International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 02, 2020
ISSN: 1475-7192

Biomarkers for assessment of Skeletal maturation

[1]Dr. Sukhdeep Singh Kahlon, [2]Dr Vijay Aggarwal, [3]Dr. Karamdeep Singh Ahluwalia, [4]Dr Ramandeep Singh Narang, [5]Dr. Balwinder Singh, [6]Dr. Monaliza Kahlon

Abstract: *While making orthodontics treatment planning the most important objective is to correct skeletal discrepancies by utilising the growth potential of patient so that most favourable results could be achieved.[1] Response to orthopaedic treatment modalities is maximum during the peak of adolescent growth spurt. The correct identification of the pre - pubertal and post-pubertal growth phases on an individual basis is very important in orthodontic diagnosis and treatment planning.[2] Orthopaedic treatment of patients with Class III malocclusion and rapid maxillary expansion achieve maximum efficacy when performed at a pre - pubertal growth phase. On the other hand, in Class II subjects the amount of supplementary mandibular growth induced by functional appliances appears to be significantly greater when the treatment is performed during the pubertal growth phase.*

Key words : *Biomarkers, Skeletal maturation, Orthopaedic*

I. Introduction

While making orthodontics treatment planning the most important objective is to correct skeletal discrepancies by utilising the growth potential of patient so that most favourable results could be achieved.[1] Response to orthopaedic treatment modalities is maximum during the peak of adolescent growth spurt. The correct identification of the pre - pubertal and post-pubertal growth phases on an individual basis is very important in orthodontic diagnosis and treatment planning.[2] Orthopaedic treatment of patients with Class III malocclusion and rapid maxillary expansion achieve maximum efficacy when performed at a pre - pubertal growth phase. On the other hand, in Class II subjects the amount of supplementary mandibular growth induced by functional appliances appears to be significantly greater when the treatment is performed during the pubertal growth phase.

Different methods have been reported in an attempt to determine the best indicator of maturity. These include height,[2] weight,[3] chronological age, sexual maturation, Frontal sinus, biological age or physiological age, Hand-wrist maturity[4,5], Cervical vertebrae, dental eruption, dental calcification stages and biomarkers.[6]

[1] Prof. & Head, Dept. Of Orthodontics, SGRD Inst. Of Dental Sciences & Research, Sri Amritsar, India
[2] Prof. & Head, Dept. Of Orthodontic, Jaipur dental College
[3] Prof. ,Dept. Of Orthodontic, Jaipur dental College, Jaipur, India
[4] Prof. & Head, Dept. Of Oral Pathology, SGRD Inst. Of Dental Sciences & Research, Sri Amritsar, India
[5] Reader, Dept. Of Oral Medicine & Radiology, SGRD Inst. Of Dental Sciences & Research, Sri Amritsar, India
[6] Medical Office Dental, Govt Dental College Amritsar, India

As chronological age and dental emergence have been shown to be poorly related to skeletal maturation. Other methods include radiographic assessment of skeletal structures. But despite being reliable these methods are invasive as they give an X-ray exposure to the patient. Moreover cervical vertebral maturity (CVM) staging though widely used has decreased reproducibility and subjective errors with intra and inter observer disagreements. Furthermore, the onset of the peak in mandibular growth cannot be accurately defined by the CVM staging.

However new possibilities might be provided by biochemical markers, i.e.biomarkers that avoid invasive X-ray exposure and represent agents that are directly involved in bone growth and remodelling.[7]

A biomarker is defined as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease.[9]Biomarkers represent agents that are directly involved in bone growth and remodelling. Detection of such molecules would help the clinicians in assessing the growth status of the orthodontic patient and the efficacy of orthodontic care to be rendered.[8] Various methods for the assessment of biomarkers are immuno radiometric assays and chemiluminescence enzyme immune assay radio immuno assays, enzyme-linked immunosorbent assay, and all are found to be comparably accurate.[1]

According to all the literature available till date on biomarkers, Insulin-like growth factor 1 (IGF-1), Insulin-like growth factor Binding Protein-3 (IGF-BP3) and Alkaline phosphatase (ALP) are common substances that have proved to be most reliable in all the studies.This paper presents a review of IGF-1 and ALP markers for the prediction of skeletal growth assessment.

