 18 years was 12.96±3.82. There was no statistically significant difference in gender distribution between CVM groups (P=0.106). The level of urinary IGF-I had no significant difference between groups, except for CVMS3 group (P=0.073). In CS3, the mean urinary IGF-I level was 0.2727, representing a significant difference from other groups (P=0.000). IGF-I levels had no significant differences between males (0.03±0.04) and females (0.08±0.011), (P=0.492).

**Conclusion:** The highest urinary IGF-I level was found in both genders in CVMS 3 and 4, which coincided with peak growth spurt in patients.

**Keywords:** Insulin-like growth factor I, Cervical vertebrae, Age determination by skeleton

***Citation for article:*** Majd H, Arash V, Rahmati Kamel M, Bijani A, Bayani MA . The use of urinary Insulin-like Growth Factor-I (IGF-I) for determining skeletal age of participants.Caspian J Dent Res 2020; 9:23-8.



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[ DOR: 20.1001.1.22519890.2020.9.1.1.3 ]

[ DOI: 10.22088/cjdr.9.1.23 ]

# تعیین فاکتور رشد شبه انسولینی ادراری (urinary IGF-I) جهت کمک به تشخیص سن اسکلتی بیماران

حدیث مجد[۱]، ولی اله آرش[۲*]، منوچهر رحمتی کامل[۳]،علی بیژنی[۴]، محمد علی بیانی[۵]

۱. دانشجوی دستیاری، کمیته تحقیقات دانشجویی، دانشگاه علوم پزشکی بابل، بابل،ایران.
۲. دانشیار، مرکز تحقیقات مواد دندانی، پژوهشکده سلامت، دانشگاه علوم پزشکی بابل،بابل،ایران.
۳. استادیار،مرکز تحقیقات سلامت و بهداشت دهان، پژوهشکده سلامت، دانشگاه علوم پزشکی بابل، بابل، ایران.
۴. استادیار، مرکز تحقیقات عوامل اجتماعی مؤثر بر سلامت، پژوهشکده سلامت، دانشگاه علوم پزشکی بابل، بابل، ایران.
۵. استادیار ، واحد توسعه تحقیقات بیمارستان روحانی، دانشگاه علوم پزشکی بابل، بابل، ایران.
*نویسنده مسئول: ولی اله آرش، گروه ارتودنتیکس، دانشکده دندانپزشکی،دانشگاه علوم پزشکی بابل، بابل، ایران.
پست الکترونیکی:vali_arash@yahoo.com تلفن: ۰۹۸۱۱۳۲۲۹۱۴۰۹+

## چکیده

**مقدمه:** مارکرهای بیوشیمیایی از جمله عواملی هستند که در رشد و ترمیم استخوان نقش دارند و می‌توان آنها را بصورت کمی در مایعات بیولوژیکی ارزیابی کرد. هدف از این مطالعه، ارزیابی تغییرات سطح فاکتور رشد شبه انسولینی ۱ (IGF-I) در ادرار بعنوان یک شاخص بلوغ و مقایسه آن با مراحل بلوغ مهره‌های گردنی (CVMSs) در سفالومتری طرفی است.

**مواد و روش ها:** در این مطالعه مقطعی ۵۰ بیمار (دختر و پسر) مراجعه کننده به دانشکده دندانپزشکی بین سنین ۱۸-۸ سال در محدوده CVMS2 تا CVMS6 تکامل مهره های گردنی که نیاز به درمان ارتودنسی و رادیوگرافی لترال سالومتری داشتند، انتخاب شدند. این افراد همگی سالم بودند. CVMSs بر أساس سفالومتری های طرفی و سطوح ادراری IGF-Iبه روش ELISAبا استفاده از کیت های ادراری ثبت شدند. مقادیر متوسط IGF-I برای هر گروه بر أساس CVMS، با تست های من ویتنی، کروسکال والیس و کای دو در نرم افزار آماری SPSS آنالیز شدند .سطح معنی داری P<0.05 در نظر گرفته شد.

