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To evaluate the correlation of dentin markers and bone markers with the root resorption during fixed orthodontic treatment :An in vivo study

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Abstract

Aims and objective: To assess the extent of root resorption in maxillary anterior teeth, to determine the correlation of dentin markers and bone markers with extent of root resorption, To assess the change in levels of bone markers and dentin markers in gingival crevicular fluid (GCF) after 6 months of orthodontic treatment .

Materials and Methods:A sample size of 60 patients coming to Department of Orthodontics and Dentofacial Orthopaedics, Inderprastha Dental College and Hospital for orthodontic treatment were considered for the study. After patient selection, they were informed about the study. If he/she agrees with the treatment protocol, the consent form was signed by the patient.

Pre-treatment RVG was recorded for both maxillary central and lateral incisors to exclude any root resorption caused due to any other dental pathology for all the 60 patients, then GCF collection was done from each patient using micropipettes from both maxillary central and lateral incisor and which was then transferred to Eppendorf tube and stored at -20°C and evaluated using ELISA technique for extracellular matrix proteins that include bone markers that are - RANKL(receptor activator of nuclear factor kappa B), OPG (Osteoprotegrin) and dentin markers that are DMP1(dentin matrix protein), DSP(Dentin Sialoprotein). The patient undergone routine orthodontic treatment in the department for six months. After six months , all the patients were re-evaluated using RVG for root resorption and indexing was done. GCF collection was done using micropipettes for the samples and then GCF was stored at -20°C, and then it was evaluated accordingly for proteins using ELISA technique .

Results: Pretreatment and post treatment values of root length assessed using RVG. It showed that apical root resorption was greatest for LIL [0.79 mm] and lowest for CIR, [0.38 mm].

However, there was statistically significant root resorption seen among all the teeth examined.

There was reduction in value of OPG levels post orthodontic treatment in all the teeth examined, the reduction observed was statistically significant in both the central incisors and it was nonsignificant in lateral incisors. Highest amount of reduction was seen in central incisor right teeth (178.08 ng/ml) and least amount of reduction was seen in lateral incisor right teeth (28.68 ng/ml).

Pretreatment and post treatment RANKL levels. It was seen that there was a statistically significant increase of RANKL in LIR teeth, whereas non-significant increase was seen in rest of the teeth examined, when pre-treatment and post treatment values were compared. Highest amount of increase was seen in lateral incisor right teeth (301.43 ng/ml) and the least amount of increase was seen in lateral incisor left teeth (44.5 ng/ml).

Pretreatment and post treatment levels of DMP 1 , it was seen that there was statistically non-significant increase in level of DMP 1 observed from pretreatment to post treatment for all the teeth examined. Highest increase was seen in LIL teeth (98.13 ng/ml) and minimum was seen in CIL teeth (0.87 ng/ml).

Pre and post treatment changes in DSP marker. There was a significant increase of DSP marker values in LIL teeth, whereas a non-significant increase was seen in CIL,CIR and LIR teeth. Highest increase was seen in LIL teeth (169.25ng/ml) and minimum was seen in CIL teeth (81 ng/ml).

Correlation between markers and root resorption was assessed using the Pearson's correlation test. It was found that decrease in OPG level is significantly correlated with root resorption and increase in RANKL level is significantly correlated with root resorption. No correlation was obtained for DSP and DMP markers increase with root resorption.

Conclusion

The extent of apical root resorption after 6 months of orthodontic treatment was found to be statistically significant for all the maxillary incisor teeth examined using RVG . The maxillary left lateral incisor teeth showed the greatest amount of root resorption once all four teeth were examined, whereas the maxillary right central incisor teeth showed the least degree of root resorption.

Amount of root resorption was found to be significantly co-related with decrease in OPG levels and increase in RANKL levels. DSP and DMP 1 were not found to be significantly correlated to root resorption.

Considering bone marker levels, it was found that there was a significant decrease in OPG levels and increase in RANKL levels. Considering dentin markers, it was found that there was a significant increase in DSP marker and non-significant increase in DMP marker after 6 months of orthodontic treatment.

Keywords: DMP, DSP, OPG, CIL.