II. IGF (Insulin like Growth Factor)

IGF-1 and IGF-2 were identified in 1957 by Salmon and Daughaday.[11] The IGFs peptides shares a remarkable structural homology with proinsulin. In 1976, Rinderknecht and Humbel[12] isolated two active substances from human serum, which owing to their structural resemblance to proinsulin were renamed "insulin-like growth factor 1 and 2" (IGF-1 and 2). The biological actions of IGFs are mediated through the IGF1 receptor (IGF1R).[14] Most of the IGF-1 peptide in the circulation are found as ternary complex, a glycoprotein (the acid-labile subunit, ALS) and an high affinity binding protein, the IGF- binding protein 3 (IGFBP3). The portion of free (active) IGF-1 is usually very low (less than 5 %). A smaller proportion of the IGFs are associated with other serum IGFBPs i.e IGFBP1-6 except IGFBP 3.[13]

IGF-1 is secreted by many tissues and its actions are determine by the secretory site. Mostly IGF-1 is secreted by the liver and is transported to distant tissues, acting as an endocrine hormone.IGF-1 is also secreted by other tissues, including cartilaginous cells, and acts locally as a paracrine hormone.[10]

IGFBP3, the predominant IGF Binding Protien in serum, and the only one that cannot traverse the capillary membrane. The ternary complex between IGF-1, IGFBP3, and ALS modulates IGF-1 action by protecting the growth factor from proteolysis and prolonging its half-life in the circulation. Generally, the IGFBPs inhibit the metabolic and proliferative actions of IGF, although some exhibits IGF potentiating effects as well. IGFBP-3 is mainly regulated by GH but also to some degree by IGF-1.

The IGFs play important role in function of almost every organ in the body. IGFs are essential for embryonic development. After birth, however, IGF-I appears to have the predominant role in regulating growth.[15]

At the cellular level, IGF-1 stimulates a mitogenic response and inhibits cell death in a wide variety of cell types, including primary cultures and cancer cell lines. IGF-1 exhibits a variety of cellular functions, including regulation of hormone synthesis and secretion, immune cell recognition, and neuromodulation. Metabolic effects of IGF-1 include elevation of glucose uptake and hypoglycemia, without lowering free fatty acid levels. In addition, IGF-1 was suggested to improve renal function by increasing renal blood flow and glomerular filtration rate.

Many variables, such as age, sex, nutritional status, and growth hormone secretion, affect serum IGF-I concentrations. The concentrations are low at birth, increase substantially during childhood and puberty, and begin to decline in the third decade.These changes parallel the secretion of growth hormone. In growth hormone deficiency the serum IGF-I concentration is very low, and with excess growth hormone secretion the serum IGF-I concentration is high.

IGF-1 was first detected in serum but can be quantified in saliva and urine. Salivary IGF-1 levels reflect serum levels, but precise quantification is difficult as salivary levels are <1% of serum levels. Moreover, gingival fluid and blood contamination may yield false results. Serum IGF-1 levels tend to peak whenever there is accelerated growth in the body whether during pubertal growth spurt, residual mandibular growth,condylar hyperplasia,or tumorous growth occurring in the body.IGF-1 levels are found to be low in protein malnutrition, impaired cognitive function, hypothyroidism, coeliac disease, anorexia nervosa, and liver disorders.

