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# EVALUATION OF RISK FACTORS FOR SEVERE APICAL ROOT RESORPTION IN THE MAXILLARY INCISORS FOLLOWING FIXED ORTHODONTIC TREATMENT

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## BEYAN

Bu tezin kendi çalışman olduğunu, planlamasından yazımına kadar hiçbir aşamasında etik dışı davranışımın olmadığını, tezdeki bütün bilgileri akademik ve etik kurallar içinde elde ettiğimi, tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara kaynak gösterdiğimi ve bu kaynakları kaynaklar listesine aldığımı, tez çalışması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığını beyan ederim.

Bashar Mohammad Daoud Shahrure

İmza

## STATEMENT

Hereby I declare that this thesis study is my own work, I had no unethical behavior in any stage from planning of the thesis until writing it, I have obtained all the information in this thesis within the academic and ethical rules, I have cited all the information and comments that are not obtained with this thesis study, and these sources are also included in the list of references, I hereby declare that I have no infringement of patents and copyrights during the study and writing of this thesis.

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Signature

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## II. CONTENTS

## III. ABBREVIATIONS

- 2D: Two-dimensions.
- 3D: Three-dimensions.
- AAC: Acellular Afibrillar Cementum.
- AC: Aesthetic Component.
- AEFC: Acellular Extrinsic Fiber Cementum.
- ANS: Anterior nasal spine.
- BMP: Bone morphogenetic proteins.
- CBCT: Cone beam computed tomography.
- CEJ: Cemento-enamel Junction.
- CIFC: Cellular Intrinsic Fiber Cementum.
- CMSC: Cellular Mixed Stratified Cementum.
- CT: Computed tomography.
- DHC: Dental Health Component.
- EARR: External apical root resorption.
- ECR: External cervical resorption.
- EGF: Epidermal growth factor.
- EIR: External inflammatory resorption.
- ESR: External surface resorption
- FGF: Fibroblast growth factor.
- IGF: Insulin growth factors.
- IIR: Internal inflammatory resorption.
- IL-1B: Interleukin 1 beta.

- IOTN: Index of Orthodontic Treatment Need.
- IRR: Internal replacement root resorption.
- NSAIDs: Non-steroidal anti-inflammatory drugs.
- OPG: Osteoprotegerin.
- OPT: Panoramic radiograph.
- PNS: Posterior nasal spine.
- PTH: Parathyroid hormone.
- RANKL: Receptor activator of nuclear factor kappa-B ligand.
- RANKL: Receptor activator of nuclear factor kappa-B.
- SNP: Single nucleotide polymorphisms.
- TGF-$\beta$: Transforming growth factor-$\beta$.
- TNF: Tumor necrosis factor.
- TNSALP: Tissue-nonspecific alkaline phosphatase.

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**Sabit Ortodontik Tedaviyi Takiben Maksiller Keser Dişlerde Oluşan Şiddetli Kök Rezorpsiyonun Risk Faktörlerinin Değerlendirilmesi**

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## 1. ÖZET

**Amaç:** Bu çalışmanın amacı maksiller kesici dişlerde, sabit ortodontik tedavi sırasında şiddetli dış kök rezorpsiyon prevalansın (Malmgren *et al.* Skor 4) retrospektif olarak belirlemek ve kök rezorpsiyonu için olası predispozan faktörleri değerlendirmektir.

**Gereç ve Yöntem:** Dış kök rezorpsiyonunun potansiyel predispozan faktörlerini belirlemek için 1990-2019 yılları arasında tedavi edilen 7000 hastanın tedavi kayıtları incelendi, hastaların kayıtlarından aşağıdaki veriler alındı: tedavinin başlangıcındaki yaş, cinsiyet, kök morfolojisi , overjet, overbite, tedavi yöntemi (çekim, çekimsiz), tedavi süresi, maksiller kesici kısımlardaki bukkal ve palatal alveoler kemik kalınlığı ve insizal kök apislerinin ve insizal kenarların hareket miktarı. Kök rezorpsiyonu ile predispozan faktörler arasındaki ilişki (chi square) testi ile değerlendirildi.

**Bulgular:** Şiddetli dış kök rezorpsiyonu prevalansı% 3.23 idi ve sonuçlar değişkenler için gruplar arasında anlamlı bir farklılık olduğunu göstermiştir: tedavi modalitesi (çekim), artmış tedavi süresi, alveolar kemiğin kortikal kalınlığı ve tedavi sonunda kesici hareket miktarı.

**Sonuç:** Çekim, artan tedavi süresi, ince alveolar kemik ve aşırı kesici diş hareketinin ortodontik tedaviyi takiben maksiller kesici dişlerde ciddi kök rezorpsiyonu için risk faktörleri olduğu sonucuna varılabilir.

**Anahtar kelimeler:** Ortodonti, eksternal kök rezorpsiyonu, anterior dişler, kök morfolojisi, kemik kalınlığı.

**Evaluation of risk factors for severe apical root resorption in the maxillary incisors following fixed orthodontic treatment**

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## 2. SUMMARY

**Objective:** The aim of this study was to retrospectively determine the prevalence of severe external root resorption (Score 4 according to Malmgren *et al*.), in maxillary incisors, during fixed orthodontic treatment and to evaluate the possible predisposing factors for root resorption.

**Material and Methods:** The treatment records of 7000 patients who have been treated between years 1990 and 2019 at the Department of Orthodontics Faculty of Dentistry Marmara University were examined to determine the prevalence and the predisposing factors of external root resorption. The following data was retrieved from the patients' records: age at the beginning of the treatment, gender, root morphology, overjet, overbite, treatment modality (extraction, non-extraction), treatment duration, buccal and palatal alveolar bone thickness for the maxillary incisors, and amount of movement of the incisal root apices and incisal edges. The relationship between root resorption and the predisposing factors was assessed using chi square and independent t-tests.

**Results:** The prevalence of severe external root resorption was 3.23%, and the results have demonstrated significant difference between the groups for the variables: treatment modality (extractions), increased treatment duration, cortical thickness of the alveolar bone, and amount of incisor movement at the end of the treatment.

**Conclusion:** It can be concluded that extractions, increased treatment duration, thin alveolar bone, and excessive incisor movement represent risk factors for severe root resorption in maxillary incisors following orthodontic treatment.

**Keywords:** Orthodontics, external root resorption, maxillary incisors, root morphology, bone thickness.

# 3. INTRODUCTION AND AIM

External apical root resorption (EARR) is an undesirable side effect commonly associated with orthodontically induced tooth movement (Årtun et al., 2009; Bartley et al., 2011). As it is considered a borderline phenomenon between cost-benefit and iatrogenesis, root resorption gained its importance due to being highly frequent with potential biological damage to the patients. Moreover, it has potential legal implications in daily orthodontic practice.

External apical root resorption (EARR) is part of the biological reaction of the orthodontic treatment; notwithstanding, it should not be considered as either normal or physiologic, but clinically acceptable. Many approaches and guidelines can prevent the occurrence of this pathology during orthodontic treatment, thereby avoiding and reducing the number of teeth affected or its severity (Consolaro, 2005).

The diagnosis of (EARR) is generally performed using periapical and panoramic radiographs (Blake et al., 1995; Rego et al., 2004; Sameshima and Sinclair, 2001) , and it is usually asymptomatic; only when partial root loss due to severe resorption occurs is when the function and retention of the affected teeth may be compromised (Dudic et al., 2009; Picanço et al., 2013). Malmgren proposed a teeth classification into scores (Malmgren et al., 1982) to assess EARR severity. It is a visual qualitative method that is relatively subjective, and it has the advantage of not depending on the standardization of the radiograph (Martins et al., 2012).

Root resorption classification score according to Malmgren *et al*. (Malmgren et al., 1982) is as follows: Score 0 – absence of resorption; Score 1 – irregularity in the apical root contour; Score 2 – resorption of up to 2 mm; Score 3 – resorption from 2 mm up to 1/3 of the root; Score 4 – loss greater than 1/3 of the root length.

Most cases of EARR are mild and clinically insignificant (Harry and Sims, 1982). However, the longevity of the dentition and, consequently, the stability of the orthodontic treatment could be at risk, if there is moderate resorption limited to one third of the apex, and more particularly in cases of severe resorption affecting more than one third of root length.

The etiology and mechanisms of action of EARR of orthodontic origin are not entirely clear; several studies (Kurol and Owman-Moll, 1998; Mirabella and Årtun, 1995; Owman-Moll et al., 1996) have discussed a multifactorial etiology involving both individual factors (age, systemic disease, individual susceptibility, root morphology, genetic factors, etc.) and factors related to the orthodontic treatment (duration, extractions, type of appliance, force applied, amplitude of movement, etc.).

Anterior maxillary teeth are proved to be more likely to present severe EARR than teeth located in the mandibular arch (Liou and Chang, 2010). It was also shown that patients treated with intrusion mechanics combined with anterior retraction had statistically greater maxillary incisor root resorption than those treated with anterior retraction without intrusion (Martins et al., 2012). This can happen due to the greater tooth movement needed to close extraction spaces (Freitas et al., 2007; Mirabella and Årtun, 1995), especially when associated with intrusive mechanics (Chiqueto et al., 2008), and torque movement (Parker and Harris, 1998), which overburdens the dental root apex.

In addition to the previous factors, factors like proximity between the roots of maxillary central incisors and the cortical bone of the socket, the incisive canal and the alveolar bone on the buccal surface, combined with the type of movement may explain the higher incidence of severe EARR in these teeth (Motokawa et al., 2012).

On the other hand, if the extraction space is used to relieve crowding, which is most likely to occur in the mandibular arch, incisors might not undergo major retractions (Nanekrungsan et al., 2012).

It was found that teeth with complete root formation at the beginning of the orthodontic treatment are more likely to develop severe EARR. Teeth with incomplete root formation at the beginning of orthodontic treatment continue to develop their roots during therapy (Lopatiene and Dumbravaite, 2008).

The periodontal ligament of adult patients becomes less vascularized, aplastic and narrow; the bone becomes denser, avascular and aplastic; and the cementum wider (Nanekrungsan et al., 2012).

The severity of malocclusion, rather than its type (e.g. Angle's classification) (Mirabella and Årtun, 1995), is a determining factor in the amount and type of tooth movement as well as in the orthodontic mechanics used and the duration of orthodontic treatment. This leads to the fact that EARR has a multifactorial cause, regardless of the sagittal characteristics of malocclusion.

Despite the increasing number of reports in the literature, no study has attempted to discuss or analyze the prevalence, and the predisposing factors of severe apical root resorption in the maxillary incisors in patients treated at Marmara University, Faculty of Dentistry, Department of Orthodontics. Therefore, the aim of this retrospective study was to determine the prevalence of severe external root resorption (Score 4 according to Malmgren *et al.*), in maxillary incisors, during fixed orthodontic treatment and to evaluate the possible predisposing factors for root resorption. Our study will be useful as self-assessment for practitioners in our department, as it will have positive impact in obtaining ideal orthodontic outcomes. By helping practitioners to determine potential risk factors, we will be able to plan the orthodontic treatment with taking in consideration the predisposing factors related to the development of apical root resorption. Therefore, our work will be directed toward delivering the most favorable treatment modality.

# 4. GENERAL INFORMATION

## 4.1. Orthodontics

### 4.1.1. What is Orthodontics?

Orthodontics is that division of dentistry that deals with the prevention and correction of irregularities of the teeth, generally entailing the straightening of crooked teeth or the correcting of a poor bite, or physiologically unacceptable contact of opposing dentition, which may be caused by imperfect development, loss of teeth, or abnormal growth of jaws. Moreover, Orthodontics is the only branch in Dentistry that uses inflammation to obtain an aesthetic outcome (teeth movement).

## 4.2. Malocclusion

Malocclusion can be defined as the deflection from the normal relation of the teeth to the other teeth in the same arch and/or to the teeth in the opposing arch (White et al., 1976). However, many variations are possible within a state of normality. Malocclusion and craniofacial complex anomalies can affect the quality of life and have adverse psychological and social impact on an individual. Orthodontic treatment provides the correction of malocclusion and facial anomalies caused by dental or skeletal discrepancies to achieve esthetic, psychosocial and functional improvements (Zhou et al., 2014). Normal occlusion was first clearly defined by Angle (1899) which was the occlusion when upper and lower molars were in relationship such that the mesiobuccal cusp of upper molar occluded in buccal cavity of lower molar and teeth were all arranged in a smoothly curving line (Proffit et al., 2007).

### 4.3. The Need of Treatment

The Index of Orthodontic Treatment Need (IOTN), involving the Dental Health Component (DHC) and the Aesthetic Component (AC), is the tool most frequently used for measuring treatment need, as it helps dentists and orthodontists to decide and understand the severity of the problem and in turn help them to judge the need of treatment. Considerations as to no treatment need, borderline need, or great need were based on five grades in the (DHC) and 10 grades in the (AC) (Bilgic et al., 2015).

### 4.4. Tooth Movement

Tooth movement results due to prolonged internal and external stimuli, that exceed the bio-elastic limits of tooth supporting structures, and it is the tissue natural response to these stimuli which leads to adaptive remodeling of the periodontal ligament and alveolar bone.

#### 4.4.1. Pathological tooth movement

Pathological tooth movement or migration can be defined as the change in tooth position that occurs when there is disruption of forces that maintain teeth in a normal relationship (Agrawal and Siddani, 2011). It is more concerned in facial aesthetics as it has an impact more in adults.

Literature suggests, the most relevant and affecting factor in pathological tooth movement is the disruption of periodontium. Moreover, any disease may result in pathological tooth movement by disrupting the equilibrium in the oral cavity (Helm and Petersen, 1989).

### 4.4.2. Physiological tooth movement

Physiological tooth movement is a slow process that occurs mainly in the buccal direction into cancellous bone or because of growth into cortical bone (Krishnan and Davidovitch, 2006). It primarily refers to the slight tipping of the tooth in its socket, and secondarily to the changes in the position of the tooth that occur during and after tooth eruption (Işeri et al., 2010). In addition, human teeth tend to drift and move toward the midline throughout life. As this movement occurs mainly because of mastication forces which can be viewed as an adaptation of teeth to the loss of interproximal tooth substance in result of wear in contact areas, and as a tendency of teeth to keep in tight contact (Sicher and Weinmann, 1944).

### 4.4.3. Orthodontic tooth movement

Tooth movement by orthodontic force application is mainly characterized by remodeling changes that are caused by mechanical loading that is varying in magnitude, frequency, and duration, in dental and paradental tissues, including dental pulp, periodontal ligament (PDL), alveolar bone, and gingiva. When exposed to such forces, these tissues express extensive macroscopic and microscopic changes (Krishnan and Davidovitch, 2006). Orthodontic tooth movement can occur rapidly or slowly, depending on the physical characteristics of the applied force, and the size and biological response of the PDL (Meeran, 2013). These force-induced strains alter the PDL's vascularity and blood flow, resulting in local synthesis and release of molecules, such as neurotransmitters, growth factors, and cytokines. These molecules can initiate cellular responses with help of various cell types in and around teeth, to provide a favorable microenvironment for tissue deposition and/or resorption (Davidovitch, 1991; Davidovitch et al., 1988). There are four different types of orthodontic tooth movement according to loading force (moment-to-force ratios); tipping, root movement, translation, and rotation (Kuhlberg and Nanda, 2005).

#### 4.4.3.1. Tipping

When the force acting on the tooth results in greater movement of the crown more than the root, tipping occurs. In addition, in tipping movement the center of rotation of the motion is always apical to the center of resistance of the tooth. Therefore, tipping can be further classified into controlled and uncontrolled tipping on the basis of the location of center of rotation (Kuhlberg and Nanda, 2005) (Figure 4.4.3.3.1). Uncontrolled tipping indicates tipping with a center of rotation between the center of resistance and the apex. While controlled tipping is tipping with the center of rotation located at the root apex (Kuhlberg and Nanda, 2005). Uncontrolled tipping produces nonuniform stress at the apex and crown, in contrast, controlled tipping produces stresses that are greatest in cervical margin (Kusy and Tulloch, 1986; Wainwright, 1973).

#### 4.4.3.2. Translation

Tooth movement consisting of uniformly distributed stresses along the periodontal surface, results in bodily movement or translation (Kusy and Tulloch, 1986; Wainwright, 1973). However, this type of movement is extremely rare and very difficult to achieve (Upadhyay and Nanda, 2015) (Figure 4.4.3.3.1).

#### 4.4.3.3. Root movement

Mechanically, it is the same movement as tipping. However, the free movement here is for the root. The root moves freely when the center of rotation is located at the crown tip or the bracket (Upadhyay and Nanda, 2015). In addition, the stresses are the greatest in the apex (Kuhlberg and Nanda, 2005). Root movement is frequently described as "torque" (Figure 4.4.3.3.1).

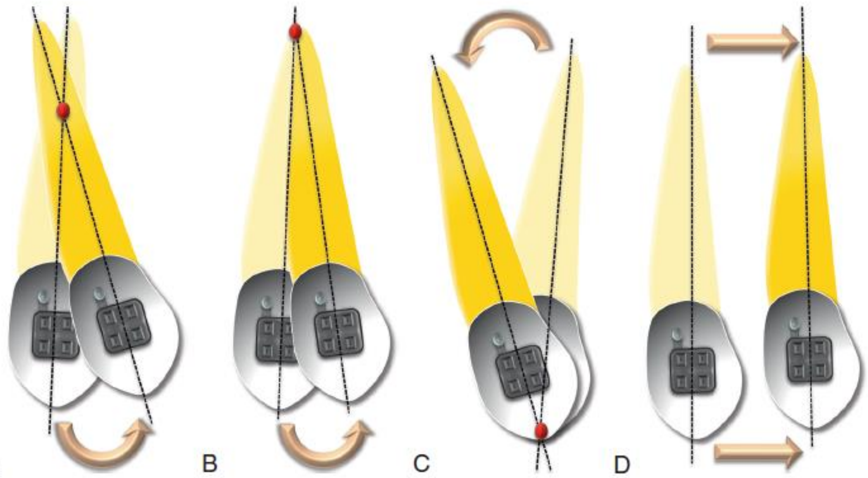



**Figure 4.4.3.3.1.** Types of tooth movement. A, Uncontrolled tipping. B, Controlled tipping. C, Root movement (torquing). D, Translation or bodily movement (Upadhyay and Nanda, 2015).

#### 4.4.3.4. Rotation

Rotation purely occurs when there is a couple, which means no net force acting on the center of resistance, and it is seen in the occlusal view (Kuhlberg and Nanda, 2005) (Figure 4.4.3.3.1).