Introduction

Root resorption, a physiological or pathologic process, causes the loss of cementum and dentin. Ottolengui made the connection to orthodontics in 1914[1]. External apical root resorption can take one of three different forms according to Andresen as: surface, inflammatory, or replacement[2]. In connection with orthodontic therapy, external apical root resorption varies across patients and between teeth in the same person, or there may be severe resorption in a few teeth. The shape of the incisor roots acts as a catalyst for root resorption, making the upper incisors more vulnerable clinical researchers have been concerned about EARR in maxillary incisors. The intensity and time of the force used are exacerbating factors for root resorption, with the time of the force being seen as a more crucial element than the intensity of the force[1].

As cementum healing might take place in the time between force applications, it appears that interrupted or intermittent orthodontic forces produce less external root resorption[3]. Root resorption is substantially more pronounced with heavy than under light forces. The key factors contributing to apical root resorption continue to be intrusive forces, lingual root torque, and jiggling movement[4]. Deviating root structure, use of up righting and torque springs, and prolonged use of Class II elastics or rectangular arch wires are some of the risk factors[5].

The set of biomarkers that has attracted a lot of attention in recent years is those that are linked to osteoclastogenesis, including RANKL and OPG. The conjugation of RANK present on osteoblasts, to the receptor activator of osteoclast and osteoclast-precursor cells is necessary for osteoclast development. In contrast, the decoy receptor OPG adheres to RANKL and inhibits osteoclastogenesis[6].

Prior human studies have noticed Dentin sialoprotein (DSP) and dentin phosphoprotein presence in the gingival calcification fluid (GCF) of resorbing teeth. On the other side, proteins that exhibit differential expression in the GCF of teeth undergoing resorption could serve as helpful indicators of root resorption[6]. During active external root resorption, a particular protein called dentine sialophosphoprotein (DSPP) is secreted into the periodontal ligament space. Dentine phosphoproteins were discovered to be connected to root resorption by **Mah and Prasad** using biochemical techniques to identify dentine proteins. Researchers have demonstrated, root resorption may be monitored in GCF of patients undergoing OTM, using the biological markers dentine phosphophoryn and dentine sialoprotein.[7]

Numerous biochemical and cellular elements that are known to be present in GCF reflect the condition of the periodontium. In contrast to untreated controls, patients with mild and severe resorption were found to have DSP, DPP and DMP-1 markers in the GCF after at least a year after fixed appliance therapy. This was confirmed by intraoral periapical radiographs.[8]

Radiographs, however, are technique-sensitive and only show two-dimensional information, especially showing apical change. They can just detect resorption after 60–70% of the mineralized tissue has been removed. Additionally, radiographs are unable to show whether root resorption is ongoing[9].

Immunoassays are sensitive and specific, so they are now the most popular method for detecting protein concentrations in samples. To measure a large number of proteins in a small sample ELISA system that utilize downsizing in formatting of chip. As a result, they offer an appealing method for gingival crevicular fluid (GCF) study. The general categories can be used to classify GCF biomarkers on basis of their biological significance.[6]

As there is no radiation exposure, molecular approaches are significantly safer than radiographic methods for determining apical root resorption. Only after root resorption has taken place in significant volumes can it be shown on radiographs. DSPP (dentin sialo phosphoprotein) in GCF is a sign of root resorption[7]; however, other investigations have found that patients with mild and severe root resorption have DSP, DPP, and DMP-1.[8]

The teeth that are affected by external root resorption and the reliable marker for detecting root resorption are also the subject of opposing research. Therefore, the purpose of this study is to assess the amount and association between dentin and bone markers and resorption of root during fixed orthodontic treatment.

Source of data

The study was conducted on 40 patients coming to the Orthodontics department, Inderprastha dental college and hospital, Ghaziabad, seeking orthodontic treatment.

Methodology

A sample size of 40 patients coming to Orthodontics department, Inderprastha Dental College and Hospital for orthodontic treatment were chosen for the study. The patients were informed about the study after selection. If he/she agreed with the treatment protocol, the consent form was signed by the patient.

Pre-treatment RVG was recorded using Vatech sensor (Figure 1) in RVG room at Inderprastha dental college and hospital and evaluated using EZ Dent-i software (Figure 2) for both maxillary central and lateral incisors to exclude any root resorption caused due to any other dental pathology for all the 40 patients, Then GCF collection was done from each patient using micropipettes from both maxillary central and lateral incisor (Figure 3) and which is then transferred to Eppendorf tube and stored at -20℃ (Figure 4) and evaluated using ELISA technique (Figure 5) at Ganesh scientific research foundation, Kirti Nagar, New Delhi, for extracellular matrix proteins that included bone markers (Figure 6) which are - RANKL(receptor activator of nuclear factor kappa B) OPG (Osteoprotegrin) and dentin markers that are DMP 1(dentin matrix protein), DSP (Dentin Sialoprotein).