**یافته ها:** در این مطالعه میانگین سنی افراد شرکت‌کننده ۳/۸۲ ±۱۲/۹۶ با محدوده ۸ تا ۱۸ سال بود .تفاوت معنی‌داری در توزیع جنسیتی در گروه‌های مختلف CVM وجود نداشت (P=0.106). سطح ادراری IGF-I در گروه‌های مختلف CVMS، به غیر از گروه CS3، تفاوت معنی‌داری نداشتند (P=0.073).در گروه CS3، میانگین سطح ادراری IGF-I، ۰/۲۷۲۷بوده که با سایر گروه‌ها تفاوت معناداری داشت (P=0.000). مقدار IGF-I بین مردان (۰/۰۱۱±۰/۰۸) و زنان (۰/۰۴±۰/۰۳) تفاوت معنی داری نداشت (P-Value=0.492).

**نتیجه گیری:** در این مطالعه بالاترین سطح IGF-I ادراری در افراد مونث و مذکر در مرحله سوم و چهارم CVM گزارش شد که مصادف با حداکثر سرعت رشدی در بیماران می‌باشد.

**واژگان کلیدی:** فاکتور رشد شبه انسولینی ۱، مهره های گردنی، تعیین سن اسکلتی

## Introduction

The determination of skeletal maturation in medicine and dentistry is of great importance. The timing of skeletal maturation is strongly influenced by gender as well as genetic and environmental factors. Different indices have been used to estimate skeletal maturation including height, chronological age, dental age, calcification of the wrists and hands and development of the cervical vertebrae.[1] Many researchers have shown that chronological age is not a reliable indicator to evaluate the state of puberty due to the significant differences in the maturation among people with the same chronological age; therefore, it is not an appropriate indicator for evaluating skeletal maturation. [2] Dental age and height indicate poor strength in the prediction of pubertal growth spurt. [3] Through wrist radiographs and lateral cephalometry, it is possible to evaluate the state of puberty. [4] Meanwhile, to prevent excessive radiation or to ensure results, alternative substitutes such as urinary insulin-like growth factor-I (IGF-I) are suggested to diagnose

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[ DOI: 10.22088/cjdr.9.1.23 ]

the skeletal maturation. [5] Having background information about the craniofacial growth and development is essential for any orthodontist. Of course, this will be possible only via understanding the normal growth pattern and its underlying mechanisms. [6] Dentofacial abnormalities in growing children are common causes for referring patients to orthodontists. These patients require functional or orthopedic treatments during growth or orthognathic surgery after peak pubertal growth. [7]

The golden time of treatment varies in different types of abnormalities; thus determining the treatment time is a substantial part to design the therapeutic approach. The issue of choosing the right time for orthopedic treatments is closely correlated with the timing of growth acceleration; hence, the developmental stage of each person, rate of skeletal maturity and remaining time for growth should be delineated. [8] A study has indicated that the greatest response to orthopedic treatment of mandible is obtained during puberty. In the case of mandible, the best results of orthopedic therapies are gained when treatment is performed in conjunction with increasing pubertal development. [9] The prediction of mandibular growth provides important information for the treatment plan and evaluation of the pre-treatment occlusion. [10] Therefore, determining the stage of skeletal maturation and amount of residual growth before orthodontic treatment planning is considered to be important. [11]

Various indices including height, chronological age, dental age, calcification of wrist bones and cervical vertebral maturational stages (CVMS)s have been studied to estimate skeletal age. Owing to significant differences in puberty timing between individuals of the same age, chronological age is not a reliable indicator to assess the puberty and skeletal age. Dental age and height are also very poor in predicting pubertal growth spurt time. Skeletal age can be assessed by lateral cephalometric radiographs of the wrist and neck. [12] Alternative tests like urinary IGF-I have been recommended to determine skeletal age in order to prevent excessive radiation or ensure results. In recent years, studies about IGF-I have represented the association of IGF-I levels with different stages of cervical vertebral maturational stages. [12,13] Most studies have been conducted on serum and fewer studies on saliva and urine samples. [14] Since the target population for predicting the skeletal age are children and adolescents, using a minimally invasive approach can be helpful in maximizing patient collaboration. Urinary IGF-I measurement has the least invasion and can be a suitable method to evaluate growth. [15]

Ryan et al. measured the amount of human salivary IGF-1, in which a low level of IGF-1 was found. Collecting salivary IGF-I is hard and there is a potential for contamination with saliva and blood fluid. Collecting and storing urine than saliva samples are relatively easier because the former is not technique-sensitive. [16] Furthermore, no laboratory kits was found in the current study specifically to measure salivary IGF-I. The kits generally were for body fluids with no specific instruction for saliva. However, precise instructions were explained for testing urine samples. Therefore, the aim of this study was to assess the level of urinary IGF-I as a puberty index and to compare it with cervical vertebral maturational stages on lateral cephalometry.