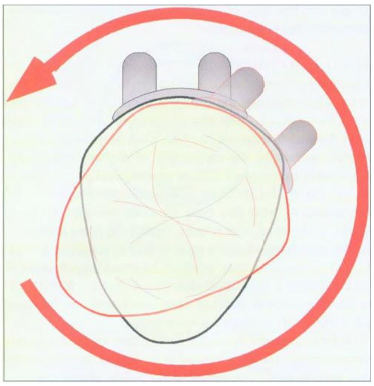


**Figure 4.4.3.4.1.** Rotation of maxillary premolar as seen in occlusal view (Kuhlberg and Nanda, 2005).

### 4.5. Tooth Root's Structure

#### 4.5.1. Cementum

Cementum, or root cementum, is a mineralized tissue covering the entire root surface; it is also referred to as a bone-like tissue. However, cementum is avascular, with no dynamic remodeling taking place, and it also increases in terms of thickness throughout individual's life. Concluding that cementum is markedly different from bone. Cementum has historically been classified into cellular and acellular cementum according to the presence of cells (cementocytes). Generally, acellular cementum is thin and covers the cervical root, whereas thick cellular cementum covers the apical root. It contains two types of fibers, extrinsic and intrinsic fibers. Intrinsic fibers are fibers of cementum proper. While extrinsic fibers, also called Sharpey's fibers, are embedded ends of the principal fibers. It is also believed that the extrinsic fibers are secreted by fibroblasts and partly cementoblasts, and that the intrinsic fibers are secreted by only cementoblasts (Yamamoto et al., 2016).

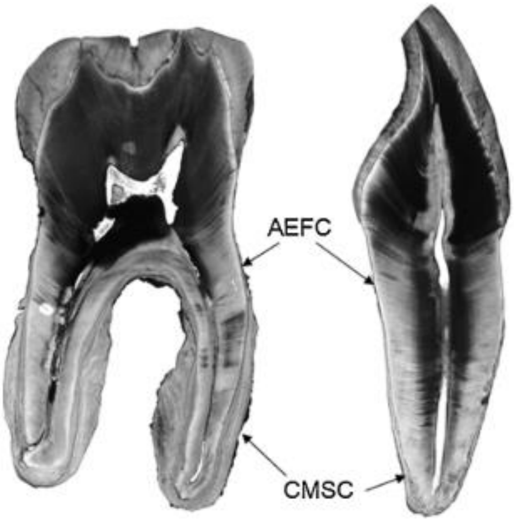
##### 4.5.1.1. Cementum classification

Three major types of cementum are distinguishable: Acellular extrinsic fiber cementum (AEFC) that contains no cementocytes and contains densely packed extrinsic fibers. Second type is Cellular intrinsic fiber cementum (CIFC), which contains intrinsic fibers, as well as cementocytes. Third major type is cellular mixed stratified cementum (CMSC), which corresponds to classical cellular cementum (Schroeder, 1993).

Acellular extrinsic fiber cementum (AEFC) covers the cervical root surface in both permanent and primary teeth. Increase in thickness is noticed with age for this type. It consists of mineralized layers of collagen fibers and non-collagenous organic matrix (Schroeder, 1992).

Cellular intrinsic fiber cementum (CIFC) is a component of the cellular mixed stratified cementum (CMSC), and contains extrinsic fibers as well as intrinsic fibers, with different thickness among individuals. Their extrinsic fibers often contain an unmineralized central core, surrounded by a highly mineralized cortical part (Bosshardt and Selvig, 1997).

Cellular mixed stratified cementum (CMSC) is often present in the interradicular and the apical parts of the roots. Occasionally, AEFC also appears as a component in addition to the main CIFC (Picture 4.5.1.1.1).




**Picture 4.5.1.1.1.** View of a mandibular molar (left), and a maxillary incisor (right).

Other varieties of cementum can be seen as the following: Acellular afibrillar cementum (AAC); which consists of a mineralized matrix, with no presence of collagen fibers or cementocytes. It is also found as the most cervical part of AEFC on enamel coronal to the cemento-enamel junction (CEJ). Last type is the intermediate cementum, which is concluded to be a part of dentin, not cementum (Yamamoto et al., 2016).

### 4.5.2. Dentin

Dentin is covered by cementum in the root, and by enamel in the crown of the tooth. Its composition is minerals (70% of weight), organic matrix (20% of weight), and water (10% of weight). The mineral part of dentin is predominantly hydroxyapatite, while the organic matrix is predominantly collagen, and the majority is Type I collagen (Goldberg et al., 2011).

Dentine is vital and highly innervated; which makes it a sensitive tissue, capable of responding to both chemical and mechanical external stimulations. Moreover, the high permeability to fluid-flow through the tubules suggest that dentin has a sensory function related to pressure that may be exerted on the outer surfaces (Zaslansky, 2008).

The formation of dentine starts with odontoblasts constantly secreting the organic matrix which is high in type I collagen. Until the tooth becomes functional, odontoblasts are important for the formation of the primary dentin (Goldberg et al., 2011). Odontoblasts are located in the outermost layer of dental pulp and they form a natural barrier between mineralized tissues, dentin, and soft tissues, dental pulp, they are also the first to recognize caries-related pathogens and sense any external irritation (Yumoto et al., 2018).

#### 4.5.2.1. Primary dentin

The primary dentin is formed before the eruption of tooth and until the moment it becomes functional. Primary dentin is further divided into mantle (peripheral) dentin, and circumpulpal dentin.

Mantle dentin is a thin layer formed by the odontoblasts in the early stages of differentiation (Figure 4.5.2.3.1). This layer is hypomineralized and increases in the mineralization slightly away from CEJ (Retrouvey et al., 2012).

The circumpulpal dentin is more mineralized than the mantle dentin and it includes the intertubular and peritubular dentins. Intertubular dentin forms after the transformation of predentin into dentin. It also forms the bulk of dentin, and is type I collagen rich. In contrast, the peritubular dentin does not result from the transformation of predentin into dentin, and it does not contain collagen fibrils, but is formed by non-collagenous proteins (Goldberg et al., 2011; Retrouvey et al., 2012).

#### 4.5.2.2. Secondary dentin

When contacts between antagonistic cusps are established, the formation of secondary dentin starts immediately, and it continues throughout individual's life (Figure 4.5.2.3.1). There is not much difference between primary and secondary dentin, the only difference is the accentuated S-curve in dentinal tubules in the secondary dentin (Goldberg et al., 2011).

#### 4.5.2.3. Tertiary dentin

The third and last type is tertiary dentin, also called reactionary or reparative dentin, is the dentin layer that forms as a reaction to carious decay or to abrasion (Goldberg et al., 2011). This occurs as a result of thermal, chemical, bacterial or mechanical trauma to the odontoblasts (Figure 4.5.2.3.1).

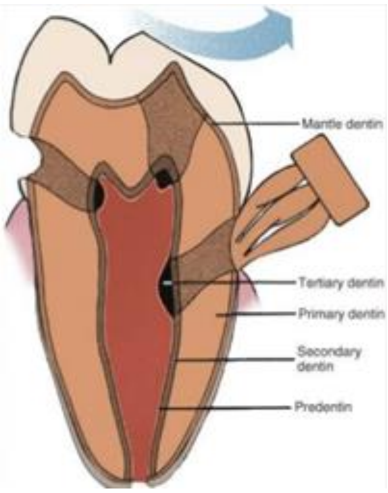



**Figure 4.5.2.3.1.** Types of dentin.

## 4.6. Root Resorption

### 4.6.1. Definition and classification

Root resorption refers to the noninfectious damage related to the loss of hard (cementum and dentin) and soft dental tissue (dental pulp) resulting from the clastic cell activity. Root resorption is considered physiological during the shedding of primary teeth, allowing the eruption of the permanent successors. In the permanent dentition, on the other hand, it is observed as a pathologic process that is predominantly asymptomatic (Aidos, 2018).

The simple classification of resorptive lesions can be as external or internal. In the former, the lesion occurs on the external surface of the root. In the latter, the lesion occurs inside the root, within the dentine of the root canal and/or pulp chamber (Darcey and Qualtrough, 2013).

Over time, several classification systems have been made for root resorption. However, the most used and widely acknowledged root resorption classification system is the one proposed by Andreasen. His classification divided root resorptions into internal (replacement and inflammatory), and external (superficial, replacement, and inflammatory) (Marinescu et al., 2019).

#### 4.6.1.1. Internal root resorption

Internal root resorption is a process that takes place inside the canal system of the tooth (Picture 4.6.1.1.1). In addition, there may be an association between internal resorption and processes that may damage the predentin as in traumatized/replanted teeth or those teeth that have undergone pulpotomy and crown preparations, as all these processes may allow osteoclastic action on the underlying dentin (Wedenberg and Zetterqvist, 1987).

Internal replacement root resorption (IRR) is most often seen as an irregularity in the radiographic image of the pulp cavity. A possible explanation for this appearance may be that metaplasia of pulp tissue occurs, leading to a deposition of bone in the pulp canal (Andreasen, 1970). This type is rare, and may lead to obliteration of the canals space with cancellous-like bone (Darcey and Qualtrough, 2013).

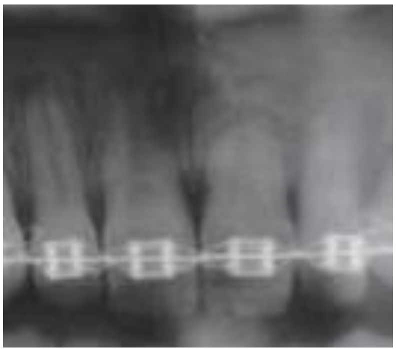
Internal inflammatory resorption (IIR) is mainly characterized by an appearance of ovoid or fusiform enlargement of pulp chamber or root canal, and it can spread laterally and apically (Darcey and Qualtrough, 2013). Inflammatory resorption is only seen in case of pulp necrosis and severe periodontal injury (Andreasen, 1970).

**Picture 4.6.1.1.1.** Resorption of the dentine within 21 presents as expansion of the root canal.

### 4.6.1.2. External root resorption

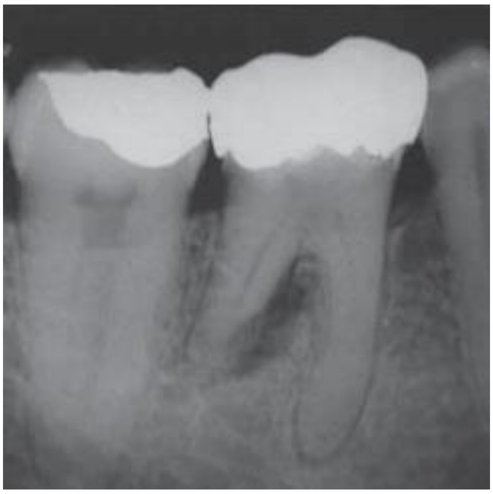
External root resorption is an irreversible loss of the outer root structure. And it can be divided to three types.

External surface resorption (ESR) is a transient and non-inflammatory process (Picture 4.6.1.2.1). These resorptions are usually self-limiting; they stop when the cause is removed. The repair of this type is mainly cementum with no reformation of dentin (Andreasen, 1985). This process is unlikely to be reported as it is known to be a subclinical situation (Tronstad, 1988). Surface resorptions are only diagnosed by radiographs; clinical examination is unremarkable and the pulp continues to be sensitive (Andreasen, 1985).



**Picture 4.6.1.2.1.** External surface root resorption of the root apices of the anterior teeth.

External inflammatory resorption (EIR) occurs after episodes of prolonged stimuli, and commonly occurs after severe dental trauma injuries (avulsion and luxation) (Picture 4.6.1.2.2). Theses dental injuries may cause damage to the root surface, and as repairing process takes place, it involves root resorption (Patel and Ford, 2007). If the root canal system has become infected by bacterial toxins, they may reach the damaged root surface via the dentinal tubules, resulting in continuing of the external resorption as it stimulates the osteoclasts that attempt to remove these infected tissues (Andreasen, 1985; Tronstad, 1988). The diagnosis of external inflammatory resorption is primarily by radiographic examination, while the tooth will show no pulpal response.



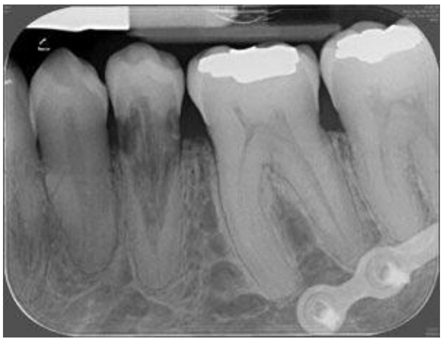
**Picture 4.6.1.2.2.** External inflammatory root resorption of the root of the lower right first molar.

External replacement resorption (ERR) is also known as ankylosis; the replacement of root surface with bone (Picture 4.6.1.2.3). It occurs as a result of periodontal ligaments necrosis (Andreasen and Kristerson, 1981). It is commonly associated with dental injuries including avulsion and luxation, where the periodontal ligaments become severely crushed or desiccated (Barrett and Kenny, 1997; Hammarström et al., 1986). The bone is being produced by the adjacent osteoblasts, after the non-vital periodontal ligaments are resorbed by osteoclasts, resulting in replacement of these tissues with bone, and fusion occurs to the root surface (Lindskog et al., 1985).

**Picture 4.6.1.2.3.** External replacement root resorption of the root of the upper anterior right central.

A new modified classification of Andreasen has been suggested, with the addition of further category into previous conditions as external cervical resorption (ECR) (Heithersay, 2004).

External cervical resorption (ECR) can be seen as a 'pink spot' in the cervical region of the crown, and it occurs when the cementum below the epithelial attachment of the gingiva becomes damaged, allowing microorganisms to provide the stimulus for the resorption process to continue (Patel and Ford, 2007). This type can be seen in radiographs, and the tooth shows an intact and visible root canal (Picture 4.6.1.2.4).



**Picture 4.6.1.2.4.** Extensive external cervical root resorption of the root of the lower left second premolar.

## 4.7. Orthodontically Induced External Apical Root Resorption

### 4.7.1. External apical root resorption

External apical root resorption (EARR) can be defined as shortening of the tooth from its apex. Literature reported that the apical third of the root is prone to resorption, which might be due to the fact that the outer surface of this zone contains cellular cementum, whereas the middle and the coronal thirds contain acellular cementum (Pamukçu et al., 2020). The effects of orthodontic factors on EARR are not fully understood but numerous studies comparing effects of multiple variables were done, reporting that many factors can be responsible and/or accelerate the root resorption in orthodontically treated patients such as: heavy forces, treatment duration, and genetic influence (Baumrind et al., 1996; Chan and Darendeliler, 2006a; Guo et al., 2016).

### 4.7.2. Severity of EARR

Maxillary incisors are more susceptible to external apical root resorption than other teeth (Janson et al., 2000; Levander and Malmgren, 1988). Malmgren's index for quantitative assessment of root resorption is the most common used and known description for degree of root resorption, and has described four scores; irregular root contour -Score 1, apical root resorption to less than 2 mm -Score 2, mild/minor resorption, root resorption apically from 2 mm to one third of the original root length -Score 3, moderate resorption, and root resorption exceeding one third of the original root length -Score 4, severe resorption (Malmgren et al., 1982) (Figure 4.7.2.1).

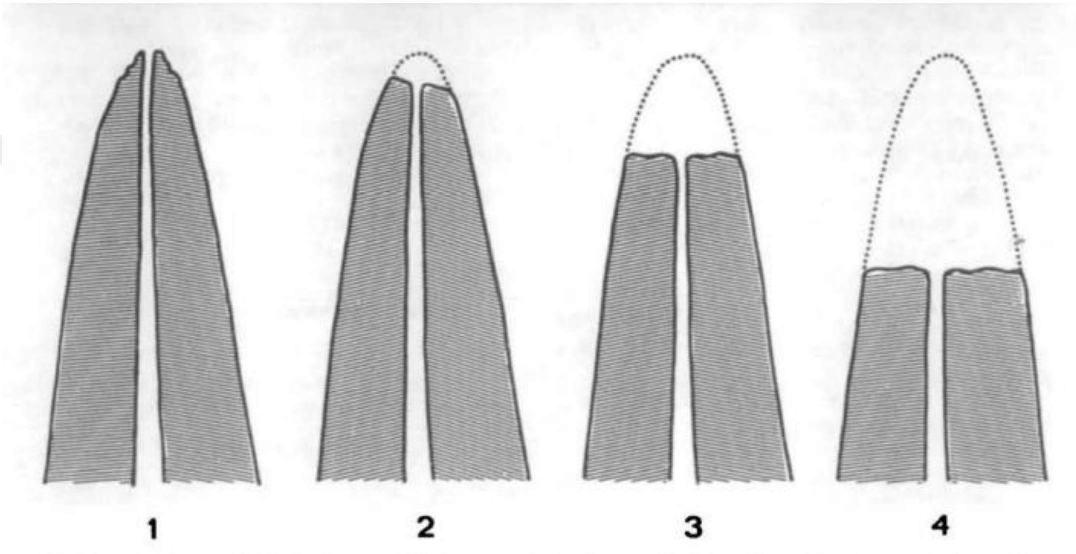



**Figure 4.7.2.1.** Root resorption index (Malmgren et al., 1982).

### 4.7.3. Prevalence of EARR

Root resorption has been reported in individuals that are orthodontically treated and untreated. Studies have reported that orthodontically induced root resorptions after 2 months of treatment can be detected histologically, but may not observable on serial radiographs. In one study that contained 625 patients, the incidence of mild to moderate root resorption following orthodontic treatment was 68%, while 32% of patients presented with severe external root resorption (Apajalahti and Peltola, 2007). In another study that included 1049 patients, severe root resorption was observed in 14.5% of the sample (Marques et al., 2010). Other studies have reported lower rate with incidence of 2.9% in sample of 129 patients (Mauès et al., 2015).

The degree of external apical root resorption is different in each study, taking into consideration the treatment protocol, sample size, age range, forces applied, and many more factors that contribute to root resorption.

### 4.7.4. Etiological factors associated with EARR

External apical root resorption is seen to be complex multifactorial; with many factors contributing to its severity and degree. EARR results from a combination of genetic predisposition, individual variability and external factors (Harris et al., 1997, 1993; Killiany, 1999).

#### 4.7.4.1. Genetic factors

Some patients seem to have low resistance to EARR under mechanical stress, while others are more likely to experience severe EARR when subjected to the same conditions (Harris et al., 1997). In this context, Al-Qawasmi et al. investigated a possible linkage of EARR associated with orthodontic treatment with polymorphic targets in the RANK, TNSALP and TNF alpha genes in 38 of Caucasian families. The authors have found an evidence of linkage between post-orthodontic EARR and the genetic variant, D18S64, and these results suggest that this locus (which lies close to the RANK gene) may contribute to susceptibility to EARR (Al-Qawasmi et al., 2003).

Previously, Al-Qawasmi et al. identified linkage and linkage disequilibrium between the IL-1B gene and occurrence of EARR in orthodontically treated patients ($p=0.0003$), this study was concerned with 35 American families (Al-Qawasmi et al., 2003). Subjects homozygous for the first allele of the IL-1B gene were defined as having a 5.6-fold increased susceptibility of post-orthodontic EARR (>2mm) compared with those heterozygous subjects and those homozygous for allele 2. Indicating that the allele 1 of IL-1B gene may induce decreased levels of the IL-1 protein in vivo, increasing the risk of being affected by root resorption under orthodontic forces (Al-Qawasmi et al., 2003).

The majority of current information about the influence of genetic factors on EARR takes source from population association studies; larger samples are used mainly to help determine whether a specific nucleotide is more frequently associated in an affected cohort (Nieto-Nieto et al., 2017).

Another study of Borges et al. has studied the genes RANKL, RANK, and OPG. Regarding the analysis of polymorphisms in these genes, several SNPs in RANK and OPG were associated with EARR, but only the association of the rs3102724 in OPG remained after multivariate analysis, leading to the suggestion that this polymorphism may be proposed as a new marker for EARR susceptibility (Borges de Castilhos et al., 2019).