After 6 months of orthodontic treatment, GCF collection was done using micropipettes for the samples and stored at -20℃, and then GCF was evaluated accordingly for proteins using ELISA technique and then post treatment RVG was taken. The initial root length using pretreatment RVG were tabulated and final root length using post treatment RVG were evaluated and tabulated. The indexing for root resorption was done using Levander and Malmgren score.[5](Table 1) The apical root resorption detected with RVG distinguished the two. Data collected was evaluated and subjected to statistical analysis.

Table 1: Levander and Malmgren[5] Root resorption Index

GRADE	DEFINITION
0	No evidence for resorption
1	Irregular root contour
2	Apical root resorption less than 2mm
3	Apical root resorption >2mm and <1/3 of original root length
4	Root resorption exceeding 1/3 of original root length

Figure 1: RVG X Ray unit

Figure 2: Evaluation of measurements in RVG using EZ Dent-I Software

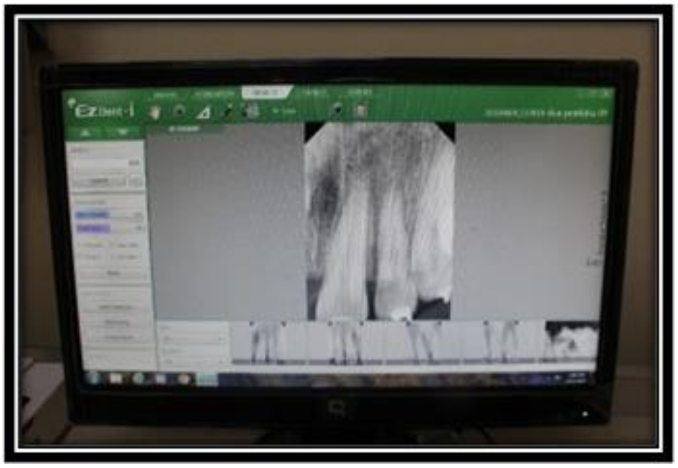
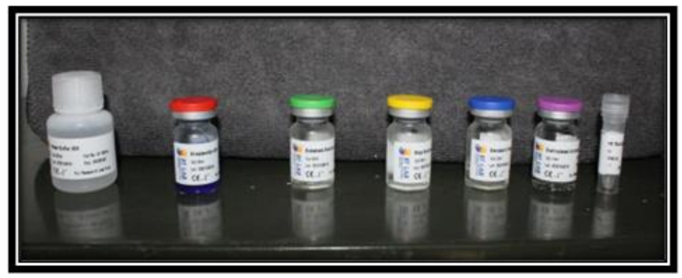


Figure 3: GCF sample collection done using micropipette.

Figure 4: Sample Storage Compartment

Figure 5: ELISA Reader

Figure 6: Elisa Kit



Result and observation

The present study was conducted to evaluate and compare the correlation of dentin markers and bone markers with the root resorption during fixed orthodontic treatment. The study was conducted with 40 patients who came to the department of orthodontics, IPDC, Sahibabad, Ghaziabad, India seeking orthodontic treatment. The patients were informed about the study and the consent form was signed. A pretreatment RVG was taken using a Vatech sensor in the department of conservative dentistry at Inderprastha dental college and hospital. The pretreatment initial root length was noted from RVG. Then pretreatment GCF collection was done using the micropipettes from all the maxillary central and lateral incisors which were then transferred to Eppendorf tube containing phosphate buffer saline solution ,then the samples were immediately stored in the cold compartment.

Once all the samples were collected , they were evaluated using ELISA technique for the presence of amount of different biomarkers – RANKL, OPG, DMP-1 , DSP at Ganesh Scientific Research Foundation.

After this the patient underwent routine fixed orthodontic treatment in the department. After 6 months of orthodontic treatment, GCF sample and RVG was taken. These samples were evaluated to detect the amount of RANKL, OPG, DMP-1, DSP using ELISA technique. The final root length was measured on RVG, the difference between the initial and final root length was calculated to assess the amount of root resorption.