Brabent et al (2003)[16] studied S-IGF-1 levels in different ages groups and found an estimated mean peak of 410 μg/l at age 14 in girls and an estimated mean peak of 382 μg/l at age 16 in boys. Juul et al. (1994)[17] reported that mean serum IGF-I concentration increased slowly in prepubertal children from 80 to 200 μg/l with a further steep increase during puberty to approximately 500 μg/l. After puberty, circulating IGF-I levels continued to fall to approximately 250 μg/l at age 25 years. IGF-I can be measured in urine (Hizuka et al., 1987)[18] and has been shown to reflect the growth hormone status of the individual (Hizuka et al., 1987, 1988[19] , Quattrin et al., 1987[20] , Yokoya et al., 1988a[21] , Albini et al., 1992[22]). In normal children, excretion increases with age and peaks during puberty (Ratcliffe et al., 1995[23]). C. M. Hall et al., (1999)[24], Gill et al., (1997)[25], Sinha et al., (2016)[26] concluded that total urinary IGF-I can be used as valid surrogate for serum IGF-I in physiological studies of normal growth. Costigan et al (1988)[27] reported the presence of IGF-I and IGF-II in human saliva, they concluded that saliva contains free IGFs but no significant quantities of specific binding proteins. Masoud et al., (2008)[28], Ishaq et al., (2012)[29], Jain et al., (2013)[30], Sinha et al., (2014)[26] Gupta et al., (2015), Jain et al., (2017)[31], Tripathi et al., (2017) studied IGF-1 levels in correlation to skeletal maturity by using the cervical vertebral stages. They concluded that serum IGF-I could be used as a skeletal maturity indicator and applied in orthodontic diagnosis.

III. ALP (Alkaline Phosphatase)

The metalloenzyme known as alkaline phosphatase (ALP) [phosphate-monoester phosphohydrolase exists as several tissue-specific isozymes. This enzyme is an ectoenzyme, which attaches to the outer face of the plasma membrane through a phosphatidyl inositol-glycophospholipid.[32] Human ALPs can be classified into four tissue-specific forms or isozyme according to the specificity of the tissue to be expressed, termed as placental alkaline phosphatase

(PLALP or Regan isozyme), Intestinal alkaline phosphatase (IALP), kidney/bone/liver alkaline phosphatase (L/B/K ALP), germ cell ALP. Bone ALP and liver ALP comprises about 95% of the total ALP activity in human serum. They are the isoforms of tissue nonspecific alkaline phosphatase (TNAP). In serum, bone ALP exists in several isoforms : B/I (70% of bone ALP and 30% of intestinal ALP), B1, B2, and B1x. Trabecular bone has higher combined (B1 + B2) bone ALP activity than cortical bone. Cortical bone show higher B1 activity, and trabecular bone has higher B2 activity.[33]

Bone ALP is a major regulator for bone mineralization. BALP is considered to be a highly specific marker for the bone-forming activity of osteoblasts. It hydrolyses inorganic pyrophosphate which is a naturally occurring inhibitor of mineralization. Bone ALP also provides inorganic phosphate for the synthesis of hydroxyapatite.

In normal subjects bone alkaline phosphatase contributes about half the total alkaline phosphatase activity in adults. The normal serum range of alkaline phosphatase is 20 to 140U/L. Levels are significantly higher in children and pregnant women. Also, elevated ALP indicates that there could be active bone formation occurring as ALP is a byproduct of osteoblast activity or a disease that affects blood calcium level (hyperparathyroidism), vitamin D deficiency, or damaged liver cells. Lower levels of ALP are less common than elevated levels. Certain conditions or diseases such as hypophosphatasia, postmenopausal women receiving estrogen therapy because of osteoporosis, men with recent heart surgery, magnesium deficiency, hypothyroidism, malnutrition, severe anaemia, children with achondroplasia and cretinism show lower levels of AP. In addition, the drugs such as oral contraceptives have been demonstrated to reduce alkaline phosphatase.