## Materials & Methods

This study was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (with the code of MUBABOL.REC.1396.62). Totally, 50 8-18-year-old patients, referred to Faculty of Dentistry were randomly selected for the present study. They needed orthodontic treatment and lateral cephalometric radiography. Inclusion criteria were no presence of systemic, congenital and hereditary diseases and growth disorders as well as no history of maxillofacial fractures. For data collection, The CVMS was recorded by observing lateral cephalometric radiographs [17] and the urinary IGF-I levels were evaluated using ELISA kit.

Lateral cephalometric radiographs were prepared in the same center by Cranex D X-ray unit (Soredex, Finland). The CVMSs were evaluated by 2 orthodontists independently so that both experts were unaware of patients' age,growth status and IGF-I level. Evaluation of CVMSs was performed based on Graber et al. [17] Given that each specialist reads each cephalometric radiograph only once, a random error of up to 5% was considered. If the two orthodontists disagreed on some cases, they would reobserve the lateral cephalometries together to agree on a mutual conclusion. Approximately, the equal number of patients for all CVMSs (stages 2-6) was entered into the present study, and the patients were divided into 5 groups.

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The next morning of taking radiographs, the patients were referred to the Razi Laboratory for morning urine sampling. For evaluation of IGF-I, ELISA kit (Sigma Aldrich, Germany) was used and the results were reported as numerical values between 0-100 ng/ml. The sensitivity of this test was 0.05 ng/ml. Each kit contained 96 tests of which 10 ones were considered as standard. Urine samples were immediately extracted and stored according to the company's instructions, at -20° C. Data were analyzed after collecting sufficient number of samples. According to the demographic data, IGF-I association with age was also investigated.

The mean urinary IGF-I level in each group was determined. Mann-Whitney, Kruskal-Wallis and Chi-square tests were used to compare the correlation between urinary IGF-I levels and CVMSs. Statistical significance was defined at $P<0.05$.

## Results

In this study, the total number of participants was 50 patients of which 19 (38%) and 31(62%) patients were male and female, respectively. The mean age of 8-18-year-old participants in the present study was 12.96±3.82. Distribution of patients in the five CVMSs is shown in table 1. There was no significant difference in the distribution of genders among these groups (p=0.106).

**Table 1. CVMSs based on gender.**

| | Cervical vertebral maturational stages | | | | |
|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 |
| | N(%) | N(%) | N(%) | N(%) | N(%) |
| Male | 5(26.3) | 6(31.6) | 5(26.3) | 0(0) | 3(15.8) |
| Female | 5(16.1) | 5(16.1) | 6(19.4) | 9(29) | 6(19.4) |
| Total | 10(20) | 11(22) | 11(22) | 9(18) | 9(18) |

Regarding the absence of normal distribution of data in these two groups, the nonparametric test was used to compare IGF-I in both males and females. The results of the current study suggested that the IGF-I had no significant difference between men (0.03±0.04) and women (0.08±0.011) (Z=-0.688, p=0.492). The mean and standard deviation of IGF-I values in different CVM groups are illustrated in table 2.

Regarding the absence of normal distribution of data, non-parametric test was used to compare IGF-I in different CVM groups. Kruskal-Wallis test was applied to compare IGF-I among CVMSs. There was a statistically significant difference only between group CVMS3 and other groups (p=0.0001).

**Table 2. Mean and standard deviation of IGF-I levels based on the CVMSs**

| Cervical vertebral maturational stages | Number | Mean | SD |
|---|---|---|---|
| 2 | 10 | 0.0000 | 0.00000 |
| 3 | 11 | 0.2727 | 0.54789 |
| 4 | 11 | 0.0182 | 0.04045 |
| 5 | 9 | 0.0000 | 0.00000 |
| 6 | 9 | 0.0000 | 0.00000 |
| TOTAL | 50 | 0.0640 | 0.27237 |

## Discussion

In the present study, the mean age of the 8-18-year-old participants was 12.96 ± 3.82. There was no statistical difference in gender distribution among CVM groups. In this study, urine samples of male and female were used, because the use of either of these alone might lead to bias in the results since some of previous studies reported different levels of IGF-I between two genders. [18] However, in the current study the mean IGF-1 level in male and female was not statistically different. This difference in result may be due to culture and ethnicity affecting puberty in both genders.