The data was then subjected to paired student t test, ANOVA test and Pearson's correlation test.

Table 2 (figure 7) shows pretreatment and post treatment values of root length assessed using RVG. It showed that apical root resorption was greatest for LIL [0.79 mm] and lowest for CIR [0.38 mm]. However, there was statistically significant root resorption seen among all the teeth examined.

Table 2: Pretreatment and post treatment values of Apical RR assessed using RVG.

RR	PRE	POST	Mean Difference	Trend	P value	Remark
CIL	26.11+0.34	25.47+0.34	-0.65	decrease	<.001	Significant
CIR	25.88+0.34	25.5+4.03	-0.38	decrease	<.001	Significant
LIL	23.48+0.56	22.69+3.59	-0.79	decrease	<.001	Significant
LIR	23.08+0.59	22.35+3.53	-0.73	decrease	<.001	Significant

Table 3 (figure 8) shows that there is reduction in value of OPG levels post orthodontic treatment in all the teeth examined , the reduction observed was statistically significant in both the central incisors and it was non-significant in lateral incisors. Highest amount of reduction was seen in central incisor right teeth (178.08 ng/ml) and least amount of reduction was seen in lateral incisor right teeth (28.68 ng/ml).

Table 3: Pretreatment and Post treatment values of OPG

OPG	PRE	POST	Mean Difference	Trend	p-value	Remarks
CIL	899.04+59.75	742.46+117.39	-156.58	decrease	0.021	Significant
CIR	851.98+72.12	673.9+106.55	-178.08	decrease	0.039	Significant
LIL	1039.78+67.18	972.04+153.69	-67.73	decrease	0.214	not significant
LIR	975.8+67.43	947.13+149.75	-28.68	decrease	0.36	not significant

