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Assessing the Alkaline Phosphatase Levels as A Bone Biomarker in Gingival Crevicular Fluid during Semi-Rapid Expansion

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ABSTRACT

In orthodontics, the expansion of the maxilla is done to treat transverse maxillary deficiency in childhood. The cause of maxillary constriction may be genetic or environmental leading to crowding of teeth, cross bite and development of malocclusions. This expansion leads to increased maxillary dimensions. **Objectives:** To detect changes in alkaline phosphatase level as a bone biomarker in crevicular fluid during the phases of semi-rapid palatal expansion. **Methods:** Fifteen growing patients with an age range from 8-13 years were selected who needed maxillary semi-rapid palatal expansion as a part of orthodontic treatment. This quasi-experimental study was based on a non-probability purposive sampling technique conducted from August 2023 to July 2024. The samples were collected by inserting paper points in the gingival sulcus. The Periodontal status was evaluated before starting the sampling. The probing depths were recorded at different levels throughout the study until the completion of the retention period. The alkaline phosphatase levels in the gingival crevicular fluid were measured at buccal and palatal sites before, during and in the retention period after treatment. The alkaline phosphatase values were compared using the ANOVA test at different points in time with $p<0.05$ considered as statistically significant. **Results:** The ANOVA test showed a statistically significant increase in enzyme activity at different sites throughout maxillary semi-rapid palatal expansion treatment. **Conclusions:** It was concluded that the enzyme alkaline phosphatase as a biomarker is an indicator of active bone metabolism in growing children while going through the maxillary semi-rapid palatal expansion treatment.

INTRODUCTION

The objectives of Orthodontic and orthopedics treatment are to correct dental as well as jaw abnormalities. Tooth movement initiated by the application of orthodontic force is characterized by alteration in the dental and periodontal tissues [1, 2]. Jaws deformities can be corrected by different methods like the use of functional appliances, expansion of jaws, and correction of cross-bites in growing children. Correction of constricted jaws can be done by Rapid palatal expansion (RPE) which is an ideal technique for widening of jaws. Similarly growing children with class 2 and 3 malocclusions of increased or negative overjet can be corrected by Functional appliances if their treatment starts at proper timing [3, 4]. Once the growth spurt of growing patients is over the active growth which normally begins to end at the age of 12–13 years in female and 14–15 years in male, the procedures for growth change, rapid palatal expansion (RPE), and class 3 overjet correction are of no use. So once the patient is mature the only option left is camouflage treatment or surgical intervention to correct jaws. So the assessment of the exact timing to start an orthopedic intervention is very important. The study of bone biomarkers can give us important information in this regard. So when to start or not an orthopedic intervention on growing patients depends mainly on the identification of

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the skeletal maturation phase. The exact timing to start treatment of growing children is different in various malocclusions [5, 6]. The methods of growth assessment are cervical vertebral method, hand and wrist analysis, and assessment of chronological and dental maturation. However, with time, these methods are not reliable assessors of growth phases [7, 8]. New opportunities available for the growth assessment are biochemical markers. The collection of gingival crevicular fluid (GCF) for the assessment of biochemical markers can protect patients from extra radiographic exposure and tell us they are directly involved in the growth of bone and its remodeling [9]. Alkaline phosphatase (ALP) has been studied as a dependable biological indicator of the maturation of bones in several studies and its levels are associated with methods for the identification of skeletal development in growing patients [10, 11]. The enzyme alkaline phosphatase in bones is produced by the osteoblasts and is an extremely specific indicator of the bone-forming activity of osteoblasts. So for children with jaw deformity, it is very important to check their growth status before the start of orthopedic treatment. The compliance to wear a functional appliance for a long time in children is mandatory [12, 13].

Maxillary transverse deficiency in growing children is commonly managed through semi-rapid palatal expansion, which induces active bone remodeling; however, monitoring this biological response in real time remains challenging in clinical orthodontics. Alkaline phosphatase (ALP) in gingival crevicular fluid is a potential non-invasive biomarker of bone formation, yet limited evidence exists on its dynamic changes during different phases of maxillary expansion, particularly in pediatric patients. Most previous studies have focused on clinical outcomes of expansion rather than biochemical markers of bone activity. Therefore, this study aimed to evaluate changes in alkaline phosphatase levels in gingival crevicular fluid during pre-expansion, active expansion, and retention phases of semi-rapid palatal expansion to assess its role as a biomarker of bone remodeling.