Yamamoto et al. evaluated various concentrations of IGF-I at different hours of the day, and reported higher levels in morning samples. They also demonstrated a positive correlation of IGF-1 accumulated in 24 hours with IGF-I morning urine. Therefore, we also collected urine samples in the morning. [19] Ryan et al. measured the amount of human salivary IGF-1, in which a low level of IGF-1 was found; hence, the accurate measurements were not possible. Furthermore, collecting salivary IGF-I is hard and there is a potential for contamination with saliva and blood fluid. Collecting and storing urine than saliva samples are relatively easier for the former is not technique-sensitive. [16]

Masoud et al. demonstrated the association between IGF-I and CVM in 83 patients (44 women, 39 men) aged 5-22 years old. The result of their study was similar to our findings. The highest levels of IGF-I were found in stage 3, followed by stage 4. [20] This is due to accelerated growth rate of children in stage 3 as the preparing stage for peak growth spurt.

Hizuka et al. collected 8 randomized urine samples for IGF-I from 8 normal individuals, 10 patients with

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acromegaly and 9 patients with hypopituitarism as well as observed that IGF-1 reflected the state of growth hormone. [21]

Ratcliff et al. have evaluated the age-related IGF-I and found that the highest levels of hormone is secreted in stage 3. [22] Nevertheless, Hall et al. stated this peak in stage 4. [23] The result of the latter study was different from our findings. Quattrin et al. examined the level of secreted IGF-I in healthy and unhealthy children in terms of growth, and expressed that the secretion of this hormone was much higher at puberty than pre-puberty period. [24] Skeletal response to growth changes can be increased at stages 3 and 4. [25] Additionally, the highest growth rates of height and mandible have been represented in stages 3 and 4 of the CVM. [26] The maximum changes in ramus length and body length as well as the largest effects on condylion are also seen in stages 3 and 4. Besides, stages 3 and 4 exhibit the largest anterior rotation of gonial angle. Based on the findings of Gu et al. the peak mandibular growth occurs during the interval between stages 3-4. Forward rotation of the mandible is associated with higher mandibular growth posteriorly as compared to anteriorly. [27]

The results of the ongoing study are the same as most of the previous studies. The peak urinary IGF-I level in men and women was measured in stages 3 and 4, representing the peak growth spurt. However, at other CVMSs, significant amounts of IGF-I could not be found in all samples, possibly because of low urinary levels of the hormone and difficulty in detecting it or due to possible laboratory errors. Urinary IGF-I levels were much lower than serum IGF-I levels. Yokoya et al. measured urinary IGF-I levels using immunoassay and found that it was about 1% of serum levels. [28] Thus, further studies with more precise kit may help to determine the urinary IGF-I level changes during puberty in orthodontic patients.

## Conclusion

Based on the current study, it could be concluded that the peak level of urinary IGF-I coincided with CVMS 3 at growth spurt so that both of them represented peak growth in children. Therefore, the urinary IGF-1 may be considered as a promising tool for evaluating the growth peak without limitation of radiographic techniques in the future. More studies with more precise kits and procedures on Iranian population are needed.

**Funding:** This study was a part of a research project (Grant No: 9644601), supported and funded by Babol University of Medical Sciences.

**Conflict of Interests:** There was no conflict of interests.

## Authors' Contributions

The study was designed by Valiollah Arash. Valiollah Arash, and Hadis Majd defined the conceptual content of the research. The study data were collected by Hadis Majd. Statistical analysis and interpretation of data were accomplished by Ali Bijani,Hadis Majd and Valiollah Arash. The manuscript was prepared by Hadis Majd and revised by Valiollah Arash and Manouchehr Rahmati Kamel. Molahmmadali Bayani contributed to the design and implementation of the research. Study supervision was performed by Valiollah Arash.

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