#### 4.7.4.2. Ethnicity

Sameshima and Sinclair in their study have reported that Asian patients had significantly less root resorption than the Hispanic and Caucasian patients for maxillary incisors and canines and the mandibular lateral incisor, while no sufficient data was obtained for the African-American patients, making the results invalid for statistical comparison (Sameshima and Sinclair, 2001, 2004).

A recent study of Wang et al. has found a significant ethnic result in terms of crown root ratio after orthodontic treatment between three different ethnic groups; Hispanic patients had lower mean root crown ratios in most teeth compared to both the Caucasians and African Americans (Wang et al., 2019).

#### 4.7.4.3. Chronological age

Some studies revealed that there is positive correlation between chronological age and root resorption. It results from the fact that all tissues involved in the root resorption process are subjected to changes with age, the periodontal membrane becomes less vascular, aplastic, and narrow, the bone more dense, avascular, and aplastic, and the cementum becomes wider. These changes are reflected by a higher susceptibility to root resorption seen in adults (Brezniak and Wasserstein, 1993).

On the other hand, other studies stated that no significant relationship is seen between root resorption and chronological age (Cheng et al., 2009).

#### 4.7.4.4. Dental age

Many studies showed that root resorption is seen less in partially formed roots in younger patients, stating that the roots appear to develop normally during the orthodontic treatment (Brezniak and Wasserstein, 1993). Moreover, teeth with incompletely formed roots reached their normal length after treatment as observed in a longitudinal study (Da Silva Filho et al., 2004).

#### 4.7.4.5. Gender

There are very few studies reported that female patients had higher incidence and severity in root resorption (Jiang et al., 2003). However, most of the studies reported that gender plays no significant role in root resorption (Consolaro, 2005; Harris et al., 1997; Parker and Harris, 1998; Picanço et al., 2013; Sameshima and Sinclair, 2001).

#### 4.7.4.6. Nutrition

According to Engstrom *et al*., root resorption has been demonstrated in animals lacking calcium and vitamin D in their diets (Engstrom et al., 1988). An experiment studied rat groups fed with diet deficient in calcium and vitamin D compared to control group with normal diet, has revealed that these rats had hypocalcemia, increased alkaline phosphatase activity, and increased circulating PTH (Engstrom et al., 1988). The increase in PTH resulted in increase in osteoclasts number in the periodontal ligament for the test group, which increased the bone resorption rate and more orthodontically induced root resorption was noticed.

#### 4.7.4.7. Alveolar bone thickness

Thin alveolus, inadequate to the demand of extensive tooth movement, is considered as a limitation of the orthodontic movement and can be considered as a risk factor for root resorption in orthodontic treatment (Handelman, 1996). In another study, it was noticed that narrow maxillary alveolar bone width contributes about 12% to the amount of root resorption during orthodontic treatment; this suggests that patients with narrow maxillary alveolar bone width are more susceptible to root resorption (Horiuchi et al., 1998).

#### 4.7.4.8. Habits

Parafunctional habits (bruxism, onychophagia –nail biting-, the habit of biting objects, tongue thrusting habit, and thumb sucking habit) were studied to assess and understand the correlation with root resorption following an orthodontic treatment. Although it showed high incidence of 33.17% in the sample, nail biting habit was not statistically significant for the development of severe external apical root resorption (Pastro et al., 2018). Biting objects habit and thumb sucking habit did not show also any significant results with the severe apical root resorption (Pastro et al., 2018). However, tongue thrusting habit associated with anterior open bite was reported as a factor for increasing the risk of EARR (Harris et al., 1997).

#### 4.7.4.9. History of previous trauma

Trauma to anterior teeth can cause root resorption prior to any orthodontic treatment (Darcey and Qualtrough, 2013). Previously traumatized teeth are more sensitive to further loss of root structure, and root resorption (Phillips, 1955). Nevertheless, traumatized teeth with no signs of root resorption prior to orthodontic treatment do not show any increased severity or degree of root resorption following orthodontic treatment in comparison with normal non-traumatized teeth (Malmgren et al., 1982).

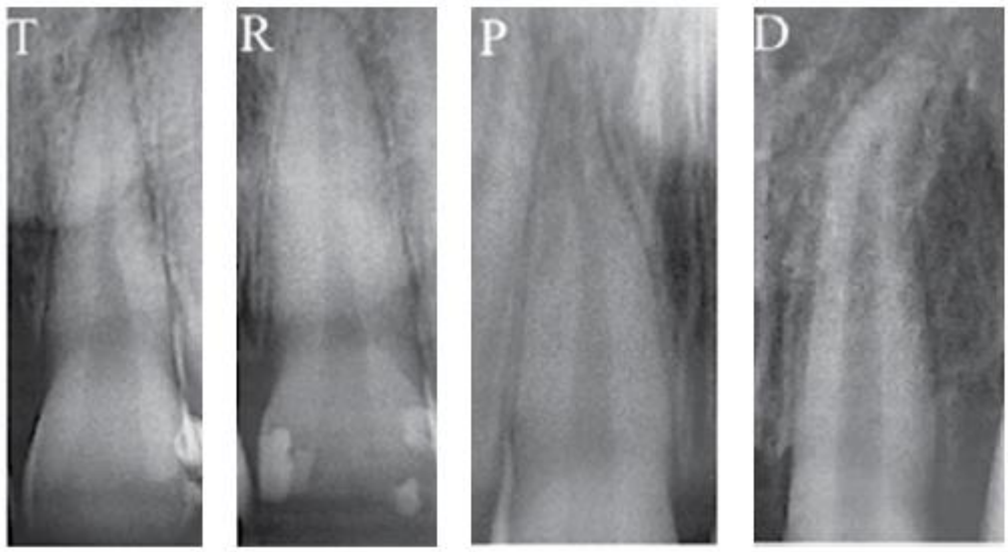
#### 4.7.4.10. Overjet and overbite

Increased overjet may contribute to the root resorption after orthodontic treatment, as more retraction needed for the maxillary incisors, putting them in higher forces, the same situation for deep bite and open bite cases, where intrusion or extrusion is needed as well (Bartley et al., 2011; Freitas et al., 2007). And combined movements of intrusion and retraction showed greater root resorption compared to retraction without intrusion (Martins et al., 2012). While other studies have reported no statistically significant results regarding overjet and overbite with EARR (Picanço et al., 2013).

### 4.7.4.11. Root morphology

As explained by Quintanilha *et al.*, maxillary anterior roots have four morphologies; triangular, rhomboid, pipette, and dilacerated (Quintanilha et al., 2019).

Studies reported that roots with atypical or irregular shapes are significantly associated with apical root resorption (Kjaer, 1995; Marques et al., 2010; Sameshima and Asgarifar, 2001). While in studies that presented more rhomboid roots in the sample, which according to most authors reduce the risk of resorption, there was no significant evidence of its contribution to root resorption (Picanço et al., 2013).




**Picture 4.7.4.11.1.** Root morphologies: triangular (T), rhomboid (R), pipette (P) and dilacerated (D) (Quintanilha et al., 2019).

### 4.7.4.12. Treatment duration

Treatment duration and incidence or severity of the EARR is controversial (Baumrind et al., 1996; Kaley and Phillips, 1991; Sameshima and Sinclair, 2001). Extended orthodontic treatment duration is cited to have contribution to apical root resorption in many studies (Jung and Cho, 2011; Liou and Chang, 2010), while other studies reported that no significant results shown to correlate orthodontic treatment duration with EARR (Årtun et al., 2009; Makedonas et al., 2013; Martins et al., 2012). Extended treatment duration might reflect more severe malocclusion and the need for different treatment mechanics, resulting in the need for longer period of time for treatment finishing (Mauès et al., 2015). Moreover, extended treatment duration may indicate a difficult treatment plan, and a non-cooperative patient, eventually leading to increased risk of EARR (Jung and Cho, 2011).

#### 4.7.4.13. Treatment modality

Studies concluded that there is an association between treatment type and root resorption (Motokawa et al., 2012). Treatments that did not require teeth extractions showed less incidence and severity of EARR (Lee et al., 1999; McFadden et al., 1989). Because of the need of retraction, more incisors movement, and longer treatment duration, treatments with extractions have been a risk factor for EARR (R. ping Jiang et al., 2010). Some authors reported that the application of inter-maxillary elastics is more likely to increase the risk of EARR (Levander et al., 1998). It was also reported in the literature that jiggling played a resorptive role as well (Baumrind et al., 1996).

#### 4.7.4.14. Magnitude of force applied

The main goal of orthodontic treatment is to move teeth as efficiently as possible with least damage to teeth and their supporting tissues. EARR may occur as an unwanted side effect of orthodontic movement, and may jeopardize successful treatment outcome.

Chan and Darendeliler examined extracted human teeth using volumetric analysis of resorption craters, and reported that teeth subjected to heavy-forces (250 g) are more susceptible to exhibit root resorption than teeth subjected to light-forces (25g) (Chan and Darendeliler, 2005). Using the same analysis, Harris *et al.* confirmed the finding of previous study, but for intrusive forces (Harris et al., 2006).

On the other hand, some authors found that increase in the orthodontically applied force magnitude has no significant correlation to EARR. In 144 adolescents, Owman-Moll studied the maxillary first or second premolars that were buccally moved with a fixed orthodontic appliance. When a continuous force of a clinically relevant magnitude (50 g) was applied, tooth movement increased gradually over time with no significant root resorption noticed. The force magnitude was doubled (100 g) and no effect in tooth movement or the severity of root resorptions was recorded. However, when the force was increased 4 times (200 g), tooth movement increased 50% but still with no significant increase in the incidence or severity of root resorptions (Owman-Moll, 1995).

#### 4.7.4.15. Direction of tooth movement

Intrusion is a critical type of orthodontic tooth movement in relation to EARR (Harris et al., 2006). Because intrusion is probably the most detrimental factor to the roots involved and to EARR, many studies were done to understand this correlation.

In a research studying the relationship between intrusion/extrusion with EARR, Han *et al.* found that intrusion causes 4 times more root resorption than extrusion, with significant results regarding extrusion reported as well (Han et al., 2005).

Moreover, patients in need of significant amount of retraction are more prone to root resorption, especially when combined with intrusion mechanics (Martins et al., 2011).

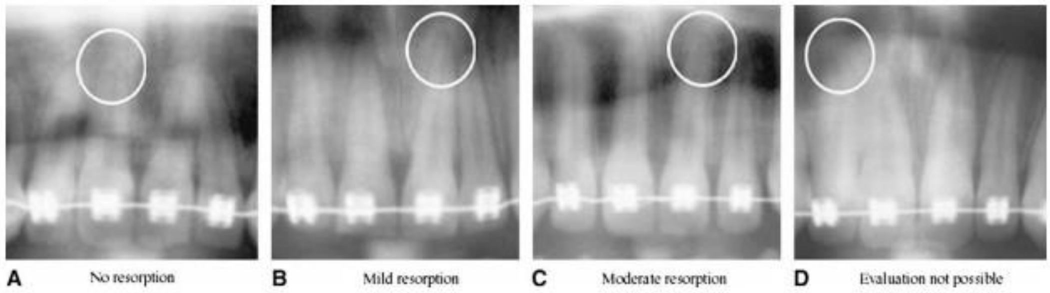
#### 4.7.4.16. Amount of tooth movement

The orthodontic forces applied to the teeth cause biological stresses on the periodontal ligament, operating equally and simultaneously on both tissues, the alveolar bone and cementum. If bone and cementum have a similar biological behavior, both are expected to be equally resorbed during tooth movement (Brezniak and Wasserstein, 2002). Cases with severe EARR are seen to be treated more frequently with tooth extraction. Therefore, in such cases, a higher amount of tooth movement is usually required, which in turn increases duration of orthodontic forces applied leading to higher chance and severity of EARR (Pastro et al., 2018). Patients submitted to tooth extractions have 2.72 times more chances of developing severe EARR according to study done by Pastro *et al*. (Pastro et al., 2018). And as extraction spaces are created, an increased movement and retraction of the apex of incisors are necessary to close extraction spaces, putting the apices under higher force magnitude, and longer treatment duration (Mauès et al., 2015).

### 4.7.5. Diagnosis of EARR

Diagnosis of EARR is done in most cases with the help of radiographs. Clinical examination is not reliable as clinical symptoms are almost absent, and increased tooth mobility is seen only in extremely severe cases with additional alveolar bone loss resulting through time (Jönsson et al., 2007). Moreover, EARR is being monitored before, during, and after orthodontic treatment usually by using two-dimensional radiographic (2D) methods like periapical or panoramic radiographs (OPT) (Makedonas and Hansen, 2008). However, apical root resorption occurring after orthodontic tooth movement is usually underestimated when evaluated on panoramic radiographs (Dudic et al., 2009) (Picture 4.7.5.1). This is because of (2D) image limitations; root resorption occurs in all aspects of root surface and in all three-dimensions, which masks the real amount of root resorption when evaluated by periapical or panoramic radiographs only

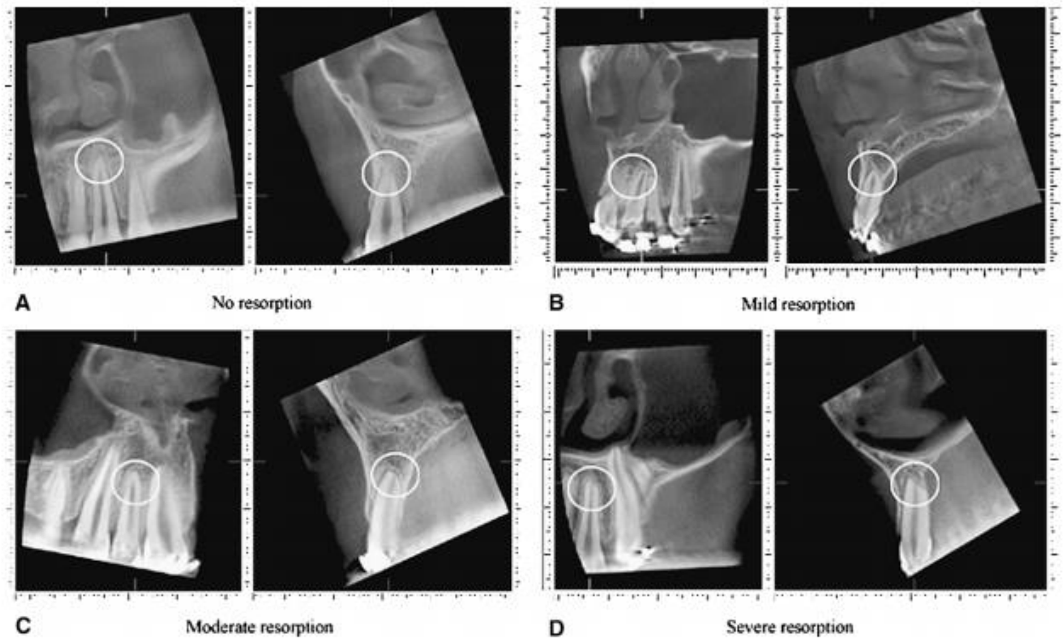
(Samandara et al., 2019). Additionally, the true extent of EARR might be misestimated due to magnification errors and problematic repeatability of this type of radiographs (Ren et al., 2013).




**Picture 4.7.5.1.** Index for evaluation of root resorption in the OPT: A, 0, no resorption in tooth 11; B, 1, mild resorption in tooth 21; C, 2, moderate resorption in tooth 21; D, evaluation impossible in tooth 12 (Dudic et al., 2009).

Cone beam computed tomography (CBCT) technology was introduced as a three-dimensional diagnostic method that offers imaging complex dental and maxillofacial structures (Ludlow et al., 2015). Compared with conventional computed tomography (CT), CBCT technology in dental practice has important advantages over the conventional CT such as minimization of the radiation dose up to 15-times, image accuracy, rapid scan time, and minimal distortion (Scarfe et al., 2006). The ability to produce distortion-free and reproducible image of roots made this technology gain a diagnostic value in the diagnosis of EARR (Dudic et al., 2009). Furthermore, three-dimensional reproduction of 2D CBCT cuts empowers precise evaluation of both linear and volumetric EARR measurements, and compensates for changes in root position or angulation amid orthodontic treatment (Akyalcin et al., 2015; Holberg et al., 2005).

In conclusion, CBCT tends to be a reliable method for analyzing EARR before or after orthodontic treatment (Samandara et al., 2019) (Picture 4.7.5.2).




**Picture 4.7.5.2.** Index for evaluation of root resorption in the CBCT: A, 0, no resorption in tooth 22; B, 1, mild resorption in tooth 21; C, 2, moderate resorption in tooth 12; D, 3, severe resorption in tooth 22 (Dudic et al., 2009).

## 4.8. Mechanism of Root Resorption

### 4.8.1. Classic pressure-tension theory

The classic pressure-tension theory came with the fact that chemical, instead of electric, signals are the stimuli for cellular differentiation occurring in the dentoalveolar complex, resulting eventually in tooth movement (Figure 4.8.1.1). This theory proposes that when orthodontic force is applied to the tooth, within a few seconds, the tooth starts to reposition within the periodontal ligament space, producing compression in some areas within the PDL and tension or stretch in other areas (Li et al., 2018; Will, 2015).

The resulting compression decreases the blood flow to the surrounding tissues following orthodontic force application. However, blood flow in areas of tension forces appears to be increased. Few minutes later, chemical mediators, prostaglandins and cytokines, are released to initiate the bone resorption at compression side, and bone deposition at tension side (Li et al., 2018). Heavy forces result in complete occluding of blood supply, leading to cells death in compression sides (hyalinization), and tooth movement occurs only at the expense of undermining bone resorption, while the blood flow is only reduced when light forces are applied, and under these circumstances, direct frontal resorption of the alveolar bone occurs (Feller et al., 2015; Iwasaki et al., 2006). In addition, frontal resorption occurs when orthodontic forces do not exceed capillary pressure, while undermining resorption occurs when capillary pressure is exceeded and hyalinization occurs within the periodontal ligament. Undermining resorption results in delayed and large tooth movements (Figure 4.8.1.2). In contrast, frontal resorption allows remodeling of the vascular and fibrous elements of the periodontal ligament permitting continuous and steady tooth movement with no significant delay (Iwasaki et al., 2006; Li et al., 2018; Masella and Meister, 2006). However, undermining resorptions are unavoidable during orthodontic treatment.

