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RESEARCH ARTICLE

# BIOCHEMICAL METHODS TO ACCESS SKELETAL MATURATION

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**ABSTRACT**

Growth is defined as a series of anatomic and physiologic changes taking place with increasing age from the beginning of prenatal life to infancy, childhood & adulthood. In planning of orthodontic treatment, anticipation of future potential of the facial skeleton is essential to ensure the successful outcome of the mechanotherapy in the treatment of dentofacial deformities. Skeletal age assessment is done by radiographic methods. Since the radiographic methods do not show the exact stage, the additional biochemical methods have been proposed to be used to predict the maturation stage accurately. This article reviews the various biochemical methods to access skeletal maturity.



## INTRODUCTION

Growth is defined as a series of anatomic and physiologic changes taking place with increasing age from the beginning of prenatal life to infancy, childhood & adulthood[1]. During growth, every bone goes through a series of changes that can be seen radiographically[2]. The sequence of changes is relatively consistent for a given bone in every person. The timing of these changes varies because each person has his or her own biologic clock[3]. The importance of age can be explained by the famous quote of Tom Stoppard "Age is a very high price to pay for maturity"[4].

The pubertal growth spurts are dependent on gender and vary in their relationship to the chronologic age. These variations determine the speed as well as the duration of the growth processes. In girls, pubertal growth spurts usually start between the ages of 10 to 12 years, in boys between 12 to 14 years with variations of 3 to 6 years on either side[5].A number of growth assessment methods like chronological age, dental age, morphological age, skeletal age & circumpubertal age are available. Chronological age is often not sufficient for assessing the developmental stage and somatic maturity of the patient. It is not a critical factor in the evaluation of overall growth potential[6]. The biological age is determined from the skeletal, dental and morphologic age and the onset of puberty. The developmental status of human growth is better measured in relation to specific stages of maturation. i.e. against a scale of developmental events rather than chronologic age. Skeletal maturation is an integral part of individual patterns of growth and development. The essential criteria for skeletal development are growth within a definite time period and development to maturity. Growth can be measured in millimeters, time periods can be determined in weeks, months or years, the maturity process, however, can be ascertained by ossification assessment[7].Skeletal maturation refers to the degree of development of ossification in bone[2]. Size and maturation may vary independently of each other[3]. In planning of orthodontic treatment, anticipation of future potential of the facial skeleton is essential to ensure the successful outcome of the mechanotherapy in the treatment of dentofacial deformities[6]. Because of individual variations on timing, duration and velocity of growth, skeletal age assessment is essential in formulating viable orthodontic treatment plans[3]. Skeletal age assessment can be done by radiographic means and biochemical means. Radiographic methods which are highly subjective techniques involve radiation exposure. If any of these methods do not show the exact stage, the additional biochemical methods have been proposed to be used to predict the maturation stage accurately[8]. This article reviews the various biochemical methods to access skeletal maturity.

### *Importance of Skeletal Maturity Indicators*[3,9.10,11]

1. To determine the potential vector of facial development.

2. To determine the amount of significant facial cranial growth potential left.
3. To decide the onset of treatment timing and type of effective treatment.
4. To evaluate the treatment prognosis.
5. To understand the role of genetics and environment on the skeletal maturation pattern.

***Radiological***

1. Hand Wrist Radiographs[12,13,14,9,3]
2. Lateral Cephlograms.[15,16,17]
3. Opg.[16,17,18,19,11,20]

***Biochemical***

1. Insulin like Growth Factor.
2. Creatinine
3. Alkaline Phospatase.

***Biochemical Methods***

Radiation leads to various problems from skin diseases to cancers and has to be avoided. Recent literature has given much emphasis on biochemical methods for detection of skeletal maturity.[21,22,23,24,25,26,27,28,29,30]

***Insulin like Growth Factor***

Insulin-like growth I (IGF-I) is a circulating growth hormone-dependent factor whose level correlates with sexual maturity. It is used to diagnose growth hormone deficiency and excess. It is measurable in the serum as well as urine and saliva. Salivary IGF-I reflects its levels in the plasma. However, salivary IGF-I levels are extremely low i.e. less than 1 % of the serum levels.In 1957, IGF-I was discovered by ***Salmon and Daughaday*** as a mediator of growth hormone function[31]. Since then, IGF-I has been extensively studied and shown to play a principal role in systemic and local regulation of both prenatal and postnatal longitudinal bone growth. A study by ***Mohan et al*** in 2003 on mice deficient in IGF-I, IGF-II and GH showed that GH and IGF-I but not IGF-II are important for pubertal growth spurt. They also demonstrated that IGF-I actions were GH dependent. However, during the period of pre-pubertal growth, IGF-I actions were both dependent and independent on GH since IGF-I was found to be directly stimulated by androgens during that perio[32].

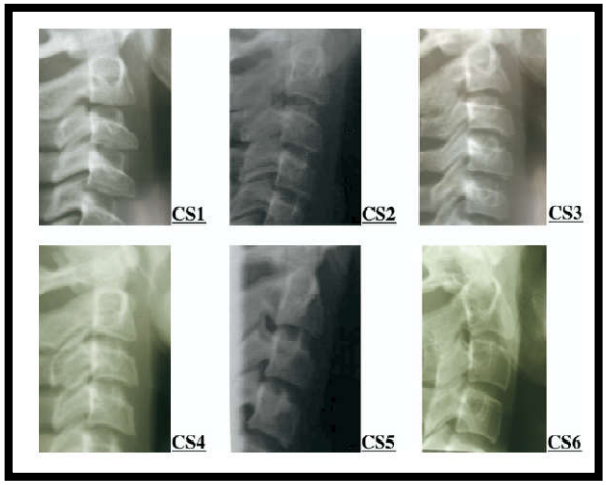


**Fig** Radiographs used as reference for the 6 cervical vertebrae stages

Serum IGF-I levels generally reflect GH status and were reported to be high in patients with acromegaly and low in those with GH deficiency. Measuring serum IGF-I was therefore considered a useful diagnostic tool for determining the growth hormone status, especially since its levels do not fluctuate throughout the day as GH levels do[33].