Alkaline phosphatase as biochemical marker

In adults with normal liver function, approximately 50% of the total AP activity in serum is derived from the liver, whereas 50% arises from bone. In children and adolescents the bone-specific isoenzyme predominates (up to 90%) because of skeletal growth. Therefore, in subjects with high liver AP, results of bone AP measurements may be artificially high, leading to false positive results. Serum total ALP is the most widely used marker of bone metabolism. Once liver disease is ruled out, serum levels of total AP provide a good impression of the extent of new bone formation and osteoblastic activity. From a clinical perspective, however detection of the bone-specific AP (BAP) isoenzyme is increasingly preferred because of its higher specificity.[33]

Krabbe et al (1980)[34] measured bone mineral content and total serum alkaline phosphatase. Concentrations of total serum alkaline phosphatase increased up to the age of 14 in boys and 11 in girls. Turan et al (2011)[35] evaluated age and sex-specific reference ranges for ALP. ALP levels demonstrated two peaks at infancy and puberty. Perinetti et al., (2011, 2012)[36, 37] evaluated the gingival crevicular fluid (GCF) alkaline phosphatase (ALP) activity in growing subjects and concluded that GCF ALP be used as a non-invasive clinical biomarker for the identification of the pubertal growth spurt in periodontally healthy subjects scheduled for orthodontic treatment. Tarvade et al., (2015)[38] evaluated the salivary alkaline phosphatase (ALP) activity in growing subjects using middle phalanx of third finger (MP3) stages and found a strong correlation of ALP levels in boys and girls and concluded that salivary ALP levels can be used as an additional diagnostic tool to optimize orthodontic treatment timing. Hegde et al (2018)[39] assessed B-ALP levels in saliva and correlated it with different skeletal maturity stages of hand wrist radiographs using Hagg and Taranger method. They conclude that B-ALP could be successfully identified and quantitatively estimated in saliva and showed

significant correlation with different skeletal age subgroups as determined by Hagg and Taranger method.Irham et al., (2017)[40], Tripathi et al., (2017)[41], Alhazmi et al., (2019)[42]assessed the level of ALP in growing subjects and compared with CVMI stages. They concluded that BALP showed promising results and can be employed as a potential biomarker for the estimation of growth status.

IV. CONCLUSION

It has been long since we have been using radiographic methods for assesment of pubertal growth. There are certain limitations and risks involved with multiple radiographs. To help over come these risks and problems related to radiographic interpretation, biochemical parameters show more convincing results in assessment of growth status. Definitely there are issues with evaluation of biomarkers. Not all biomarkers can be assessed by same technique. There are issues in standardising the equipments and normal values for biomarkers in population groups. Biomarkers for growth status can be assessed using blood, urine or salivary secretions. Urinary and salivary samples have chances of contamination. Studies have show convincing results that noninvasive biomarkers can be used as substitute for invasive methods for assessment of growth status of individual.

REFRENCES

1. Tripathi T, Gupta P, Rai P. Biochemical markers as skeletal maturity indicators. Int J Orthod Rehabil [serial online] 2017 [cited 2020 Jul 23];8:60-6.

2. Hunter CJ, The correlation of facial growth with body height and skeletal maturation at adolescence. Angle Orthod 1966; 36: 44-54.

3. Green LJ, Interrelationship among height, weight and chronological, dental and skeletal age. Angle Orthodox 1961; 31: 189-93.

4. Fishman LS, Chronological versus skeletal age, an evaluation of craniofacial growth. Angle Orthod 1979; 49: 181-9.

5. Hägg U, Taranger J, Maturation indicators and the pubertal growth spurt. Am J Orthod 1982; 82: 299-309.

6. Sushma Dhiman, Sandhya Maheshwari, Sanjeev K. Verma. Assessment of maturity in orthodontics: A review. Journal of Advanced Clinical & Research Insights (2015), 2, 100– 103

7 Giuseppe Perinetti; Lorenzo Franchi; Attilio Castaldo; Luca Contardo .Gingival crevicular fluid protein content and alkaline phosphatase activity in relation to pubertal growth phase. Angle Orthod (2012) 82 (6): 1047–1052.

8. Gaur A, Maheshwari S, Verma SK. Detection of molecular biomarkers as a diagnostic tool in the planning and progression of orthodontic treatment. J Orofac Sci 2017;9:80-4.

9. WHO International Programme on Chemical Safety Biomarkers in Risk Assessment: Validity and Validation. 2001. Retrieved from http://www.inchem.org/documents/ehc/ehc/ ehc222.htm.