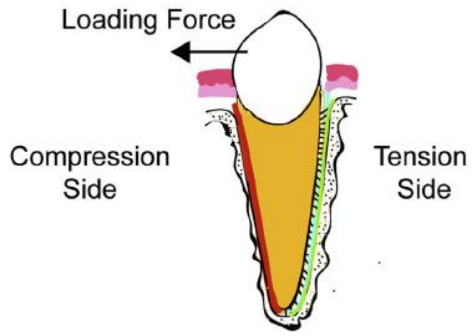



**Figure 4.8.1.1.** Compression and tension sides due to orthodontic loading.

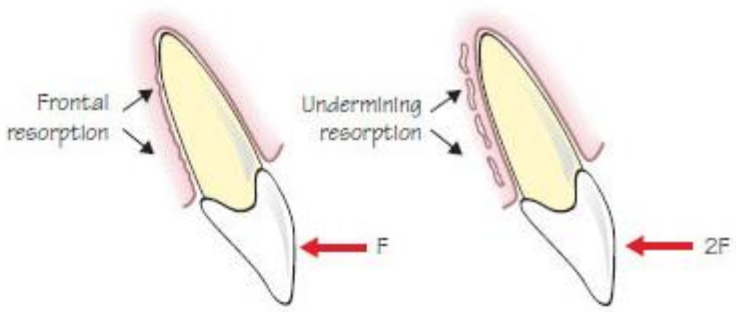



**Figure 4.8.1.2.** Frontal and undermining resorptions.

### 4.8.2. Tipping vs. bodily movements

The site of orthodontically induced resorption on a root surface is determined mainly by whether the tooth is moved bodily or tipped, and occurs mostly on those parts of the root surfaces that are exposed to high compressive stress; but it may also occur on root surfaces that are exposed to tensile stress within the periodontal ligament, but to a lesser degree (Ajmera et al., 2014; Chan and Darendeliler, 2006). The higher the strain, the higher the root resorption (Chan and Darendeliler, 2006).

Tipping movements produces more resorptive forces, which is also more common and intense than resorptive forces generated by bodily movements, which are distributed along the root surfaces and resorbing the cementum at zones of compression of the periodontal ligament (Ajmera et al., 2014). Additionally, in tipping movements, compressive stresses are located and intensified in the apical part of the root which is thin area receiving higher forces, and in comparison with bodily movements, bodily movements have a concentrated stress per unit surface area in much thicker portion of the root cervically (Consolaro, 2014; Cuoghi et al., 2014). Furthermore, alveolar bone around the cervical one-third of the root is seen to be the thinner, and more elastic, giving it the ability of absorbing much more of the orthodontically induced mechanical stresses when compared to the alveolar bone located apically, which is thick, and has less elasticity (Cuoghi et al., 2014; Segal et al., 2004).

### 4.8.3. Role of OPG/RANKL/RANK system

On a cellular level, physiologic and pathologic (orthodontic) root resorption is regulated by a key network formed by osteoprotegerin (OPG), receptor activator of nuclear factor – (KB) ligand (RANKL), and its cognate receptor RANK ligands. These factors are known to share homologous features with tumor necrosis factors, and their function is paracrine regulatory of osteoclastogenesis (Horowitz et al., 2001; Katagiri and Takahashi, 2002; Khosla, 2001; Schoppet et al., 2002). Additionally, they play a role in bone remodeling and metabolism during the orthodontic treatment as well (Jiang et al., 2015; Oshiro et al., 2002; Yan et al., 2015).

The role of RANKL is to enhance bone resorption, and together with another very important protein ligand, M-CSF (which binds to its receptor c-fms), by encouraging and guiding osteoclasts activity; formation, fusion, differentiation, activation and survival (Malyankar et al., 2000; Shoji-Matsunaga et al., 2017; Walsh and Choi, 2014; Zupan et al., 2013). RANKL biological effects are produced the time it binds to RANK. In contrast, the biological effect of OPG is to neutralize RANKL which prevents RANKL-RANK bond. Therefore, its effect is opposite to those mediated by RANKL (Kang et al., 2010).

Dental complex expresses theses three factors. RANKL is expressed by different cell type like odontoblasts, pulp , PDL fibroblasts, and cementoblasts, while RANK receptor is expressed by the odontoclasts in resorption lacunae (Fukushima et al., 2003; Harokopakis-Hajishengallis, 2007). However, OPG is expressed by odontoblasts, ameloblasts and dental pulp cells (Heinrich et al., 2005; Tyrovola et al., 2008).

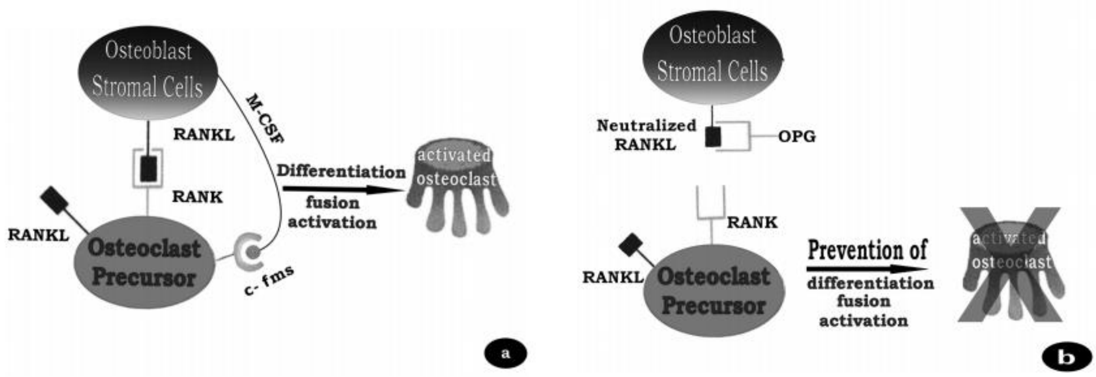



**Figure 4.8.3.1.** The major biologic actions of the OPG/RANKL/RANK system: a) binding of RANKL and RANK and activation of osteoclasts, b) neutralization of RANKL by OPG and prevention of RANKL-RANK interaction (Tyrovola et al., 2008).

RANKL is induced by hypoxia occurring in compression side as result of the occlusion of blood flow (Dandajena et al., 2012; Huang et al., 2014). Consequently, RANKL activates osteoclastogenesis, and cells differentiation is initiated (Kanzaki et al., 2006). However, tension sides appear to have increased OPG synthesis which stimulates bone formation. Nonetheless, this RANKL to OPG ratio in periodontal ligament cells is suggested to also contribute to root resorption during orthodontic tooth movement (Figure 4.8.3.2). The compressed PDL cells can produce large amounts of RANKL and up-regulate osteoclastogenesis in cases of severe external apical root resorption (Tyrovola et al., 2008). This explains the increase of RANKL and decrease of OPG in severe root resorption cases (Kanzaki et al., 2006; Nishijima et al., 2006; Yamaguchi et al., 2006).

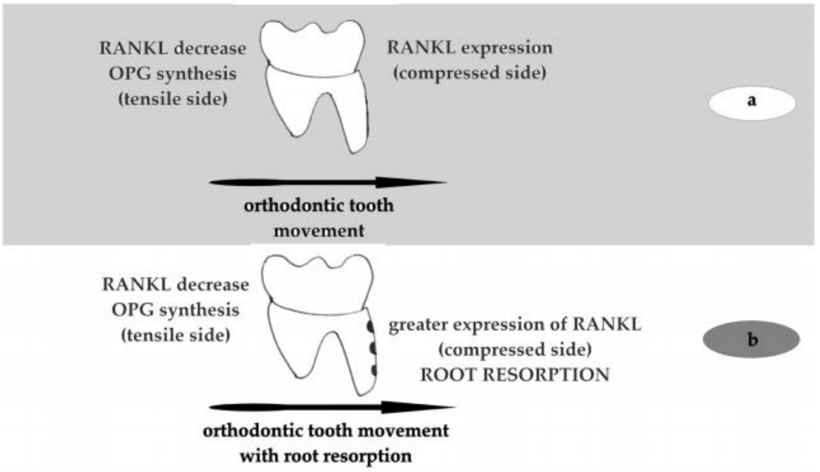



**Figure 4.8.3.2.** Regulation of bone remodeling by RANKL/OPG (Tyrovola et al., 2008).

In conclusion, OPG and RANKL's relative expressions on the tensioned and the compressed sides of the root regulate bone resorption and deposition occurring during orthodontic tooth movement.

### 4.9. The Repair Process

Once orthodontic forces applied to the tooth are ceased, active root resorption will stop, and repair process is initiated (Cheng et al., 2010). And this repair occurs as three processes; partial, functional and anatomical (Owman-Moll and Kurol, 1998). Partial repair starts when the newly formed cementum starts partially covering the exposed dentine. When the exposed dentine becomes fully covered by cementum, mainly a thin layer, with the original form being not established again, it is called functional repair. Finally, for the anatomical repair, root's surface is restored to its original form, making it the most preferred process (Krishnan, 2017) (Figure 4.9.1). The anatomic repair process takes longer time, 8 weeks at least, than partial and functional repair process which is reported to be taking place during the first 4-6 weeks (Cheng et al., 2010; Owman-Moll et al., 1995).

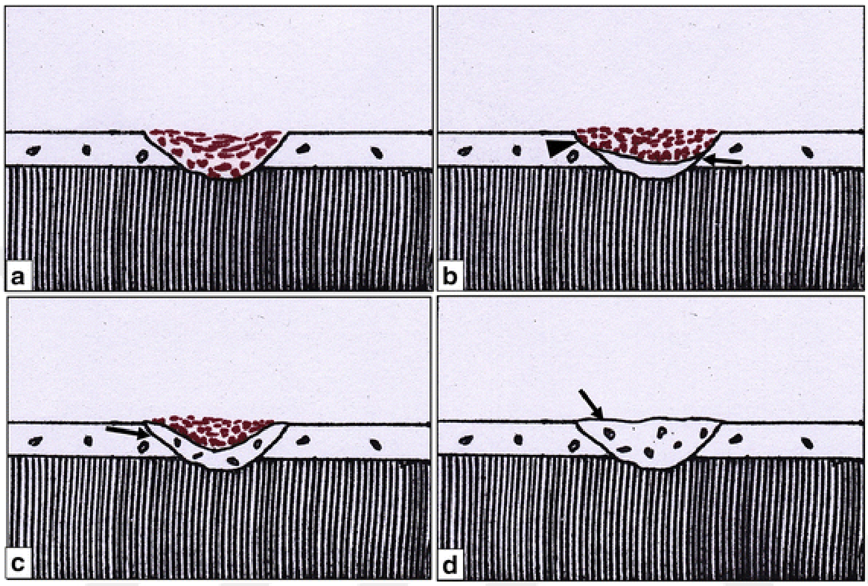



**Figure 4.9.1.** Schematic presentation of three repair processes. A) No repair, B) Partial repair, C) Functional repair, D) Anatomic repair.

On a cellular level, early repair process starts with fibroblast-like cells that are present in the periodontal ligament penetrating the resorption lacunae (Jäger et al., 2008). These fibroblast-like cells in addition to cementoblastic cells start the deposition of an initial uncalcified thin cementoid repair matrix on existing collagenous structures, and their activity is influenced by growth factors and local cytokines including insulin like growth factors (IGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), and transforming growth factor-$\beta$ (TGF-$\beta$) (Jäger et al., 2008; Saygin et al., 2000).

Acellular cementum is predominantly found in areas of initial and early repair in the resting phase after cessation of orthodontic forces. While cellular cementum is present in the later repair areas (Mehta et al., 2017). Acellular cementum forms more slowly (Bavle et al., 2011). The repair process begins at the center of the resorption site with deposition of acellular cementum followed by deposition of cellular cementum extending to involve the entire surface of the resorption crater (Mehta et al., 2017). Additionally, healing becomes faster to fill larger voids produced by orthodontic forces, resulting accordingly in getting the cementocytes trapped within their lacunae for the complete mineralization of the increments to take place (Krishnan, 2017; Mehta et al., 2017).

### 4.10. The Effects of Systemic Medications

Studies showed that the examined prescription pharmaceutical drugs can have variable effects on the orthodontic tooth movement associated with root resorption. Notwithstanding the finding that the quality of evidence is considered poor, the clinician is always expected to treat the related recommendations with caution, because good practice indicates that it is necessary to recognize patients who consume drugs and consider the potential consequences (Makrygiannakis et al., 2018).

Although number of carried studies investigating the pharmaceutical substances in human body is not high, surprisingly. And as the root resorption associated with orthodontic movement is not an uncommon consequence following the treatment, further studies should be done, because such relevant information is beneficial in maintaining high standards of clinical and dental care.

Any pharmaceutical agent can potentially affect the signaling pathways linked to orthodontic tooth movement and cement and root dentine homeostasis (Iglesias-Linares and Hartsfield, 2017; Jiang et al., 2015; Xiao et al., 2015). The administration of vitamin C to the body showed an increase in orthodontically induced root resorption (Miresmaeili et al., 2015). This effect is mainly the result of the osteoclasts formation stimulated by vitamin C (Hart et al., 2015; Otsuka et al., 2000). The decrease in osteoclastic activity is seen with the administration of non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, meloxicam and bisphosphonates (Arias and Marquez-Orozco, 2006; Black et al., 2000; Martin et al., 2015). The administration of normal doses of statins, simvastatin, also decreases the osteoclastic activity and it enhances bone formation as well (Ishihara et al., 2017; Montazerolghaem et al., 2016).

The root resorption was not affected by acetaminophen, or aspirin. Although aspirin affects the osteoclasts number negatively, but still no effect is noted regarding root resorption and tooth movement (Arias and Marquez-Orozco, 2006; Gonzales et al., 2009). Fluoxetine, a selective serotonin reuptake inhibitor antidepressant, is expressed in both osteoblasts and osteoclasts, and is not seen to also to have any effect in root resorption (Mirhashemi et al., 2015; Rafiei et al., 2015). Dietary calcium supplements reduce the number of osteoclasts and decrease alveolar bone resorption, but no influence on root resorption is reported (Makrygiannakis et al., 2018; Taddei et al., 2014; Yoo et al., 2017). Zinc compounds are noted to stimulate the activity of osteoblasts and decrease bone resorption, but it was suggested that their effect is normalized with time, because these effects are dependent on the duration of its administration (Liu et al., 2017; Yamaguchi et al., 1982).

Finally, administration of celecoxib, prednisolone and L-thyroxine, were observed to have an inconsistent effect regarding effects on root resorption associated with orthodontic tooth movement (Gonzales et al., 2009; Hashemi et al., 2012; Seifi et al., 2015).

### 4.11. The Need of Root Canal Treatment

Diagnosis and treatment of root resorptions usually require interdisciplinary work; orthodontists, endodontists, and periodontist may all work together to obtain a good clinical outcome.

The endodontist is stated as the specialist to take care of tooth resorption. However, not all cases of resorption should be endodontically treated. Nevertheless, even the cases that do not require a root canal treatment must be checked and observed by the endodontist. Cases of root resorption that need to be treated endodontically are the following: a) pulp necrosis by microbial contamination; b) aseptic pulp necrosis; c) initial calcific metamorphosis of the pulp; d) internal resorption (Consolaro and Bittencourt, 2016).

Orthodontically induced root resorption is always external, without any contribution of dental pulp. No chronic periapical lesion is present, which is associated to pulp necrosis and contamination of the root canal system, having bacteria and their products leaking through the apical foramen, therefore there is no need to provide endodontic treatment (Consolaro and Bittencourt, 2016). If the cause is found to be the orthodontic movement, rest phase of at least 8 weeks is considered the best treatment (Krishnan, 2017).

Dental pulp only takes part in resorptions starting and progressing internally, where it acts directly in the resorption process (Consolaro and Bittencourt, 2016).

The resorption process taking place at the external part of the root can't be controlled through the pulp as the causes are acting upon the periodontal ligament. Moreover, no evidence justifying endodontic treatment, by means of obturation, to control the external resorption processes if the pulp is vital (Consolaro and Bittencourt, 2016).

In conclusion, the first step of management of orthodontically induced external root resorption cases is to understand and to identify the cause accurately. Second, planning of a reasonable and possible treatment approach, to be performed later.

# 5. MATERIALS AND METHODS

## 5.1. Ethical Approval

The Ethical Committee of the Institute of Health Sciences, Marmara University approved of this retrospective study which assessed the records of 7000 patients from the archives of Marmara University, Faculty of Dentistry, Department of Orthodontics.

## 5.2. Patient Selection

Treatment files of 7000 patients, who have been treated in Marmara University, between years of 1990 and 2019, were examined with respect to the following:

Inclusion criteria:

- Completed fixed orthodontic treatment.
- Presence of pretreatment and post-treatment panoramic and cephalometric radiographs.
- Completed root growth of the maxillary incisors before fixed orthodontic treatment.
- No visible root resorption in the maxillary incisors before the treatment.
- Presence of score 4 root resorption according to Malmgren *et al*. in one or more of the maxillary incisors following fixed orthodontic treatment.

The exclusion criteria were as following:

- Teeth with endodontic treatment.
- Incomplete development of root apex.
- Mild or moderate apical resorption of the incisors.
- Patients with missing radiographic records.
- Patients with trauma history to the incisors before starting the treatment.

- Patients treated with removable appliances.
- Patients treated with surgical approach.
- Patients presented with cleft lip/palate.

After scanning of all patients' archive was done, total number of subjects with severe external anterior root resorption was found to be 120. Of the original sample size, 3285 subjects were excluded and were distributed as the following: 2316 patients with missing files, 244 patients treated with removable appliances and did not go through fixed orthodontic treatment, 375 patients treated with orthognathic surgery, and 350 patients presented with cleft lip/palate.

For the study group consisted of subjects presented with severe EARR, second scanning was performed for the 120 patients, and 30 patients were excluded as a reason of incomplete records, and were distributed as the following: 2 patients with missing pre-operative cephalometric radiographs, and 28 patients with missing post-operative cephalometric radiographs.