Figure 7: Pretreatment and Post Treatment root resorption values

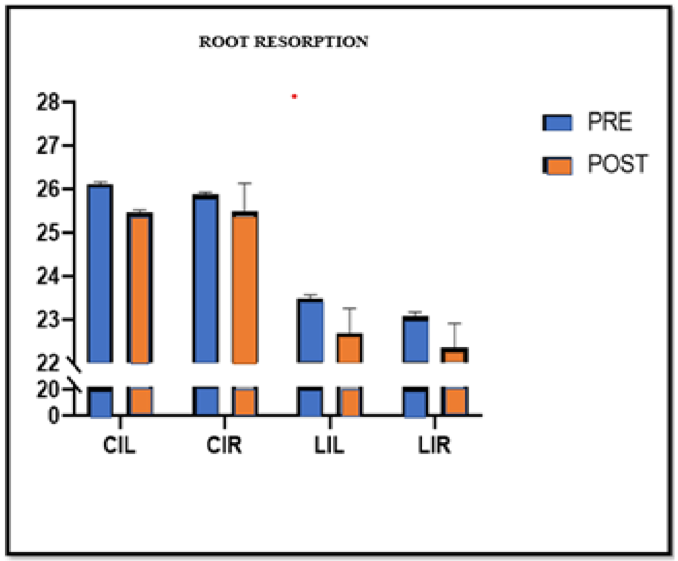


Figure 8: Pretreatment and Post treatment values of marker OPG

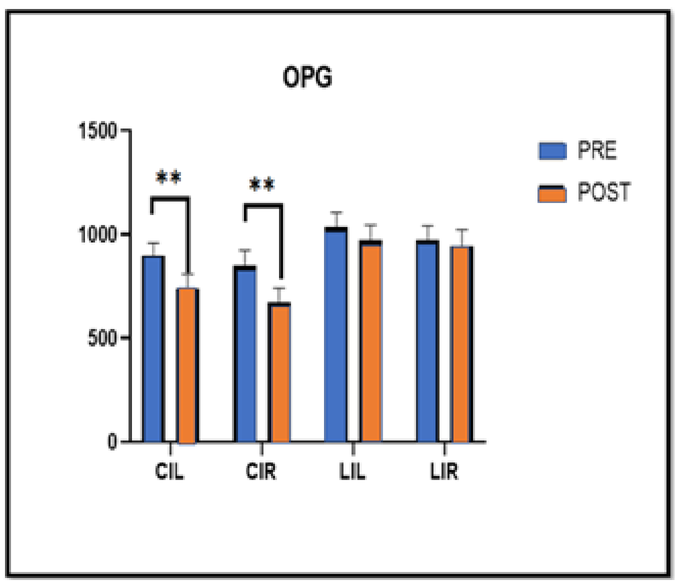


Table 4 (figure 9) shows the value of pretreatment and post treatment RANKL levels. It was seen that there was a statistically significant increase of RANKL in LIR teeth, whereas non-significant increase was seen in rest of the teeth examined, when pretreatment and post treatment values were compared. Highest amount of increase was seen in lateral incisor right teeth (301.43 ng/ml) and the least amount of increase was seen in lateral incisor left teeth (44.5 ng/ml).

Table 4: Pretreatment and Post treatment values of RANKL

RKL	PRE	POST	Mean Difference	Trend	p-value	Remarks
CIL	828.83+131.05	900.5+59.85	71.68	increase	0.149	not significant
CIR	805.08+127.29	871.88+48.34	66.8	increase	0.145	not significant
LIL	1144.63+84	1189.13+188.02	44.5	increase	0.325	not significant
LIR	969.75+72.85	1271.18+200.99	301.43	increase	0.01	Significant

Table 5 (figure 10) shows the pretreatment and post treatment levels of DMP 1 , it was seen that there was statistically non-significant increase in level of DMP 1 observed from pretreatment to post treatment for all the teeth examined. Highest increase was seen in LIL teeth (98.13 ng/ml) and minimum was seen in CIL teeth (0.87 ng/ml).

Table 5: Pretreatment and Post treatment value of DMP 1

DMP	PRE	POST	Mean Difference	Trend	p-value	Remarks
CIL	870.51+81.83	871.38+137.78	0.87	increase	0.496	not significant
CIR	791.88+72.2	838.3+132.55	46.43	increase	0.295	not significant
LIL	1029.23+80.2	1127.35+178.25	98.13	increase	0.135	not significant
LIR	967.95+70.86	1033.43+163.4	65.47	increase	0.197	not significant