10. Z Laron. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol. 2001 Oct; 54(5): 311–316.

11. Salmon WD, Jr, Daughaday W. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 1957;49:825–36.

12. Rinderknecht E, Humbel RE. Polypeptides with non-suppressible insulin-like and cell-growth promoting activities in human serum: isolation, chemical characterization, and some biological properties of forms I and II. Proc Natl Acad Sci U S A 1976;73:2365–9.

13. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor binding protein (IGFBP) superfamily. Endocr Rev 1999;20:761–87

14. Werner H. Molecular biology of the type I IGF receptor. In: Rosenfeld RG, Roberts CT, Jr, eds. The IGF system—molecular biology, physiology and clinical applications. Totowa, NJ: Humana Press, 1999:63–88.

15. GEORGIOS D. AGROGIANNIS, STAVROS SIFAKIS, EFSTRATIOS S. PATSOURIS,ANASTASIA E. KONSTANTINIDOU. Insulin-like growth factors in embryonic and fetal growth and skeletal development (Review). Mol Med Rep. 2014 Aug; 10(2): 579–584.

16. Georg Brabant, Alexander von zur Mühlen, Christian Wüster, Michael B. Ranke, Jürgen Kratzsch, Wieland Kiess, Jean-Marie Ketelslegers, Lars Wilhelmsen, Lena Hulthén, Bernhard Saller, Anders Mattsson, Jürgen Wilde, Rudolf Schemer, Peter Kann. Serum Insulin-Like Growth Factor I Reference Values for an Automated Chemiluminescence Immunoassay System: Results from a Multicenter Study. Horm Res 2003;60:53–60.

17. A Juul , P Bang, N T Hertel, K Main, P Dalgaard, K Jørgensen, J Müller, K Hall, N E Skakkebaek. 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. The Journal of Clinical Endocrinology & Metabolism1994 Mar;78(3):744-52.

18. Hizuka, N., Takano, K., Tanaka, I., Asakawa, K., Miyakawa, M., Horikawa, R. & Shizume, K. (1987) Demonstration of insulin-like growth factor I in human urine. Journal of Clinical Endocrinology and Metabolism, 64, 1309–1312.

19. Hizuka, N., Takano, K., Asakawa, K., Sukegawa, I., Horikawa, R., Yoshizawa, Y., Saito, S. & Shizume, K. (1988) Urinary IGF-I measurement and its clinical application. Acta Paediatrica Scandi-navica, 347(Suppl.), 127–133.

20. Quattrin, T., Albini, C.H., Vandlen, R.L. & MacGillivray, M.H. (1987) Quantitation of urinary somatomedin-C in children with normal and abnormal growth. Journal of Clinical Endocrinology and Metabo- lism, 65, 1168–1171.

21. Yokoya, S., Suwa, S., Maesaka, H. & Tanaka, T. (1988a) Immuno- reactive somatomedin-C/ insulin-like growth factor I in urine from normal subjects, pituitary dwarfs, and acromegalics. Pediatric Research, 23, 151–154.

22. Albini, C.H., Quattrin, T., Mills, B., Sherman, B., Johansonn, A. & MacGillivray, M.H. (1992) Urinary growth hormone and insulin-like growth factor-I. Clinical Paediatrics, 31, 542–545.

23. Ratcliffe, S.G., Masera, N., Skinner, A.M., Jones, J., Morrell, D., Pan, H., Price, D.A., Preece, M.A. & Clayton, P.E. (1995) Urinary insulin-like growth factor I in normal children: Relationship to age, pubertal status and urinary growth hormone. Growth Regulation, 5, 53– 59.

24. C. M. Hall, M. S. Gill, P. Foster, L. Pennells,V. Tillmann, J. Jones, D. A. Price and P. E. Clayton. Relationship between serum and urinary insulin-like growth factor-I through childhood and adolescence: their use in the assessment of disordered growth. Clinical Endocrinology (1999) 50, 611–618.