METHODS

The institutional review board's permission was taken two months before the start of the study. The IRB number was (IBR Number 464). A written consent was taken from the patients/parents before the sampling. This quasi-experimental study was based on a non-probability purposive sampling technique due to the limited availability of patients of semi-rapid expansion. The duration was one year from 1 Aug 2023 to 31 July 2024. Patients having male gender only (to avoid gender biases), aged 10-14 years, and having narrow maxilla in transverse plane were included in the study, while, patients having any systematic disease patient or poor oral hygiene, history of undergoing any kind of oral surgery including ortho-gnathic surgery, and having a history of orthodontic treatment were excluded. The sample size of 15 was calculated by using the Open Epi sample size calculator using the following assumptions confidence level of 95%, population size of 1450, percentage frequency of outcome factor in the population of 51% and confidence limits of 5% [11]. 15 patients who visited the orthodontic department of de 'Montmorency College of Dentistry, Lahore with complaints of narrow maxilla were selected. Their oral hygiene and periodontal status were evaluated before selection for study. Also any systemic disease were ruled out. The maxillary expander was inserted in the mouth but we collected GCF one day before the insertion of the appliance. The sampling was done by inserting paper points in the gingival sulcus for collection of GCF, at all the three buccal and three lingual sides i.e. mid, mesial and distal sites. After insertion of the appliance GCF sample was also collected on day 0, day 1, and day 21. Then appliance was deactivated after completion of active semi-rapid palatal expansion for 3 months and the sample was collected again. Gingival massaging was done to activate GCF before the insertion of the appliance and whenever sampling was done to activate it. The patients were properly instructed to monitor their oral hygiene strictly and poor oral hygiene-containing patients were not included in the study. ELISA technique was utilized to analyze the ALP levels. Statistical analysis was done by entering the collected data through SPSS (Statistical Package for Social Sciences) version 21.0. The enzyme alkaline phosphatase activity was calculated and measured and the mean values of the enzyme were determined. The ANOVA test was applied for enzyme activity to check any significance of values. A value of $p \leq 0.05$ was considered a statistically significant reading.

RESULTS

A total of 15 male patients were observed between the ages of 10 and 14 years, to avoid gender bias we included only males in the current study. All the patients were in the growing age. ANOVA test was used to investigate the levels of alkaline phosphatase at Day 0, Day 1, Day 7, and Day 21 till the end of 03 months. It was observed a statistically significant difference ($p<0.05$) in mean levels of alkaline phosphatase. The mean alkaline phosphatase level rises from day 0 to day 90. It was also observed that there was a statistically substantial increase in levels between day 21 and day 0. The results also showed a noteworthy increase in alkaline phosphatase levels even till termination of 03 months of the retention period which is suggestive of increased osteoblastic activity. No significant differences were found in the selected patients of 10-14 years of age (Figure 1).

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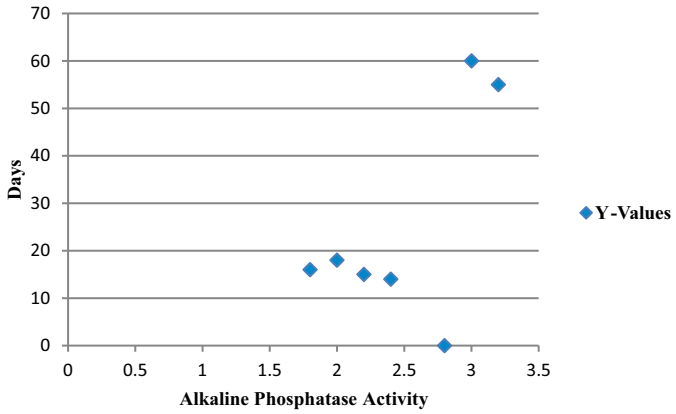

Figure 1: Alkaline Phosphatase Activity at Different Levels

The mean values of ALP activity at each time point are presented in Table 1. The data revealed a progressive increase in ALP levels, with statistically significant differences observed between the time points ($p < 0.05$).

Table 1: Mean Alkaline Phosphatase Activity at Different Time Points

Time Point	Mean ALP Levels (± SD)
Day 0 (Baseline)	0.52 ± 0.10
Day 1	0.85 ± 0.12
Day 7	1.25 ± 0.15
Day 21	2.05 ± 0.20
After 3 months	2.90 ± 0.25