Figure 9: Pretreatment and Post treatment values of markers RANKL

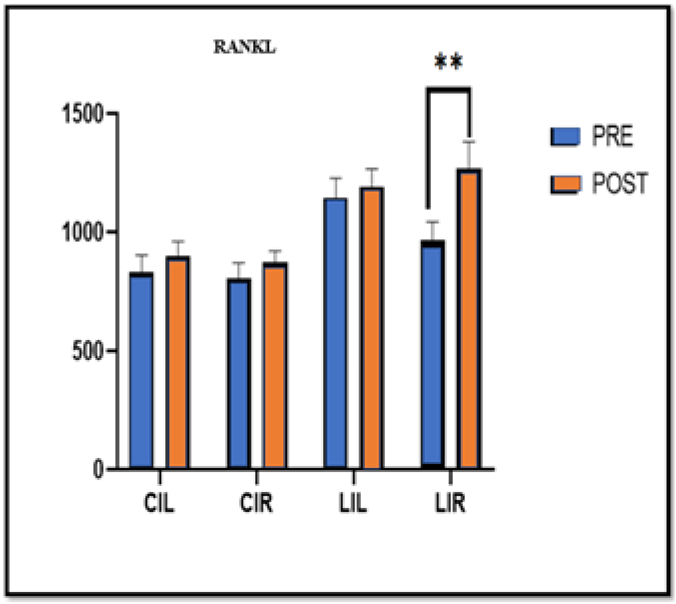


Figure 10 Pretreatment and Post treatment values of DMP 1 Marker

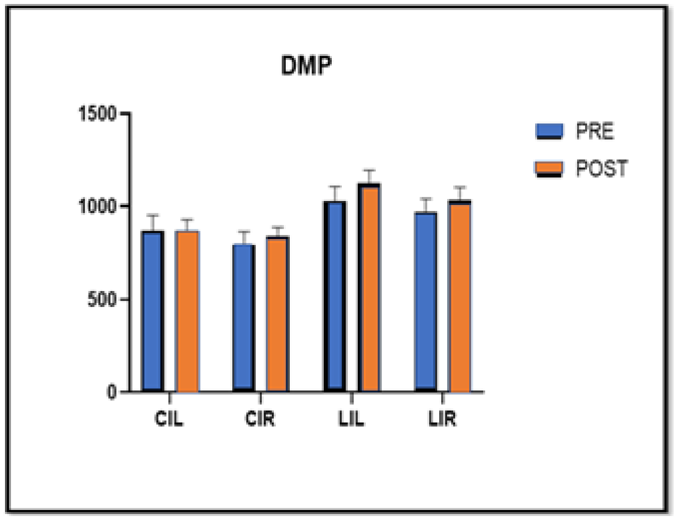


Table 6 (figure 11) shows pre and post treatment changes in DSP marker. It showed that there was a significant increase of DSP marker values in LIL teeth, whereas a non-significant increase was seen in CIL,CIR and LIR teeth. Highest increase was seen in LIL teeth (169.25ng/ml) and minimum was seen in CIL teeth (81 ng/ml).

Table 6: Pretreatment and post treatment changes in DSP marker.

DSP	PRE	POST	Mean Difference	Trend	p-value	Remarks
CIL	870.37+77.16	951.38+150.43	81	increase	0.213	not significant
CIR	832.89+81.6	937.68+148.26	104.79	increase	0.166	not significant
LIL	939.98+88.73	1109.23+175.38	169.25	increase	0.037	Significant
LIR	1069.73+70.86	1195.08+188.96	125.35	increase	0.15	not significant

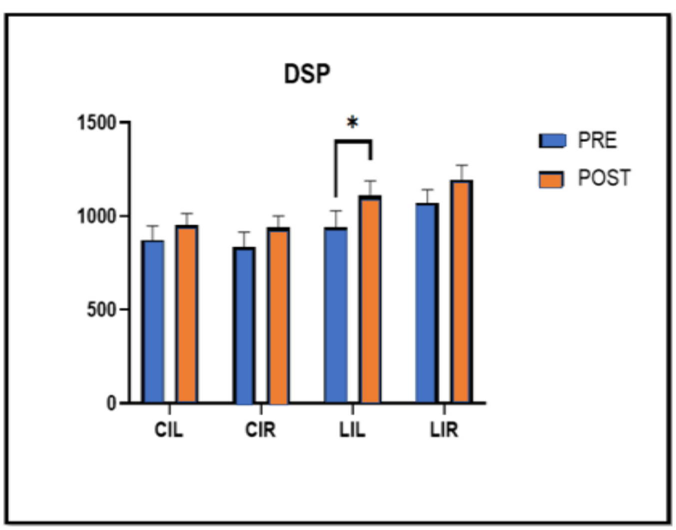
Correlation between markers and root resorption was assessed using the Pearson's correlation test (Table 7). It was found that decrease in OPG level is significantly correlated with root resorption and increase in RANKL level is significantly correlated with root resorption. No correlation was obtained for DSP and DMP markers increase with root resorption.

Table 7: Pearson's correlation test

Variables	Pearson's r coefficient	P-Value	Significance
OPG	-0.69	0.05	*
RKL	0.2	0.01	**
DSP	0.04	0.62	-
DMP	-0.03	0.7	-

Note: *p<0.05,**p<0.01,***p<0.001

Figure 11: Pretreatment and Post treatment values of marker DSP



Discussion

Orthodontic treatment is frequently accompanied by concerns about apical root resorption. Apical root resorption becomes irreversible when it extends to the dentin. The loss of the cells that cover the tooth roots' surface, the activity of osteoclast cells, and hyalinization are characteristics of ARR.

In current study, the apical root resorption of maxillary incisors before and 6 months after fixed orthodontic treatment was assessed, it was seen that there was a significant reduction in root length in the post treatment sample of all the teeth examined, suggesting of significant root resorption in all the teeth examined, where it was highest for LIL [0.79±0.2 mm] and lowest for CIR [0.38±0.1 mm].

The maxillary incisors, maxillary premolars, and mandibular second premolars were shown to have the highest incidence of apical root resorption by **Newman et al**[10] when they looked into external root resorption. The root resorption in all tooth groups was compared by **Apajalahati S et al**[11] using pre- and post-treatment panoramic radiography. Mandibular and maxillary incisors revealed the most apical root resorption among the tooth groups evaluated.