**Table 5.1** Initial and final sample sizes.

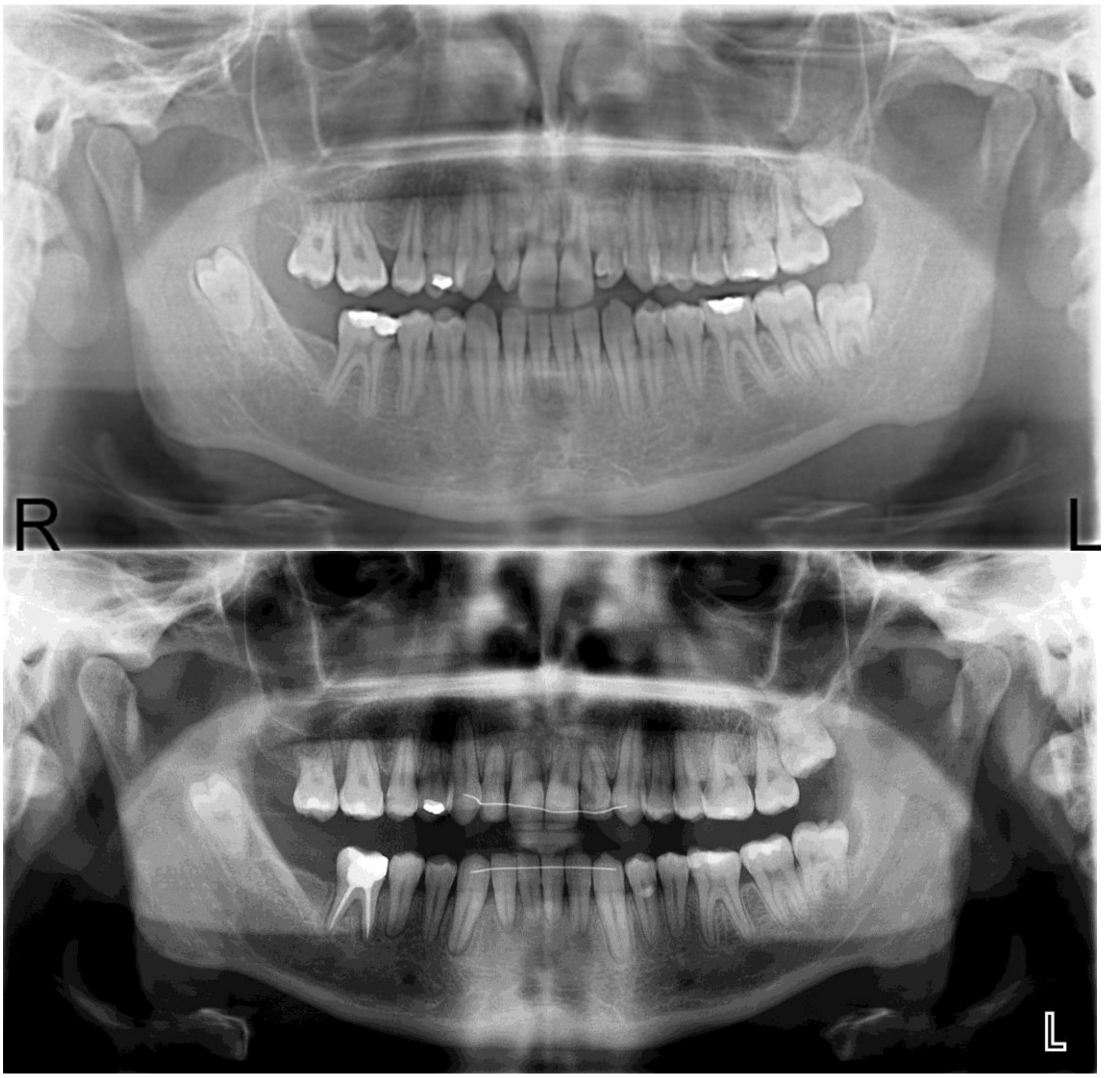
| Sample | Initial sample size | Excluded subjects | Final sample size |
|---|---|---|---|
| **Original sample** | 7000 | 3285 | 3715 |
| **Severe EARR** | 120 | 30 | 90 |

### 5.3. Treatment Protocol

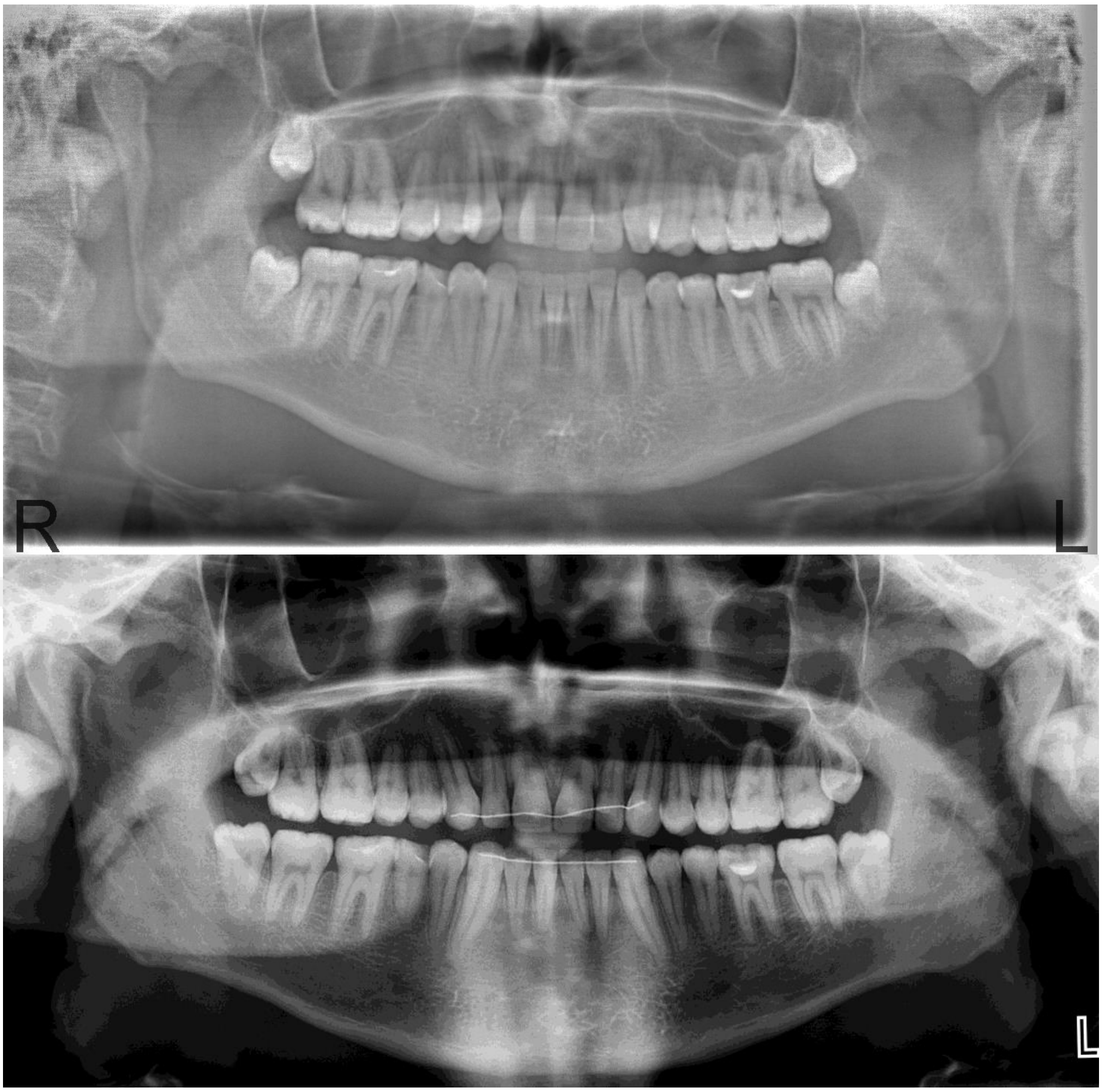
Patients presented to the clinic in Marmara University, Faculty of Dentistry, Department of Orthodontics have been diagnosed, examined, and treated under supervision of the specialists and professors. Treatment started with fixed appliances of 18-slot brackets. The initial phase, alignment of the dentition, was initiated by round NiTi wires, followed by rectangular wires. The working phase followed later, ending with stainless steel wires, and elastics were used as needed.

### 5.4. Data Collection

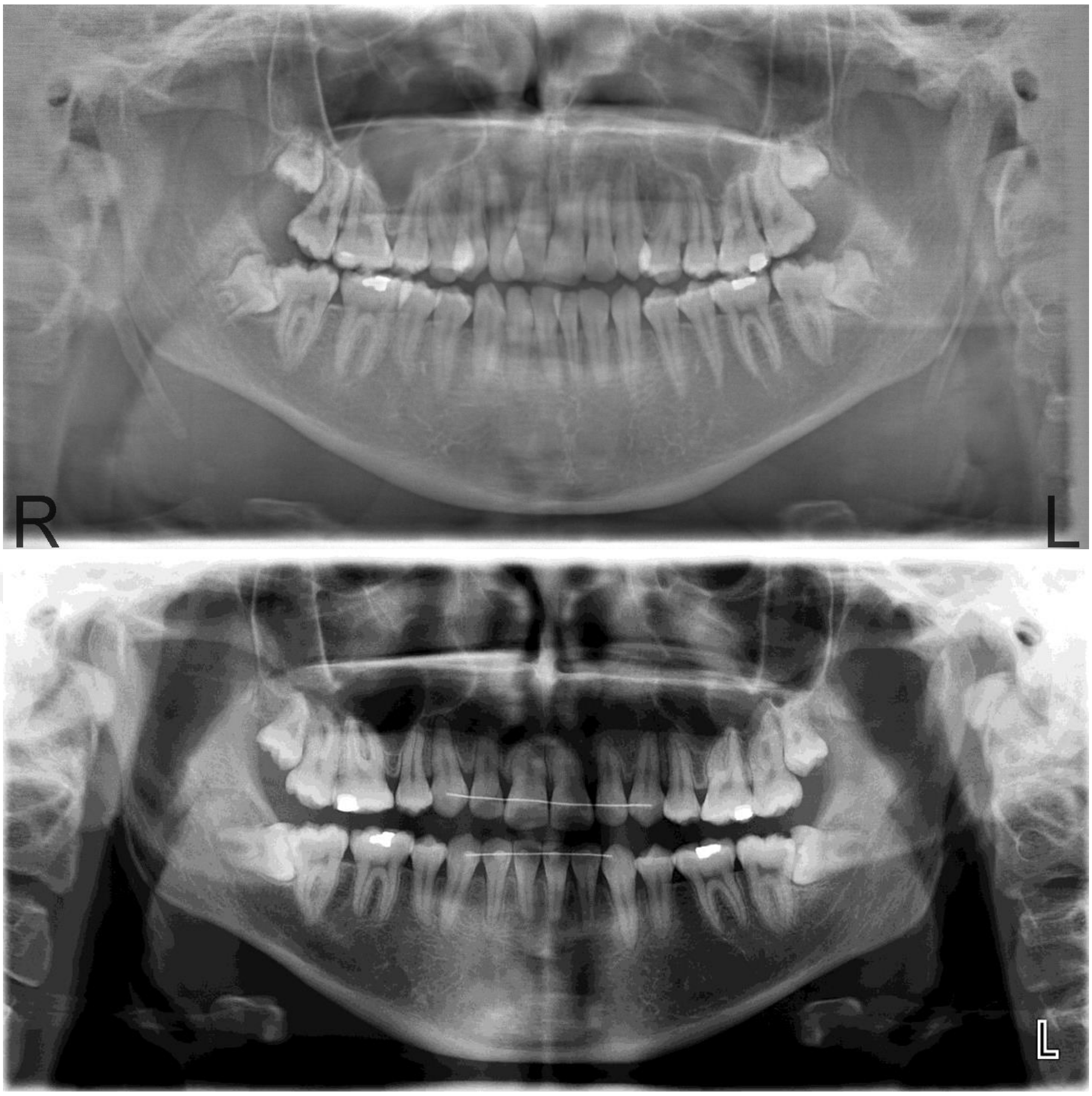
The initial archive scanning was performed by checking and evaluating the pre-operative and post-operative panoramic radiographs of the whole sample, and subjects presented with severe (Score 4) external apical root resorption were selected.




**Picture 5.4.1.** Pre-operative (above) and post-operative (below) panoramic radiographs.




**Picture 5.4.2.** Pre-operative (above) and post-operative (below) panoramic radiographs.




**Picture 5.4.3.** Pre-operative (above) and post-operative (below) panoramic radiographs.

To determine potential predisposing factors of root resorption, the following data were retrieved from the patients' files:

- Age at the beginning of the treatment.
- Gender.
- Root morphology.
- Overjet.
- Overbite.
- Treatment modality (extraction, non-extraction).
- Treatment duration.
- Buccal and palatal alveolar bone thickness in the maxillary incisors region.

- Amount of movement of the incisal root apices and incisal edges in both horizontal and vertical directions.

### 5.5. Data Assessment

Once all subjects with severe root resorption (Score 4) were identified, a matching group of control subjects were randomly selected among the patients identified with minimal root resorption (Score 1) for statistical comparisons.

Root morphology was assessed on panoramic radiographs according to the classification proposed by Quintanilha *et al*. as follows: triangular, rhomboid, pipette and dilacerated.

Overjet, overbite, buccal and palatal maxillary alveolar bone thickness, and amount of movement of the incisal root apices and incisal edges were assessed on cephalometric radiographs using NemoTech cephalometric tracing software (Version 10.4.2).

### 5.6. Cephalometric Analysis

Cephalometric radiographs were used to record the changes in overjet, overbite, buccal and palatal maxillary alveolar bone thickness, and amount of movement of the incisal root apices and incisal edges between pre-orthodontic treatment and post-orthodontic treatment records among the two groups; anterior root resorption group and control group. NemoTech cephalometric tracing software was used to trace all cephalometric radiographs and these radiographs were traced by the same examiner to avoid bias.

### 5.6.1. Cephalometric points related to skeletal landmarks

1. S: Sella. The midpoint of sella turcica or hypophyseal fossa or pituitary fossa.
2. N: Nasion. The most anterior point of the frontonasal suture in the middle.
3. Po: Porion. The superior point of the external auditory meatus.
4. Or: Orbitale. The lowest point on the inferior margin of the orbit.
5. PNS: The posterior nasal spine. The most posterior extent of the hard palate.
6. ANS: The anterior nasal spine. The most anterior extension of the maxilla.
7. A: Subspinale. The point at the deepest midline concavity on the maxilla between the anterior nasal spine and prosthion.

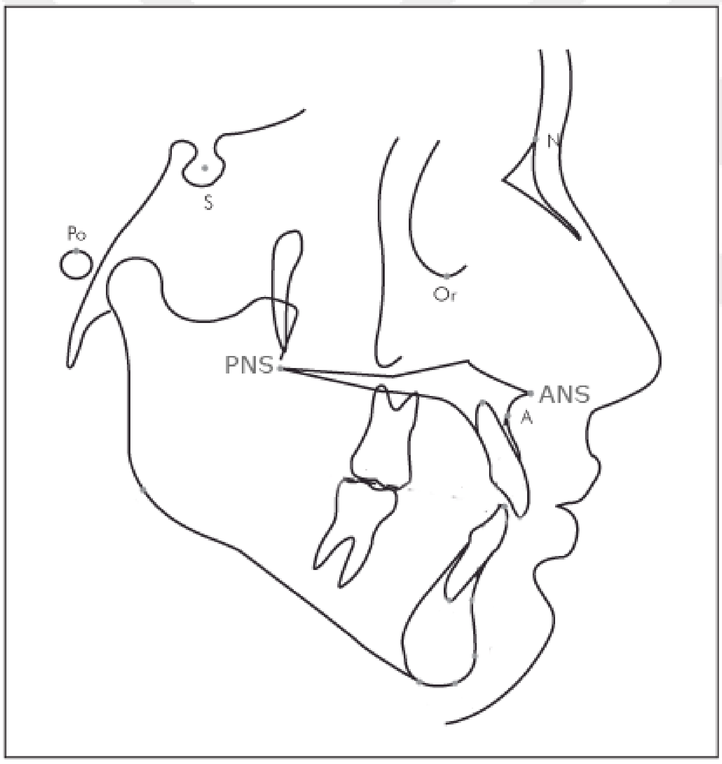



**Figure 5.6.1.1.** Cephalometric skeletal landmarks.

### 5.6.2. Cephalometric points related to dental landmarks

1. U1i: The incisal edge of maxillary central incisor
2. U1a: The root apex of maxillary central incisor

### 5.6.3. Cephalometric planes and lines

Cephalometric planes and lines that are used for initial tracing and measuring variables are as the following:

1. Sella Nasion (SN) line: Line crossing between sella turcica and Nasion points.
2. Palatal Plane (PP): Plane connecting anterior nasal spine with posterior nasal spine.
3. Frankfort Horizontal Plane (FH): Plane crossing from the Porion to the Orbitale.
4. Line parallel to the palatal plane: A constructed line parallel to the palatal plane passing through the apex of the root, with marking the anterior and posterior limits passing through the bone (UA: Upper anterior alveolus, UP: Upper posterior alveolus).
5. Horizontal line: A constructed line intersecting the S point with angle of 7 degrees to SN line.
6. Vertical line: A constructed vertical line dropped perpendicular to the horizontal line and intersecting the S point.

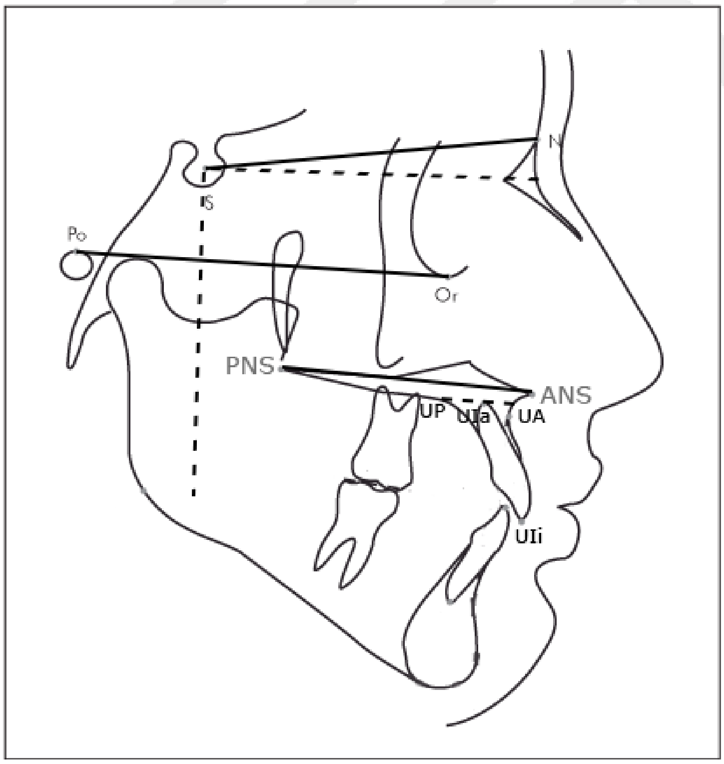



**Figure 5.6.4.1.** Cephalometric lines and planes used.

### 5.6.4. Method of measurement

Overjet, overbite, buccal and palatal maxillary alveolar bone thickness, and amount of movement of the incisal root apices and incisal edges were measured on cephalometric radiographs using NemoTech cephalometric tracing software. The variables were measured after the cephalometric tracing was performed using Marmara analysis, which is followed for all the patients at Orthodontic Department, Faculty of Dentistry at Marmara University.

Calibration of both pre and post-operative cephalometric radiographs was performed as initial step prior to recording any measurement. Cephalometric radiographs were calibrated using the length of the middle cranial base for every patient; the growth of middle cranial base is completed in early periods and at the age of 7 years, maintaining its stability in all developmental phases (Björk and Skieller, 1983). Two cephalometric points located in the middle cranial base showed high stability over years (Björk and Skieller, 1983; Hatewar et al., 2015). The points are known to be as the following: the intersection point of the lower contours of the anterior clinoid processes and the contour of the anterior wall of the sella, also called as Walker's point (T, W), and the intersection point of the middle cranial fossa by the greater wing of the sphenoid bone, also called as Wing point (w) (Arat et al., 2010; Björk and Skieller, 1983). It is also found that (T-w) line is reliable method for examining overall changes (M. Arat et al., 2001; Z. M. Arat et al., 2010; Hatewar et al., 2015).


**Figure 5.6.5.1.** Middle cranial base points. T: Tuberculum sella, the intersection point of the lower contours of the anterior clinoid processes and the contour of the anterior wall of the sella, Walker's point. W: the intersection point of the middle cranial fossa by the greater wing of the sphenoid bone.

### 5.6.4.1. Overjet and overbite

Overjet, the horizontal distance between maxillary and mandibular central incisors, and overbite, the vertical overlap between maxillary and mandibular central incisors, were measured directly through Marmara analysis in the pre-operative cephalometric radiographs of the subjects.