DISCUSSION

Orthodontic treatment of growing children at an exact time is very important. Most of the children at growing age seek orthodontic advice due to jaw deformity or crowding of teeth [13]. The main problems of jaws in growing age are proclined upper anterior teeth, negative overjet, crowding of teeth, cross bites and constricted upper jaws [13, 14]. The etiology of these discrepancies is many like hereditary factors, environmental factors and sometimes a combination of these two. If these ailments are addressed at the proper time most favorable results are achieved. Similarly, constriction of maxillary dentition is a common reason for irregular crooked dentition. The contributing features may be genetics, environmental or functional factors [15-18]. Rapid Palatal Expansion using semi-rapid protocol is the method which can correct it. A rapid palatal expander is an appliance which is fitted in the oral cavity. Many patients are not compliant enough to bear an appliance in their mouth for long period. So the chances of the patient drained out are high. So it is very important to know the exact status of growth before the placement of the appliance in the oral cavity. Long duration of the appliance in the mouth can also promote the accumulation of plaque and poor oral hygiene [15]. The semi-rapid palatal expansion of the palate can be done by a bonded or banded hyrax expander [6]. Typically, the RPE is done in growing patients to get skeletal effects but in patients who are skeletally mature option left is semi-rapid palatal expansion through surgical intervention [19]. These days' the role of biomarkers is increasing for the assessment of growth status in growing children. Their advantage is extra radiographic rays are avoided and the exact status of growth may be known for the start of the orthopedic intervention [14]. Enzyme alkaline phosphatase is considered a bone biomarker. Its increased levels can predict active bone turnover so that orthodontic and orthopedic intervention can be carried out [8, 12]. The raised levels of ALP are related to active bone formation which can play a vibrant role in the indication to start the exact treatment timings of orthopedic intervention. Any change in levels of alkaline phosphatase can be a sign of active bone conversion during orthodontic movement of teeth [20-23]. In current study, we tried to find out the growth status of children by checking their alkaline phosphatase levels before the start of treatment to get the maximum benefits of active growth. The frequency of bone formation through osteoblasts is broadly connected with the activity of ALP [24]. As the use of orthodontic and orthopedic appliances takes enough time to get beneficial skeletal effects so early removal of the appliance may lead to a relapse of lengthy treatment leading to incorrect results. Similarly, the early start of orthopedic intervention can also lead to non-compliance in the second phase of treatment. Batra and other researcher colleagues also noticed a decreased alkaline phosphatase level on the 21st day [20]. The results of current study are consistent with findings reported by Batra *et al.*, who observed a peak in ALP levels during the initial phase of orthodontic treatment, followed by a gradual decline as the bone stabilized [20]. However, unlike Batra's study, present findings indicate that ALP levels remained elevated even after 3 months of retention, which may suggest that the semi-rapid protocol induces prolonged osteoblastic activity. Similarly, studies by López *et al.* and Wang *et al.* have documented increased ALP levels during rapid palatal expansion, emphasizing its role in monitoring bone turnover [22, 23]. In contrast, some researchers have reported a decline in ALP activity within a shorter retention period [24]. This discrepancy could be attributed to variations in appliance design, expansion protocols, and patient-specific factors such as age and skeletal maturity. Present study focused exclusively on male patients aged 10–14 years, a group characterized by active skeletal growth, which may account for the prolonged elevation in ALP levels observed. Overall, current findings underscore the importance of biochemical markers in orthodontic treatment planning. Further studies with larger sample sizes and diverse patient populations are warranted to validate these results and explore their implications for

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clinical practice. In Present study the level of alkaline phosphatase was still raised till the completion of 3 months of retention period. It indicated that active osteoblastic activity was going on even after 3 months of retention period. This result shows us that we can increase the time of retention up to 6 months leading to a minimal relapse [25, 26]. Early removal of the appliance may lead to a relapse of treatment leading to incorrect results [26]. The advantage of using a Hyrax expander for the semi-rapid expansion of the palate is that it does not exasperate the mucosa of the palate and is more hygienic. The reason for selecting palatal expansion cases was to avoid extra retention of the appliance in the mouth as it is a lengthy procedure with a high relapse history. So biomarkers are an important means of knowing active bone formation going on in growing patients.

This study is limited by its small sample size and single-center design, which may restrict generalizability of findings. The short follow-up period also limits evaluation of long-term stability of biomarker changes. In addition, variability in individual periodontal status may have influenced ALP levels. Future research should include larger multicenter samples with longer follow-up and comparison with additional bone turnover markers to strengthen evidence for clinical application.

CONCLUSIONS

It was concluded that the enzyme alkaline phosphatase as a biomarker is an indicator of active bone metabolism in growing children while going through the maxillary semi-rapid palatal expansion treatment.

Authors' Contribution

Conceptualization: AS[1]
Methodology: AS[1], AS[2], MA, NA, SH, SM
Formal analysis: AS[2]
Writing and Drafting: AS[1], AS[2], MA, NA, SH, SM
Review and Editing: AS[1], AS[2], MA, NA, SH, SM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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