25. Gill, M.S., Whatmore, A.J., Tillmann, V., White, A., Addison, G.M., Price, D.A. & Clayton, P.E. (1997) Urinary IGF and IGF binding protein-3 in children with disordered growth. Clinical Endo- crinology, 46, 483–492.

26. 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 Dec;150(6): 1020-1027

27. D C Costigan , H J Guyda, B I Posner. Free insulin-like growth factor I (IGF-I) and IGF-II in human saliva. J Clin Endocrinol Metab.1988 May;66(5):1014-8.

28. 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 Aug;134(2):209-16.

29. Ishaq RA, Soliman SA, Foda MY, Fayed MM. Insulin-like growth factor I: a biologic maturation indicator. Am J Orthod Dentofacial Orthop. 2012 Nov;142(5):654-61.

30. Sapna Jain , Sandhya Jain, Anuradha Deoskar, V S Sai Prasad . Serum IGF-1 levels as a clinical tool for optimizing orthodontic treatment timing.Prog Orthod. 2013 Nov 14;14:46.

31. Nimisha Jain, Tulika Tripathi, S K Gupta, Priyank Rai, Anup Kanase, Shilpa Kalra. Serum IGF-1, IGFBP-3 and their ratio: Potential biochemical growth maturity indicators. Prog Orthod.2017 Dec;18(1):11.

32. The role of alkaline phosphatase in cartilage mineralization. Golub EE, et al. Bone Miner. 1992.

33. Ujjawal Sharma, Deeksha Pal, and Rajendra Prasad. Alkaline Phosphatase: An Overview. Indian J Clin Biochem. 2014 Jul; 29(3): 269–278.

34. S Krabbe, C Christiansen. Longitudinal study of calcium metabolism in male puberty. I. Bone mineral content, and serum levels of alkaline phosphatase, phosphate and calcium. Acta Paediatr Scand. 1984 Nov;73(6):745-9.

35. Serap Turan, Burcu Topcu, İbrahim Gökçe, Tülay Güran, Zeynep Atay, Anjumanara Omar, Teoman Akçay, Abdullah Bereket. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. J Clin Res Pediatr Endocrinol. 2011;3(1):7-11.

36. G Perinetti, T Baccetti, L Contardo, R Di Lenarda. Gingival crevicular fluid alkaline phosphatase activity as a non-invasive biomarker of skeletal maturation. Orthod Cranifac Res 2011 Feb;14(1):44-50.

37. Perinetti G, Baccetti T, Di Leonardo B, Di Lenarda R, Contardo L. Dentition phase and chronological age in relation to gingival crevicular fluid alkaline phosphatase activity in growing subjects. Prog Orthod 2011;12:100-6.

38. Dr. Suchita M. Tarvade (Daokar). Dr. Sheetal Ramkrishna, Dr. Sanjay Sarode. Salivary alkaline phosphatase- a biochemical marker for growth prediction. Indian Journal of Basic and Applied Medical Research; June 2015: Vol.-4, Issue- 3, P. 17-22.

39. Hegde SS, Revankar AV, Patil AK. Identification of bone-specific alkaline phosphatase in saliva and its correlation with skeletal age. Indian J Dent Res 2018;29:721-5.

40. Fadhlina Irham, Siti Bahirrah. The Level of Alkaline Phosphatase in Saliva as Biomarker for Pubertal Growth Phase. Advances in Health Science Research,2017, volume 8 , 102:105.

41. Tulika Tripathi, Prateek Gupta, Priyank Rai, Jitender Sharma, Vinod Kumar Gupta, Navneet Singh, and Mahesh Verma. Longitudinal evaluation of the association between Insulin-like growth factor-1, Bone specific alkaline phosphatase and changes in mandibular length. Sci Rep. 2019; 9: 11582.

42. Nora Alhazmi; Carroll Ann Trotman; Matthew Finkelman; Dillon Hawley; Driss Zoukhri; Evangelos Papathanasiou. Salivary alkaline phosphatase activity and chronological age as indicators for skeletal maturity.Angle Orthod (2019) 89 (4): 637–642.