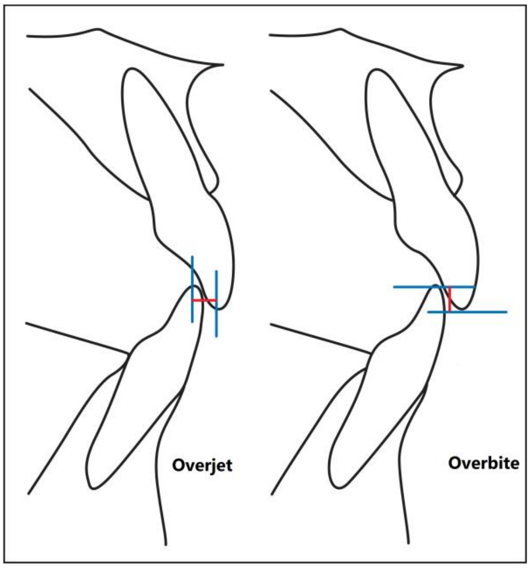



**Figure 5.6.5.1.1.** Overjet and overbite.

#### 5.6.4.2. Alveolar bone thickness

Alveolar bone thickness (width) is the sum of width of buccal (anterior), abbreviated as UA, and posterior (palatal) alveolar bone, abbreviated as UP (Handelman, 1996). Upper anterior bone (UA) is measured using a line drawn through the apex of the maxillary central incisor to the limit of labial cortex, and parallel to the palatal plane (ANS-PNS). Upper posterior bone (UP) is measured using a line drawn through the apex of the maxillary central incisor to the limit of palatal cortex, and parallel to the palatal plane (ANS-PNS) (Handelman, 1996). The alveolar bone thickness was measured in pre-operative cephalometric radiographs.

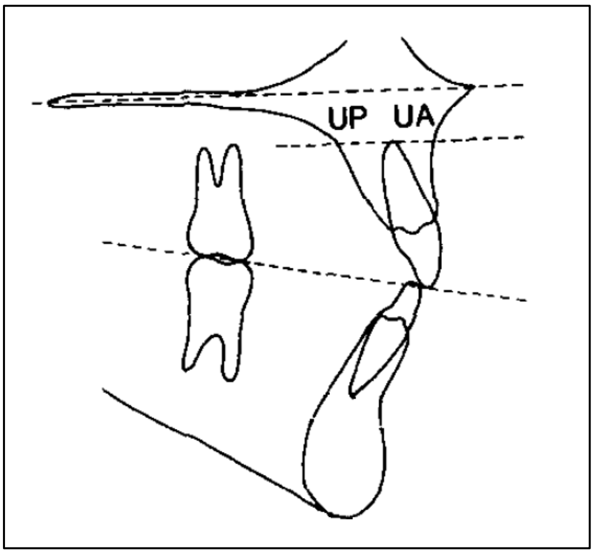
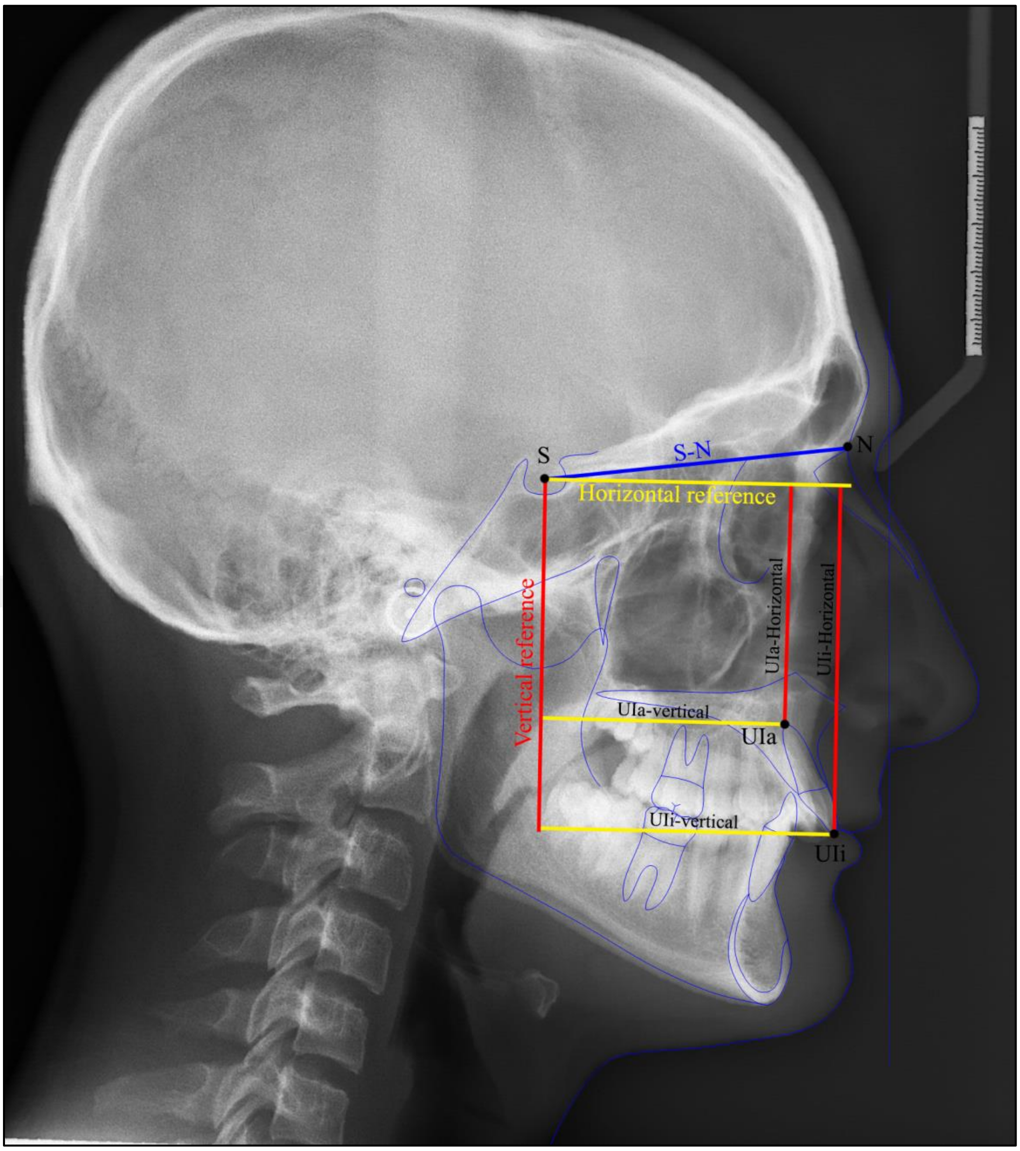



**Figure 5.6.5.2.1.** Alveolar bone width. UA: Upper anterior alveolar bone, UP: Upper posterior alveolar bone.

### 5.6.4.3. Amount of incisor movement

In order to measure the amount of movement the incisors had, assessment through pre and post-operative cephalometric radiographs was done. For both, incisal edge and root apex, movement in vertical and horizontal directions was measured. Measurements were performed using a vertical and horizontal reference for all subjects in pre and post-operative radiographs. The horizontal reference is a constructed line intersecting the Sella (S) point with angle of 7 degree to the Sella-Nasion (SN) line; this line is also parallel to the Frankfort Horizontal plane (FH). For the vertical reference, a constructed line dropped perpendicular to the horizontal reference and intersecting the Sella (S) point was used. The perpendicular distances from root apex and incisal edge to horizontal and vertical references were recorded, in both pre and post-operative radiographs. Final distance (post-operative) was subtracted from the initial distance (pre-operative) and the result was written down for each subject in the study and the control groups.




**Picture 5.6.5.3.1.** Vertical and horizontal references and distances to root apex and incisal edge.

The root resorption causes shortening in total root and tooth length, leaving the root apex blunt and difficult to be seen in cephalometric radiographs. This limitation was overcome by measuring the initial tooth length in pre-operative cephalometric radiographs, and later transferring exactly the same length to the post-operative radiograph as a reference to measure from.

# 6. RESULTS

## 6.1. Prevalence

To calculate the prevalence of severe EARR in our study, the initial sample presented with severe root resorption was used.

**Table 6.1** Incidence of severe EARR.

| Sample | Sample size | Incidence of severe EARR |
|---|---|---|
| **Total patients** | 3715 | 3.23% |
| **Severe EARR** | 120 | |

The results showed that 3.23% of total patients developed severe EARR, while 96.77% showed clinically acceptable root resorption (mild and moderate).

## 6.2. Statistical Analysis

Statistical analysis of the obtained data was performed using the IBM SPSS Statistics software for Windows, Version 26.0. The relationship between root resorption and the predisposing factors were assessed using the following statistical tests: chi square test for intergroup comparison of gender, root morphology, treatment modality; independent t-test for comparison of ages, treatment duration, overjet, overbite, alveolar bone thickness, and amount of tooth movement between the two groups.

Intraoperator reliability of the method was evaluated by repeating the resorption assessments on randomly selected 20 panoramic films after a two-week interval. To evaluate the agreement between the scorings of root resorption at two different time points, the Kappa test was used. The reliability of the measurements of overbite, overjet, buccal and palatal alveolar bone thickness in the maxillary incisors region and amount of movement of the incisal root apices were evaluated by repeating these measurements after a two week interval on randomly selected 20 cephalometric films using Dahlberg formula to estimate the random error.

## 6.3. Reliability of Measurements

### 6.3.1. Score of root resorption

**Table 6.2** Kappa test to evaluate the error in scoring root resorption.

| **Root Resorption** | **Kappa Coefficient** | **Asymptotic Standard Error** | **Strength of agreement** | **Proportion of observed agreement** | **P-value** |
|---|---|---|---|---|---|
| **Severe EARR** | 0.643 | 0.325 | Substantial | 0.95 | 0.002 |

Kappa test has showed that the percentage of agreement was substantial and kappa coefficient was 0.643 and scoring of root resorption was reliable.

### 6.3.2. Random error of measurements

**Table 6.3** Measurement error according to the Dahlberg formula.

| Variable | | Measurement Error |
|---|---|---|
| **Overjet** | | 0.15 |
| **Overbite** | | 0.07 |
| **Horizontal Displacement** | **Incisal Edge** | 0.14 |
| | **Root Apex** | 0.12 |
| **Vertical Displacement** | **Incisal Edge** | 0.17 |
| | **Root Apex** | 0.18 |
| **Bone Thickness** | | 0.23 |

Random error calculation using Dahlberg formula showed that the largest linear error found was for the bone thickness (UA+UP) variable, 0.23 mm.

## 6.4. Inter-Group Comparison

### 6.4.1. Age and treatment duration

**Table 6.4** Intergroup comparison of age and treatment duration (independent t-test).

| | Control Group (n=90) | | Resorption Group (n=90) | | P-value |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | |
| **Initial age (years)** | 15.355 | 2.45 | 16.69 | 2.97 | 0.0012 |
| **Treatment time (years)** | 2.48 | 0.927 | 3.7 | 1.3 | 0.0001 |

Differences in initial age at the beginning of treatment and treatment duration were statistically significant between both groups.

### 6.4.2. Gender, treatment type, and root morphology

**Table 6.5** Intergroup comparison of gender, treatment type and root morphology (chi square test).

| Variable | Distribution | Control Group (n=90) | Resorption Group (n=90) | P-value |
|---|---|---|---|---|
| **Gender** | **Male (n=84)** | 40 (47.62%) | 44 (52.38%) | 0.55 |
| | **Female (n=96)** | 50 (52.08%) | 46 (47.92%) | |
| **Type of Treatment** | **Without extraction (n=124)** | 74 (59.68%) | 50 (40.32%) | 0.0001 |
| | **With extraction (n=56)** | 16 (28.57%) | 40 (71.43%) | |
| **Root Morphology** | **Triangular (n=79)** | 35 (44.3%) | 44 (55.7%) | 0.575 |
| | **Rhomboid (n=69)** | 38 (55%) | 31 (45%) | |
| | **Pipette (n=16)** | 9 (56.25%) | 7 (43.75%) | |
| | **Dilacerated (n=16)** | 8 (50%) | 8 (50%) | |

Inter-group comparisons of the resorption and the control groups in terms of gender, type of treatment, and root morphology, showed that there is only one statistically significant difference between the groups which is the treatment type presented with premolar extractions.

### 6.4.3. Overjet, overbite, and alveolar bone thickness

**Table 6.6** Intergroup comparison of overjet, overbite, and bone thickness in millimeters (independent t-test).

| Variable | Control Group (n=90) | | Resorption Group (n=90) | | P-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Overjet** | 4.39 | 2.24 | 4.61 | 2.93 | 0.572 |
| **Overbite** | 2.19 | 2.01 | 1.93 | 3.17 | 0.512 |
| **Bone Thickness** | 15.067 | 1.998 | 12.541 | 2.13 | 0.0001 |

Among cephalometric measurements including overjet, overbite, and bone thickness, statistically significant difference was seen only in bone thickness between the resorption and the control groups.

### 6.4.4. Tooth movement

**Table 6.7** Intergroup comparison of amount of tooth movement in horizontal and vertical directions in millimeters (independent t-test).

| Tooth Movement | | Control | | Resorption | | P- value |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| Horizontal Displacement | Incisal Edge | 1.41 | 1.34 | 2.82 | 2.22 | 0.0001 |
| | Root apex | 1.17 | 1.08 | 1.69 | 1.35 | 0.0048 |
| Vertical Displacement | Incisal Edge | 1.14 | 1.15 | 1.447 | 0.958 | 0.0534 |
| | Root apex | 1.02 | 1.01 | 1.81 | 1.12 | 0.0001 |

Statistically significant differences were seen in both horizontal and vertical directions at the root apex level, while at the incisal level there was only statistically significant difference in the horizontal direction.

**Table 6.8** Distribution of subjects in terms of posterior (backward) and anterior (forward) movements in the horizontal direction (chi square test).

| Horizontal Displacement | Control | | Resorption | | P-value |
|---|---|---|---|---|---|
| | Posterior | Anterior | Posterior | Anterior | |
| Incisal Edge | 37 | 53 | 36 | 54 | 0.879 |
| Root Apex | 58 | 32 | 69 | 21 | 0.072 |

Anterior displacement is when incisal edge or root apex moves forward leading to negative (-) subtraction result. Posterior displacement is when the subtraction result is positive (+).

**Table 6.9** Distribution of subjects in terms of intrusion (upward) and extrusion movements (downward) in the vertical direction (chi square test).

| Vertical Displacement | Control | | Resorption | | P-value |
|---|---|---|---|---|---|
| | Intrusion | Extrusion | Intrusion | Extrusion | |
| **Incisal Edge** | 44 | 46 | 27 | 63 | 0.009 |
| **Root Apex** | 36 | 54 | 20 | 70 | 0.0001 |

Difference in the distribution of the vertical displacements among subjects was statistically significant between the resorption and control groups.

# 7. DISCUSSION AND CONCLUSION

## 7.1. Discussion

### 7.1.1. Discussion of aims

The purpose of this study was to retrospectively determine the prevalence of severe external root resorption (score 4 according to Malmgren et al.), in maxillary incisors, during fixed orthodontic treatment and to evaluate the possible predisposing factors for root resorption.

Root resorption is known as one of the most common complications following orthodontic treatment. Being irreversible makes it considered as a true difficulty and a limitation to obtain a perfect orthodontic outcome as it is an undesirable and frequent side effect of the orthodontic treatment, which can affect its stability.

As patients are being more aware of the prognosis of orthodontic treatments, the need of providing them with the best outcome is rising. Thus, it is very important to understand the reason behind any unwanted treatment result. And the greater knowledge derived from high quality researches and studies will help the clinician to minimize any unwanted events and effects caused by orthodontic treatment, such as severe EARR.

The most affected teeth are known to be the maxillary incisors (Levander and Malmgren, 1988). Well aligned and sound maxillary incisors is a key to successful outcome, and orthodontists should put effort and pay attention to fine details affecting these teeth; consequently, affecting the patient's smile. Maintaining the health of patient's dentition and conserving the tooth's structure are the main goals of dental treatment, provided by general practitioners and specialists. And orthodontists play a major role in maintaining and conserving the patient's dentition during the orthodontic treatment.

Root resorption cannot be avoided during orthodontic treatment, it always occurs, ranging from minor irregularities in root apices, to severe ones affecting more than one third of the root length. Fortunately, most EARR cases are seen to be mild cases, with no clinical significance. However, when it involves more of root structure it becomes severe, and it may put the longevity of dentition and the orthodontic treatment stability at risk.

In addition, the importance of maintaining and controlling the health of patient's dentition is gained as a result of potential legal implications in daily dental and orthodontic practice. When excessive movements or prolonged treatment are expected, patients should be informed about the potential risks, and the decision has to be made to limit any excessive movement, consider the most favorable mechanics, and avoid any prolonged treatment plans. Orthodontists should always work to avoid subjecting their patients to any biological damage.

Our study will serve the purpose of a self-assessment for practitioners in the department of Orthodontics in Marmara University, with the goal of obtaining satisfying orthodontic treatment outcomes in the future by creating an awareness of factors related with severe root resorption. With providing the useful information necessary to complete and fulfill the treatment objectives, practitioners are going to use our findings as a guide for their future practice. And a review of previous and preceding treatment mechanics and treatment plans is going to be available to be considered to assist them in selecting the most favorable, reasonable and least harmful treatment modalities.

**Picture 7.1.1.1.** Panoramic radiograph showing perfect orthodontic treatment outcome.

### 7.1.2. Discussion of materials and method

The final sample, after exclusion criteria was set, consisted of 90 patients. And the study sample was then matched with a control group, consisted of 90 patients as well. The gender ratio was 44 males to 46 females in study group, and 40 males to 50 females in control group. The mean age at the beginning of orthodontic treatment in study group was 16.69 years, and 15.35 years in control group.

As evaluation process involved 3715 patients, radiographic films, panoramic radiographs, were the first element to be inspected, and patients with no present clear radiographic films –initial or final- were excluded of the study.

Panoramic radiographs are the most common diagnostic tool in dentistry. In orthodontics, panoramic films are used as a diagnostic tool when it comes to missing, supernumerary, and impacted teeth. Additionally they are helpful in cases of trauma and temporomandibular joints disorders. Panoramic radiography is considered a useful tool for detecting root resorption (Dudic et al., 2009).

The root morphology of the anterior teeth was a determining factor that classified the study group into four different subgroups according to the root shape; triangular, rhomboid, dilacerated, and pipette. Triangular root shape was the most common in the study group, while rhomboid roots were the most common in control group. Evaluation of root morphology was done using panoramic radiographs. The main limitation in this evaluation was the poor quality of radiographic films for some patients, which made the evaluation process more challenging.

Another determining factor the study group was classified according to was the type of treatment. Patients were classified according to the treatment modality that took place as non-extraction and extraction cases. It was important to subdivide subjects into two groups to study the effect of treatment type followed and the severe EARR.

Lateral cephalometric analysis was another key element used in the study. The lateral cephalometric radiograph is a standard component of clinical records taken for orthodontic diagnosis and treatment planning (Proffit et al., 2007). It was initially introduced by two scientists; Hofrath in Germany and Holly Broadbent in the United States in 1931, and its main objective was to assess growth and development in the craniofacial complex (Hans et al., 2015; Miedzik and Syryńska, 2007). The relative use of cephalometric analysis in orthodontic diagnosis and treatment planning has changed throughout the years. With time the cephalometric radiograph became an important diagnostic tool in orthodontics, and treatment objectives were drawn to achieve certain final values.