In this study, difference in pretreatment and post treatment values of dentin marker levels and bone marker levels were evaluated using ELISA technique. There was statistically significant reduction of OPG levels seen in post treatment values as compared to pretreatment values in all the teeth examined. This result was in accordance to the study conducted by **M. Yamaguchi et al**[12] **and Widayati R et al**[13] which indicated that the alterations were more pronounced in the severe root resorption group, the increase in osteoclast production in the severe root resorption group was mediated by a reduced level of OPG. The periodontal ligament's extracellular matrix is distorted by orthodontic forces, which also change cellular structure and cytoskeletal organisation. Both root and bone resorption are regulated by RANKL/RANK/OPG, and the underlying cellular mechanisms seem to be similar. Odontoblasts and PDL-fibroblasts both express OPG. Due to mechanical stress from orthodontic movement, RANKL is involved in root resorption. PDL cells increase RANKL but decrease OPG expression, which indicates root resorption.

In the current study, it was concluded that RANKL levels were significantly higher in LIR teeth whereas non-significant increase was seen in rest of the teeth examined, after 6 months of orthodontic treatment and this was in accordance with studies conducted by **George A and Evans CA[14], M. Yamaguchi et al[12], . T. Kojima et al[15], O Liliana et al[16], Kapoor P et al[17].**

Patients' compressed PDL cells with significant root resorption produced high levels of RANKL, reduced the generation of OPG, and induced the development of osteoclasts[12].

It has been hypothesised that the RANK/RANKL system is crucial for osteoclast activation during orthodontic tooth movement[15]. Orthodontic force compresses the PDL, which causes PDL to increase RANKL levels. The expression of RANKL during the application of orthodontic forces is involved in osteoclast precursor signalling, and it has also been discovered that RANKL is expressed by odontoclast cells, which are involved in root resorption. The normal process of root resorption in exfoliated primary teeth may also be controlled by the RANK/RANKL system. Therefore, root resorption brought on by the application of orthodontic forces involves the RANK/RANKL system.

When DSP levels were examined for this current study, it was found that there was a significant increase seen LIL teeth and a non-significant increase was seen for rest of the teeth examined, these data were in accordance to studies conducted by **Sha et al[7], K shalene et al[8], B laura et al[9], Uma HL and nausheerahmed[18], Mona M et al[19]., Kapoor P et al[17]**.

During active external root resorption, a particular protein called dentine sialophosphoprotein (DSPP) is secreted into the periodontal ligament space. Dentine sialoprotein and dentine phosphoproteins are N- and C-terminal proteolytic cleavage products of DSPP. DSPP can therefore be referred to as a marker for identifying root resorption.

DSP are dentin-specific matrix proteins that have been proposed to be involved in the mineralization of pre-dentin into dentin since root resorption is a frequent side effect of orthodontic treatment. A biological marker for root resorption may be determined by calculating the amount of DSP produced during root resorption. Only on the pulpal surface does secondary dentin continuously deposit during life. Remodelling in dentin is different from bone so, these proteins are not regularly released into the surrounding area. These proteins can only be released into the periodontal ligament space when there is active external root resorption.

For DMP 1 marker , it was noted in current study that there was a non-significant increase of the marker levels seen in all the teeth examined post orthodontic treatment . This Non-significant increase may be due to less time period and less sample size which was taken for the current study, this data was in accordance to study conducted by **B laura et al[9], Mah J. Prasad N[20], Mona M et al[19], Kapoor P et al[17]**

However, in a study done by **Mona M. Et al[19]** ,Dentin-specific markers such as DMP 1, DSPP, and its functional domains DPP and DSP, were found to be promising biomarkers for ERR. It's possible that enhanced bone remodelling during orthodontic tooth movement in addition to continuous resorption activity is the cause of DMP 1 presence in crevicular fluid[9].

Conclusion

The following results can be drawn from the present study-

The extent of apical root resorption after 6 months of orthodontic treatment was found to be statistically significant for all the maxillary incisor teeth examined using RVG . The maxillary left lateral incisor teeth showed the greatest amount of root resorption once all four teeth were examined, whereas the maxillary right central incisor teeth showed the least degree of root resorption.

Amount of root resorption was found to be significantly co-related with decrease in OPG levels and increase in RANKL levels. DSP and DMP 1 were not found to be significantly correlated to root resorption.

Considering bone marker levels, it was found that there was a significant decrease in OPG levels and increase in RANKL levels. Considering dentin markers, it was found that there was a significant increase in DSP marker and non-significant increase in DMP marker after 6 months of orthodontic treatment.

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