Recently in 2008, ***Masoud et al*** carried out a cross-sectional study to correlate IGF-I levels with cervical skeletal maturity and comparing the mean IGF-I levels at each of those stages[33]. The sample consisted of 83 patients (44 female, 39 male) on recall to begin orthodontic treatment, in active treatment or in post treatment follow-up. Lateral cephalograms were obtained as a part of standard treatment. Blood spot sample was collected using lancets with no visible needles and stored in sealed plastic bags in a freezer for no more than 4 months.

One-way ANOVA post-hoc analysis showed that IGF-I levels at CS5 were significantly higher than at CS1, CS2, CS3 and CS6 with $P<0.001$ and than at CS4 with $P<0.05$. There was a sharp increase in IGF-I levels from CS3 to peak levels at CS5 whereas there was a decline between CS5 and CS6. Mean IGF-I levels were significantly higher than at the other stages. IGF-I levels were still relatively high in many subjects who were at CS6 and had supposedly completed their growth.

Inherent disadvantage of cervical vertebrae staging is that the final stage of development does not necessarily indicate the completion of growth, especially mandibular growth. Several studies have shown that mandibular growth continues after radiographic skeletal maturity[33,34]. Also, mandibular condyle is more sensitive to IGF-I than long bones and adults with acromegaly continue to experience mandibular growth well after their statural growth is complete[34]. Thus, IGF-I might be a good indicator of residual mandibular growth.

Blood spot IGF-I correlates well with skeletal age as determined by cephalometric radiographic techniques. Blood spot IGF-I levels are low in pre-pubertal cervical stages & rise sharply to the peak in late puberty. Longitudinal data is needed to confirm the usefulness of this technique, to accurately determine the timing, and possibly the intensity of a patients growth spurt and to determine whether IGF-I levels are good predictors of residual facial growth.

***Salivary Alkaline Phosphatase***

Saliva is an oral fluid, and interest in it as a diagnostic medium in medicine and dentistr[35,36] has advanced exponentially in the last 10 years. Salivary components for any diagnosis include enzymes and immunoglobulins, hormones of host origin, bacteria and bacterial products, ions, fibroblasts and volatile compounds.[37] The enzyme ALP plays a role in bone metabolism. It is a membrane-bound glycoprotein produced by many cells, such as polymorpho nuclear leukocytes, osteoblasts, macrophages, and fibroblasts within the area of the periodontium and gingival crevice. ALP is essential for bone mineralisation and proposed as a diagnostic aid in periodontology and orthodontics. Christesen[38],Takimato[39], Insoft[40] have shown increase in serum ALP levels during puberty. But as it is an invasive procedure, many times its objected by patients and parents. Baccetti and Perinetti[26] have shown increase in GCF ALP level during puberty. But collection of GCF is a tedious procedure. It can be hypothesized that there will be increases in salivary ALP during puberty. Salivary collection is a non-invasive procedure easy to perform. The ALP rises significantly in parallel with the growth velocity between the ages of 8-12 in girls and 10-14 in boys and thereafter it falls rapidly to adult levels. It is a physiologic response to the growth spurt and does not signify

disease. Their level also rises in gingival inflammation and also in bone deposition. Perinetti *et al*.[26] found that gingival crevicular fluid (GCF) ALP levels rises during puberty and these studies were correlated with MP3, cervical vertebrae maturation indicators and also with hand wrist radiographic have seen significant results suggesting ALP is biomarker and can be considered as the noninvasive method to determine maturation stage.

***Creatinine***

The other index of maturity are the ratio of creatinine to creatinine in the urine, this ratio is thought to fall progressively with age after about the age of 14 years, probably under hormonal influences. Girls maturing early have a lower ratio than those of the same chronological age maturing late. A measurement of this ratio might be used to add information regarding the maturity along with skeletal and other data obtained at same time. Various studies were conducted in serum, saliva, and GCF to correlate its finding with the skeletal maturity indicators of the radiological origin.

## CONCLUSION

Maturational development embodies the biologic progression through life. In the growing years, indicators of the level of maturational development of the individual provide the best means for evaluating biologic age[41]. Maturational development can be assessed with the help of radiographical indicators**.** However, it must be kept in mind that every child demonstrates a unique sequential pattern of events. No child is the same as the other. Skeletal indicators of maturation have been proved to be the most reliable[42]. A combination of skeletal and dental indicators tends to give a very accurate picture of each child's developmental status. Finally it must be kept in mind that in orthodontic practice it may be more relevant to evaluate the development of the patient in relation to his own growth potential in order to assess whether peak velocity growth is imminent, present or completed. Garn e t al[43] stated that the ossification sequence and timing of the skeletal maturity within the MP3 and other indicators show polymorphism and sexual dimorphism which can limit their clinical predictive use. Since these methods are mainly morphological, while new possibilities might be offered by biochemical markers. Biomarkers avoid radiographic exposure, and they represent agents that are involved directly inborn growth and remodeling. The choice of indicators to be used finally depends upon an orthodontist's preference.

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