The aim of cephalometric analysis is to estimate and understand the relationships of the maxilla and mandible to the cranial base, and their relationship to each other, and to understand the relationship of the maxillary and mandibular dentition to each other and to the surrounding tissues in vertical, sagittal, and transverse planes. Conventional analysis is performed by manually tracing radiographic landmarks to measure the wanted linear and angular values. Later, cephalometric analysis and tracing became digitalized with the help of computers and software, making the analysis less time and effort consuming for orthodontists.

The rest of studied variables, overjet, overbite, bone thickness, and tooth movement were measured using cephalometric radiographs. Another limitation we faced in our study is the calibration and standardization of cephalometric radiographs dimensions and measurements. As our sample contained growing patients, a stable and non-changing reference was necessary to be followed. Middle cranial base was found to maintain its stability in all pubertal growth periods, which allowed us to use it as a calibration tool (Arat et al., 2001; Arat et al., 2010; Torlakovic and Færøvig, 2011).

As alveolar bone width was measured on cephalometric radiographs, limitation of not clear and poor quality radiographic films was faced again. Few times the root apex was difficult to be located precisely. Moreover, for determining the lining and width of alveolar bone, it was necessary to locate its upper posterior and anterior landmarks, and it was challenging to locate the anterior point, particularly. The distance between anterior bone (UA) and the root apex, and between posterior bone (UP) and the root apex in a line drawn parallel to the palatal plane (ANS-PNS) were measured and the sum resulted in alveolar bone thickness (Handelman, 1996).

For the last and most determining factor in our study, tooth movement, producing additional stable and constant references was necessary to provide accurate measurements, and to have a negligible effect of growth affecting these distances. The angle between Frankfort Horizontal (FH) plane and the Sella-Nasion line was reported in literature to be 7 degrees, and within an individual, does not vary significantly over time (Huh et al., 2014). This angle was the base we built on to create horizontal and vertical references for linear measurements. A parallel line to Frankfort Horizontal plane was drawn intersecting the Sella (S) point in a clockwise direction with an angle of 7 degrees (Picture 5.6.5.3.1). Another vertical line dropped from the (S) point perpendicular to the horizontal reference, and both lines were used to measure horizontal and vertical movements in incisor edge and root apex. These lines are used as references to evaluate dental and skeletal changes for orthognathic surgery cases as well (Boeck et al., 2010). Post-operative values were subtracted from pre-operative ones, and absolute values were used for statistical comparisons. Later on, the displacement values were classified into positive and negative values; positive results indicate backward/upward movement, i.e., retraction or intrusion, while negative values indicate forward/downward movement, i.e., proclination or extrusion. Some researches added the incisors inclination to the palatal plane angle as a determinant measurement for apical root displacement, before and after the treatment (Kim et al., 2018) (Figure 7.1.2.1).

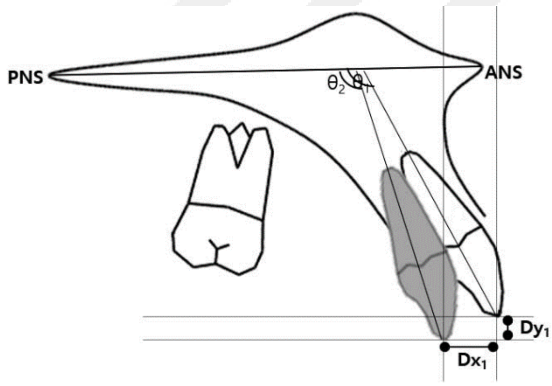



**Figure 7.1.2.1.** Evaluation of maxillary central incisor displacement; Dx, horizontal movement of the incisal edge; Dy, vertical movement of the incisal edge; θ, inclination of the central incisor to the palatal plane (Kim et al., 2018).

### 7.1.3. Discussion of results

In agreement with the results of other researches, this study found a low prevalence of teeth with severe EARR (3.23%) with the loss of more than 1/3 of root length, while 96.77% showed clinically acceptable root resorption classified as mild and moderate, and as part of the biological tissue reaction to orthodontic treatment. Authors have reported that prevalence of 1%-5% of patients experiencing severe EARR can be seen following an orthodontic treatment (Årtun et al., 2009; Killiany, 1999; Mauès et al., 2015; Mirabella and Artun, 1995).

To ensure the reliability of the scoring made by the examiner, kappa test was used and kappa coefficient was calculated to assess the degree of agreement between two sets of scoring. The percentage of agreement was substantial and kappa coefficient was 0.643 and scoring of root resorption was reliable. To estimate the random error of the method, Dahlberg formula was used (Dahlberg, 1940). The largest linear error found was for the bone thickness (UA+UP) variable, 0.23 mm. All measurements were highly reliable, and the repeated measurements were close to each other which reduced the observer bias to a minimum.

After evaluating the results for inter-group comparison of the study and control groups, the following variables were found to be significant ($p<0.05$). In relation to age at the beginning of treatment, the difference was significant. As control group included younger patients when compared to resorption group, it can be affirmed that older patients have a higher risk to develop severe EARR following orthodontic treatment (Table 6.4). This finding is seen to be approved by many authors, who suggested that root resorption is more prevalent in adults than in children (Nanekrungsan et al., 2012; Sameshima and Sinclair, 2001, 2001; Tian et al., 2013). On the other hand, some authors reported that age was not a significant factor affecting root resorption for patients receiving orthodontic treatment (Elhaddaoui et al., 2016; Kim et al., 2018; Pastro et al., 2018). The reason that adults seem to be more susceptible to root resorption is that with aging, the periodontal ligament becomes less vascularized, aplastic and narrow; thickness of cementum increases; and density of bone increases as well (Thilander et al., 2011).

Another significant factor found was treatment duration; control group presented shorter treatment duration, mean of 2.48 years, when compared to resorption group, mean of 3.7 years (Table 6.4). Patients who underwent longer orthodontic treatment had higher risk to develop severe EARR. Long treatment time results in longer periods of stimulation of the root and accumulation of root resorption (Mauès et al., 2015). The possible correlation between the duration of active treatment and the incidence and severity of EARR was controversial; some studies concluded that there is positive correlation between EARR and treatment duration (Dindaroğlu and Doğan, 2017; Nanekrungsan et al., 2012; Pastro et al., 2018; Topkara et al., 2012). While other studies found no significant association between root resorption and treatment duration (Elhaddaoui et al., 2016; Kim et al., 2018).

The inter-group comparison has also revealed that there was no significant relationship between severe EARR and gender of the patient (Table 6.5). Most of authors reported there is no relationship between root resorption and gender, and it was agreeing with our results (Consolaro, 2005; Jiang et al., 2010; Parker and Harris, 1998; Pastro et al., 2018; Picanço et al., 2013; Ramanathan and Hofman, 2009). However, very few studies reported that gender played a role in orthodontic root resorption, and females were seen to be more susceptible than males (Jiang et al., 2003; Kalra et al., 2019).

Treatment type or treatment modality was an important factor to be investigated in our study. Treatment type may also affect the treatment duration in which they both are linked and affected simultaneously. The results showed a significant relationship between treatment type and severe EARR (Table 6.5). The resorption group presented 40 patients that were treated with extraction protocol, and mainly the upper first premolars, while just 16 patients were treated with the same treatment modality in control group. As extractions result in prolonged treatment time needed to close extraction spaces, relieve crowding, and retract anterior teeth, authors agree with this finding, reporting that treatment type should be chosen wisely with patients accompanied with higher risk factors to develop EARR (Deng et al., 2018; Elhaddaoui et al., 2016; Jacobs et al., 2014; Mauès et al., 2015; Pastro et al., 2018; Picanço et al., 2013).

The root morphology was found to have no significant relationship with severe EARR (Table 6.5). This finding was contradicting with many authors; it was considered that teeth with pipette or dilacerated (abnormal) root shape have a higher risk of root resorption (Ahuja et al., 2017; Elhaddaoui et al., 2016; Marques et al., 2010; Quintanilha et al., 2019; Sameshima and Sinclair, 2001). This finding is likely to be the result of having high percentage of rhomboid roots in the sample, which reduces the risk of root resorption (Levander et al., 1998; Picanço et al., 2013; Quintanilha et al., 2019; Sameshima and Sinclair, 2001).

In terms of cephalometric analysis, the inter-group comparison showed no significant effect of overjet and overbite in the resorption group when compared to control group, indicating that at the beginning of treatment, these variables are not a risk factor to the development of severe EARR (Table 6.6). The mean overjet and overbite values at the beginning of orthodontic treatment did not show a statistically significant difference. The mean overjet in the resorption group was 4.61 mm, which was slightly higher than that in the control group, 4.39 mm. The mean overbite in the resorption group, 1.93 mm, was seen to be less than that in the control group, 2.19 mm. This was probably due to the increased number of open bite cases in the resorption group. The differences in mean overbite and overjet between the two groups were not statistically significant. These findings contradict most of the authors, and the justification for this is the high percentage of patients with increased overjet and overbite in control group, and their treatment included fewer extractions when compared to resorption group (fixed functional appliances, intermaxillary elastics). Increased overjet is considered to be a risk factor because the correction indicates that anterior teeth need to move long distances to reduce maxillary anterior protrusion, and active torque with rectangular wire was also required (Brin et al., 2003; Nanekrungsan et al., 2012; Sameshima and Sinclair, 2001). The greater movements of teeth and active torque application have been shown to result in EARR. Some authors reported that there was no correlation between increased overjet and overbite and EARR (Jung and Cho, 2011; Picanço et al., 2013). And others reported that increased overjet for more than 5 mm can be a risk factor, which is agreeing with our results as the mean was less than this value (Maués et al., 2015). As deep bite cases increase the need for intrusion mechanics and correction of curve of Spee, authors have reported that deep bite can be a risk factor to EARR (Martins et al., 2012). Moreover, some studies have shown that the reduction in occlusal function in cases of open bite is a beginning of atrophy in the periodontal ligament which becomes hypofunctional, with weak resistance to external stimuli which increases susceptibility to root resorption (Elhaddaoui et al., 2016; Sringkarnboriboon et al., 2003).

Bone thickness was also evaluated to cephalometrically, and it showed statistically significant results (Table 6.6). With relatively thin alveolar bone seen in resorption group (12.5 mm), in comparison with thicker bone in control group (15 mm), this result confirms the authors' hypothesis that thin alveolar bone is a risk factor for severe EARR because teeth are being pushed against the thin cortical bone (Ahn et al., 2013; Handelman, 1996; Horiuchi et al., 1998; Picanço et al., 2013).

The last variable related to cephalometric analysis was the tooth movement, where mathematical calculation was done to measure the absolute values of apical root displacement, and the incisal edge displacement, in vertical and horizontal directions. Results showed significant relationship between the amount of tooth movement -net displacement of the root apex and incisal edge during the treatment-, and severe EARR. Horizontal incisal edge and apical root displacement were 2.82 mm, and 1.69 mm for the resorption group, and 1.41 mm, and 1.17 mm for the control group, respectively. Vertical incisal edge and apical root displacement were 1.45 mm, and 1.81 mm for the resorption group, and 1.14 mm, 1.02 mm for the control group, respectively (Table 6.7). This finding is approved by many authors; the increase in tooth movement is a risk factor of EARR (Agarwal et al., 2014; Dudic et al., 2009; Kim et al., 2018; Motokawa et al., 2012; Weltman et al., 2010). Furthermore, tooth movement was investigated further to understand the effect of movement in horizontal and vertical directions, and to understand the effect of movement of incisal edge and root apex in the occurrence of severe EARR. In horizontal displacement, no difference was seen between the two groups with respect to the number of patients with either proclination (anterior) and retraction (posterior) movements (Table 6.8). Additionally, most anterior displacements were seen at the level of the incisal edge, while the posterior displacements were seen the most at the root apex. For the vertical displacement, statistically significant differences were seen in the distribution of subjects with extrusion (downward) and intrusion (upward) displacements in both groups, as extrusion was seen to be the most in the resorption group at both levels of incisal edge and root apex, it was indicated that extrusion affects the occurrence of severe EARR (Table 6.9). This finding is contradicted by many authors, who reported that intrusion is most likely to be a risk factor for root resorption when compared to extrusion; intrusion of teeth causes about four times more root resorption than extrusion (Han et al., 2005; Parker and Harris, 1998). This finding can be justified because the extractions of premolars, space closure, and retractions of incisors result in controlled and uncontrolled tipping of these teeth, which affect the incisors angulation and have extrusive forces (Jayaratne et al., 2017; Luiz et al., 2016; Ruellas et al., 2013; Sarver and Weissman, 1995).

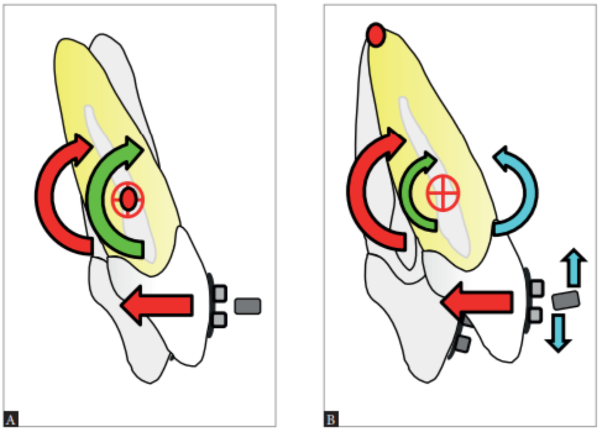



**Figure 7.1.3.1.** Tipping movement. A) Uncontrolled tipping B) controlled tipping. The red arrows represent the force applied to teeth and the moment of force. The blue arrows represent the force of a wire into the bracket and the moment of a couple. The green arrow is the resultant moment (moment of force minus moment of a couple) (Luiz et al., 2016).

In Orthodontics department, Marmara University, two space closure mechanics are applied; sliding mechanics and closing loops. Once the canine retraction has been completed, the anterior segment was retracted mainly using closing loops. Consequently, retraction of incisors result in uprighting and relative extrusion as the crown was retracted below the center of rotation (Kuhlberg and Nanda, 2005).

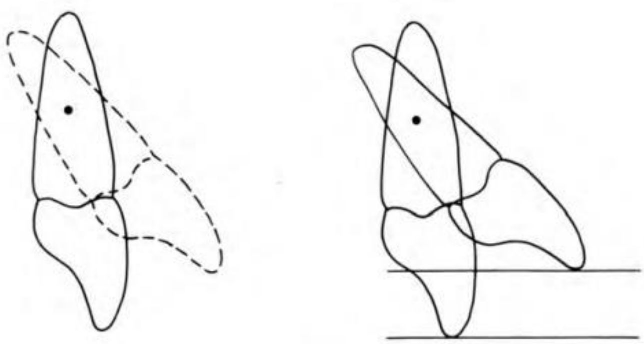


**Figure 7.1.3.2.** Retraction of incisors can result in extrusive movement.

The same extrusive effect was also seen with sliding mechanics; as incisors are pulled below the center of rotation, and torque loss occur (Jayaratne et al., 2017; Ruellas et al., 2013). This extrusive movement results in worsening any deep bite present before retraction, and maxillary or mandibular incisors should be intruded to compensate this effect. Intrusion of mandibular incisors was the most common protocol followed in the department using utility arch and reverse curve NiTi wires.

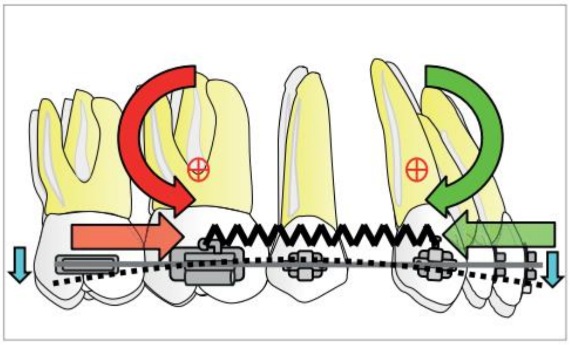


**Figure 7.1.3.3.** Force system generated by a closed coil spring applying force bellow the center of resistance of the segments (Luiz et al., 2016).

Another reason was the relatively high number of patients presented with open bite in the resorption group, because extrusion of the upper and lower incisors was a common orthodontic treatment for anterior open bites (Freitas et al., 2007). Moreover, as our measurements were performed prior to the orthodontic treatment and after, and the measurements of mid-treatment phase were not included, it was difficult to clearly exclude intrusion as a risk factor. The reason behind this is the complex of movement contributing; incisors may be intruded during working phase of the orthodontic treatment, but during finishing and the final leveling stages, these teeth may exhibit extrusive movements as a result of brackets repositioning, or as a side effect of the inter-maxillary elastics.

The results of the present investigation conducted on the available records of fixed orthodontic patients treated in Marmara University Faculty of Dentistry Department of Orthodontics between 1990 and 2019 showed that the prevalence of severe root resorption of the upper incisors was 3.23%. Older age at the onset of treatment, prolonged treatment duration, treatment with premolar extractions, presence of a thin alveolar bone, excessive amounts of horizontal and vertical displacement of the teeth were identified to be risk factors for the occurrence of severe root resorption. These factors should be taken into consideration when making treatment plans for future patients in order to minimize the risk of severe root resorption and to optimize the treatment results. A further clinical study designed to elucidate the prognosis and longevity of these severely resorbed teeth in the long term may provide interesting and useful findings which could provide a better understanding of the outcome of this undesirable clinical phenomenon.

### 7.2. Conclusion

According to the methodology applied and the conditions established in this study, it can be concluded that:

- The prevalence of severe EARR in upper incisors in fixed orthodontic patients treated in Marmara University, Faculty of Dentistry, Department of Orthodontics is 3.23%.
- Older patients are more susceptible to severe EARR.
- Patients with prolonged treatment duration are at higher risk to develop severe EARR than patients undergoing short treatments.
- Patients treated with extractions have a higher chance of presenting severe EARR than patients treated without extractions.
- Patients with thin alveolar bone are more likely to develop severe EARR than patients with thick alveolar bone.
- Excessive tooth movement increases the risk of severe EARR, and care should be taken when such movement is needed.
- Gender, root shape, overjet, and overbite are not considered as risk factors for developing of severe EARR.

# 8. REFERENCES


Agarwal, A., Agarwal, N., Sharma, V., Singh, G., and Tikku, T. (2014). The effect of central incisor′s root proximity to the cortical plate and apical root resorption in extraction and non-extraction treatment. *Journal of Orthodontic Science*, *3*(2), 46.

Agrawal, N., and Siddani, P. (2011). Reactive positioning of pathologically migrated tooth following non-surgical periodontal therapy. *Indian Journal of Dental Research*, *22*(4), 591.

Ahn, H. W., Moon, S. C., and Baek, S. H. (2013). Morphometric evaluation of changes in the alveolar bone and roots of the maxillary anterior teeth before and after en masse retraction using cone-beam computed tomography. *Angle Orthodontist*, *83*(2), 212–221.

Ahuja, P. D., Mhaske, S. P., Mishra, G., Bhardwaj, A., Dwivedi, R., and Mangalekar, S. B. (2017). Assessment of root resorption and root shape by periapical and panoramic radiographs: A comparative study. *Journal of Contemporary Dental Practice*, *18*(6), 479–483.

Aidos, F. A. (2018). Root Resorption Classifications: A Narrative Review and a Clinical Aid Proposal for Routine Assessment. *European Endodontic Journal*, *3*(3), 134.

Ajmera, S., Shivanand Venkatesh, and Ganeshkar, S. V. (2014). Volumetric evaluation of root resorption during orthodontic treatment. *Journal of Clinical Orthodontics : JCO*, *48*(2), 113–119.

Akyalcin, S., Alexander, S. P., Silva, R. M., and English, J. D. (2015). Evaluation of three-dimensional root surface changes and resorption following rapid maxillary expansion: A cone beam computed tomography investigation. *Orthodontics and Craniofacial Research*, *18*(S1), 117–126.

Al-Qawasmi, R. A., Hartsfield, J. K., Everett, E. T., Flury, L., Liu, L., Foroud, T. M., Roberts, W. E. (2003). Genetic predisposition to external apical root resorption in orthodontic patients: Linkage of chromosome-18 marker. *Journal of Dental Research*, *82*(5), 356–360.

Al-Qawasmi, R., Hartsfield, J. K., Everett, E. T., Flury, L., Liu, L., Foroud, T. M., … Roberts, W. E. (2003). Genetic predisposition to external apical root resorption. *American Journal of Orthodontics and Dentofacial Orthopedics*, *123*(3), 242–252.

Andreasen, J. O. (1970). Luxation of permanent teeth due to trauma A clinical and radiographic follow-up study of 189 injured teeth. *European Journal of Oral Sciences*, *78*(1–4), 273–286.

Andreasen, J. O. (1985). External root resorption: its implication in dental traumatology, paedodontics, periodontics, orthodontics and endodontics. *International Endodontic Journal*, *18*(2), 109–118.

Andreasen, J. O., and Kristerson, L. (1981). The effect of limited drying or removal of the periodontal ligament: Periodontal healing after replantation of mature permanent incisors in monkeys. *Acta Odontologica Scandinavica*, *39*(1), 1–13.

Apajalahti, S., and Peltola, J. S. (2007). Apical root resorption after orthodontic treatment-a retrospective study. *European Journal of Orthodontics*, *29*(4), 408–412.

Arat, M., Koklu, A., Ozdiler, E., Rubenduz, M., and Erdogan, B. (2001). Craniofacial growth and skeletal maturation: a mixed longitudinal study. *European Journal of Orthodontics*, *23*(4), 355–361.

Arat, Z. M., Turkkahraman, H., English, J. D., Gallerano, R. L., and Boley, J. C. (2010). Longitudinal growth changes of the cranial base from puberty to adulthood. A comparison of different superimposition methods. *The Angle Orthodontist*, *80*(4), 537–544.

Arias, O. R., and Marquez-Orozco, M. C. (2006). Aspirin, acetaminophen, and ibuprofen: Their effects on orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics*, *130*(3), 364–370.

Årtun, J., Van't Hullenaar, R., Doppel, D., and Kuijpers-Jagtman, A. M. (2009).

Identification of orthodontic patients at risk of severe apical root resorption. *American Journal of Orthodontics and Dentofacial Orthopedics*, *135*(4), 448–455.

Barrett, E. J., and Kenny, D. J. (1997). Avulsed permanent teeth: A review of the literature and treatment guidelines. *Endodontics and Dental Traumatology*, *13*(4), 153–163.

Bartley, N., Türk, T., Colak, C., Elekdağ-Türk, S., Jones, A., Petocz, P., and Darendeliler, M. A. (2011). Physical properties of root cementum: Part 17. Root resorption after the application of 2.5° and 15° of buccal root torque for 4 weeks: A microcomputed tomography study. *American Journal of Orthodontics and Dentofacial Orthopedics*, *139*(4), e353-60.

Baumrind, S., Korn, E. L., and Boyd, R. L. (1996). Apical root resorption in orthodontically treated adults. *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *110*(3), 311–320.

Bavle, R. M., Sharada, P., and Kumar, G. S. (2011). Cementum. *Orban's Oral Histol. Embryol. 13th Ed. New Delhi: Elsevier*, 131–151.

Bilgic, F., Gelgor, I. E., and Celebi, A. A. (2015). Malocclusion prevalence and orthodontic treatment need in central Anatolian adolescents compared to European and other nations' adolescents. *Dental Press Journal of Orthodontics*, *20*(6), 75–81.

Björk, A., and Skieller, V. (1983). Normal and abnormal growth of the mandible. A synthesis of longitudinal cephalometric implant studies over a period of 25 years. *European Journal of Orthodontics*, *5*(1), 1–46.

Black, D. M., Thompson, D. E., Bauer, D. C., Ensrud, K., Musliner, T., Hochberg, M. C., … Cummings, S. R. (2000). Fracture risk reduction with alendronate in women with osteoporosis: The fractureintervention trial. *Journal of Clinical Endocrinology and Metabolism*, *85*(11), 4118–4124.

Blake, M., Woodside, D. G., and Pharoah, M. J. (1995). A radiographic comparison of apical root resorption after orthodontic treatment with the edgewise and Speed appliances. *American Journal of Orthodontics and Dentofacial Orthopedics*, *108*(1), 76–84.

Boeck, E. M., Kuramae, M., Lunardi, N., dos Santos-Pinto, A., and Mazzonetto, R. (2010). Cephalometric evaluation of surgical mandibular advancement. *Brazilian Oral Research*, *24*(2), 189–196.

Borges de Castilhos, B., Machado de Souza, C., Simas Netta Fontana, M. L. S., Pereira, F. A., Tanaka, O. M., and Trevilatto, P. C. (2019). Association of clinical variables and polymorphisms in RANKL, RANK, and OPG genes with external apical root resorption. *American Journal of Orthodontics and Dentofacial Orthopedics*, *155*(4), 529–542.

Bosshardt, D. D., and Selvig, K. A. (1997). Dental cementum: the dynamic tissue covering of the root. *Periodontology 2000*, *13*(1), 41–75.

Brezniak, N., and Wasserstein, A. (1993). Root resorption after orthodontic treatment: Part 2. Literature review. *American Journal of Orthodontics and Dentofacial Orthopedics*, *103*(2), 138–146.

Brezniak, N., and Wasserstein, A. (2002). Orthodontically Induced Inflammatory Root Resorption. Part I: The Basic Science Aspects. *Angle Orthodontist*, *72*(2), 175–179.

Brin, I., Tulloch, J. F. C., Koroluk, L., and Philips, C. (2003). External apical root resorption in Class II malocclusion: A retrospective review of 1- versus 2-phase treatment. *American Journal of Orthodontics and Dentofacial Orthopedics*, *124*(2), 151–156.

Chan, E., and Darendeliler, M. A. (2005). Physical properties of root cementum: Part 5. Volumetric analysis of root resorption craters after application of light and heavy orthodontic forces. *American Journal of Orthodontics and Dentofacial Orthopedics*, *127*(2), 186–195.

Chan, E., and Darendeliler, M. A. (2006). Physical properties of root cementum: Part 7. Extent of root resorption under areas of compression and tension. *American Journal of Orthodontics and Dentofacial Orthopedics*, *129*(4), 504–510.

Cheng, L. L., Türk, T., Elekda-Türk, S., Jones, A. S., Yu, Y., and Darendeliler, M. A. (2010). Repair of root resorption 4 and 8 weeks after application of continuous light and heavy forces on premolars for 4 weeks: A histology study. *American Journal of Orthodontics and Dentofacial Orthopedics*, *138*(6), 727–734.

Cheng, L. L., Türk, T., Elekdağ-Türk, S., Jones, A. S., Petocz, P., and Darendeliler, M. A. (2009). Physical properties of root cementum: Part 13. Repair of root resorption 4 and 8 weeks after the application of continuous light and heavy forces for 4 weeks: A microcomputed-tomography study. *American Journal of Orthodontics and Dentofacial Orthopedics*, *136*(3), 320.e1-320.e10.

Chiqueto, K., Martins, D. R., and Janson, G. (2008). Effects of accentuated and reversed curve of Spee on apical root resorption. *American Journal of Orthodontics and Dentofacial Orthopedics*, *133*(2), 261–268.

Consolaro, A. (2005). *Reabsorções dentárias nas especialidades clínicas. 2ª ed. Maringá: Dental Press*.

Consolaro, Alberto. (2014). Force distribution is more important than its intensity! *Dental Press Journal of Orthodontics*, *19*(1), 5–7.

Consolaro, Alberto, and Bittencourt, G. (2016). Why not to treat the tooth canal to solve external root resorptions? Here are the principles! *Dental Press Journal of Orthodontics*, *21*(6), 20–25.

Cuoghi, O. A., Aiello, C. A., Consolaro, A., Tondelli, P. M., and Mendonça, M. R. de. (2014). Resorption of roots of different dimension induced by different types of forces. *Brazilian Oral Research*, *28*.

Da Silva Filho, O. G., De Freitas Mendes, O., Ozawa, T. O., Ferrari, F. M., and Correa, T. M. (2004). Behavior of partially formed roots of teeth submitted to orthodontic movement. *Journal of Clinical Pediatric Dentistry*, *28*(2), 147–154.

Dahlberg, G. (1940). Statistical methods for medical and biological students. *Statistical Methods for Medical and Biological Students.*

Dandajena, T. C., Ihnat, M. A., Disch, B., Thorpe, J., and Currier, G. F. (2012). Hypoxia triggers a HIF-mediated differentiation of peripheral blood mononuclear cells into osteoclasts. *Orthodontics and Craniofacial Research*, *15*(1), 1–9.

Darcey, J., and Qualtrough, A. (2013). Resorption: Part 1. Pathology, classification and aetiology. *British Dental Journal*, *214*(9), 439–451.

Davidovitch, Z. (1991). Tooth movement. *Critical Reviews in Oral Biology and Medicine*, Vol. 2, pp. 411–450.

Davidovitch, Z., Nicolay, O. F., Ngan, P. W., and Shanfeld, J. L. (1988, July). Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. *Dental Clinics of North America*, Vol. 32, pp. 411–435.

Deng, Y., Sun, Y., and Xu, T. (2018). Evaluation of root resorption after comprehensive orthodontic treatment using cone beam computed tomography (CBCT): A meta-analysis. *BMC Oral Health*, *18*(1).

Dindaroğlu, F., and Doğan, S. (2017). Root Resorption in Orthodontics. *Turkish Journal of Orthodontics*, *29*(4), 103–108.

Dudic, A., Giannopoulou, C., Leuzinger, M., and Kiliaridis, S. (2009). Detection of apical root resorption after orthodontic treatment by using panoramic radiography and cone-beam computed tomography of super-high resolution. *American Journal of Orthodontics and Dentofacial Orthopedics*, *135*(4), 434–437.

Elhaddaoui, R., Benyahia, H., Azeroual, M. F., Zaoui, F., Razine, R., and Bahije, L. (2016). Resorption of maxillary incisors after orthodontic treatment – clinical study of risk factors. *International Orthodontics*, *14*(1), 48–64.

Engstrom, C., Granstrom, G., and Thilander, B. (1988). Effect of orthodontic force on periodontal tissue metabolism: a histologic and biochemical study in normal and hypocalcemic young rats. *Am J Orthod Dentofac Orthop*, *93*, 468–495.

Feller, L., Khammissa, R. A. G., Schechter, I., Moodley, A., Thomadakis, G., and Lemmer, J. (2015). *Periodontal Biological Events Associated with Orthodontic Tooth Movement: The Biomechanics of the Cytoskeleton and the Extracellular Matrix*.

Freitas, M. R., Soares Beltrão, R. T., Janson, G., Castanha Henriques, J. F., and Chiqueto, K. (2007). Evaluation of root resorption after open bite treatment with and without extractions. *American Journal of Orthodontics and Dentofacial Orthopedics*, *132*(2), 143.e15-143.e22.

Fukushima, H., Kajiya, H., Takada, K., Okamoto, F., and Okabe, K. (2003). Expression and role of RANKL in periodontal ligament cells during physiological root-resorption in human deciduous teeth. *European Journal of Oral Sciences*, *111*(4), 346–352.

Goldberg, M., Kulkarni, A. B., Young, M., and Boskey, A. (2011). Dentin: Structure, composition and mineralization. *Frontiers in Bioscience - Elite*, *3 E*(2), 711–735.

Gonzales, C., Hotokezaka, H., Matsuo, K. I., Shibazaki, T., Yozgatian, J. H., Darendeliler, M. A., and Yoshida, N. (2009). Effects of steroidal and nonsteroidal drugs on tooth movement and root resorption in the rat molar. *Angle Orthodontist*, *79*(4), 715–726.

Guo, Y., He, S., Gu, T., Liu, Y., and Chen, S. (2016). Genetic and clinical risk factors of root resorption associated with orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics*, *150*(2), 283–289.

Hammarström, L., Pierce, A., Blomlöf, L., Feiglin, B., and Lindskog, S. (1986). Tooth avulsion and replantation — A review. *Dental Traumatology*, *2*(1), 1–8.

Han, G., Huang, S., Von Den Hoff, J. W., Zeng, X., and Kuijpers-Jagtman, A. M. (2005). Root resorption after orthodontic intrusion and extrusion: An intraindividual study. *Angle Orthodontist*, *75*(6), 912–918.

Handelman, C. S. (1996). *The anterior alveolus : its importance in limiting orthodontic treatment and its influence on the occurrence of iatrogenic sequelae*. 95–110.

Hans, M. G., Palomo, J. M., and Valiathan, M. (2015). *History of imaging in orthodontics from Broadbent to cone-beam computed tomography*.

Harokopakis-Hajishengallis, E. (2007). Physiologic root resorption in primary teeth: molecular and histological events. *Journal of Oral Science*, Vol. 49, pp. 1–12.

Harris, D. A., Jones, A. S., and Darendeliler, M. A. (2006). Physical properties of root cementum: Part 8. Volumetric analysis of root resorption craters after application of controlled intrusive light and heavy orthodontic forces: A microcomputed tomography scan study. *American Journal of Orthodontics and Dentofacial Orthopedics*, *130*(5), 639–647.

Harris, E. F., Kineret, S. E., and Tolley, E. A. (1997). A heritable component for external apical root resorption in patients treated orthodontically. *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *111*(3), 301–309.

Harris, E. F., Robinson, Q. C., and Woods, M. A. (1993). An analysis of causes of apical root resorption in patients not treated orthodontically. *Quintessence International (Berlin, Germany : 1985)*, *24*(6), 417–428.

Harry, M. R., and Sims, M. R. (1982). Root resorption in bicuspid intrusion. A scanning electron microscope study. *Angle Orthodontist*, *52*(3), 235–258.

Hart, A., Cota, A., Makhdom, A., and Harvey, E. J. (2015, July 1). The Role of Vitamin C in Orthopedic Trauma and Bone Health. *American Journal of Orthopedics (Belle Mead, N.J.)*, Vol. 44, pp. 306–311.

Hashemi, M., AOtoufi, A., Badiee, M., Abdolazimi, Z., and Younesian, F. (2012). Orthodontic Tooth Movement and Root Resorption Following Treatment with Various Doses of Celecoxib in Rats. In *Journal Dental School* (Vol. 29).

Hatewar, S. K., Reddy, G. H., Singh, J. R., Jain, M., Munje, S., and Khandelwal, P. (2015). A new dimension to cephalometry: DW plane. *Journal of Indian Orthodontic Society*, *49*(4), 206–212.

Heinrich, J., Bsoul, S., Barnes, J., Woodruff, K., and Abboud, S. (2005). CSF-1, RANKL and OPG regulate osteoclastogenesis during murine tooth eruption. *Archives of Oral Biology*, *50*(10), 897–908.

Heithersay, G. S. (2004). Invasive cervical resorption. *Endodontic Topics*, *7*(1), 73–92.

Helm, S., and Petersen, P. E. (1989). Causal relation between malocclusion and periodontal health. *Acta Odontologica Scandinavica*, *47*(4), 223–228.

Holberg, C., Steinhäuser, S., Geis, P., and Rudzki-Janson, I. (2005). Cone-Beam Computed Tomography in Orthodontics: Benefits and Limitations. *Journal of Orofacial Orthopedics / Fortschritte Der Kieferorthopädie*, *66*(6), 434–444.

Horiuchi, A., Hotokezaka, H., and Kobayashi, K. (1998). Correlation between cortical plate proximity and apical root resorption. *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *114*(3), 311–318.

Horowitz, M. C., Xi, Y., Wilson, K., and Kacena, M. A. (2001). Control of osteoclastogenesis and bone resorption by members of the TNF family of receptors and ligands. *Cytokine and Growth Factor Reviews*, Vol. 12, pp. 9–18.

Huang, H., Williams, R. C., and Kyrkanides, S. (2014). Accelerated orthodontic tooth movement: Molecular mechanisms. *American Journal of Orthodontics and Dentofacial Orthopedics*, *146*(5), 620–632.

Huh, Y. J., Huh, K. H., Kim, H. K., Nam, S. E., Song, H. Y., Lee, J. H., and Park, Y. S. (2014). Constancy of the angle between the Frankfort horizontal plane and the sella-nasion line: A nine-year longitudinal study. *Angle Orthodontist*, *84*(2), 286–291.

Iglesias-Linares, A., and Hartsfield, J. K. (2017). Cellular and Molecular Pathways Leading to External Root Resorption. *Journal of Dental Research*, Vol. 96, pp. 145–152.

Işeri, H., Kurt, G., and Kişnişci, R. (2010). Biomechanics of Rapid Tooth Movement by Dentoalveolar Distraction Osteogenesis. In *Current Therapy in Orthodontics* (pp. 321–337). Elsevier.

Ishihara, T., Miyazaki, M., Notani, N., Kanezaki, S., Kawano, M., and Tsumura, H. (2017). Locally Applied Simvastatin Promotes Bone Formation in a Rat Model of Spinal Fusion. *Journal of Orthopaedic Research*, *35*(9), 1942–1948.

Iwasaki, L. R., Gibson, C. S., Crouch, L. D., Marx, D. B., Pandey, J. P., and Nickel, J. C. (2006). Speed of tooth movement is related to stress and IL-1 gene polymorphisms. *American Journal of Orthodontics and Dentofacial Orthopedics*, *130*(6), 698.e1-698.e9.

Jacobs, C., Gebhardt, P. F., Jacobs, V., Hechtner, M., Meila, D., and Wehrbein, H. (2014). *Root resorption, treatment time and extraction rate during orthodontic treatment with self-ligating and conventional brackets*.

Jäger, A., Kunert, D., Friesen, T., Zhang, D., Lossdörfer, S., and Götz, W. (2008). Cellular and extracellular factors in early root resorption repair in the rat. *European Journal of Orthodontics*, *30*(4), 336–345.

Janson, G. R. P., De Luca Canto, G., Rodrigues Martins, D., Castanha Henriquesand, J. F., and De Freitas, M. R. (2000). A radiographic comparison of apical root resorption after orthodontic treatment with 3 different fixed appliance techniques. *American Journal of Orthodontics and Dentofacial Orthopedics*, *118*(3), 262–273.

Jayaratne, Y. S. N., Uribe, F., and Janakiraman, N. (2017). Maxillary incisors changes during space closure with conventional and skeletal anchorage methods: a systematic review. *Journal of Istanbul University Faculty of Dentistry*, *51*(3 Suppl 1), S90—S101.

Jiang, C., Li, Z., Quan, H., Xiao, L., Zhao, J., Jiang, C.,Wang, J. (2015, September 1). Osteoimmunology in orthodontic tooth movement. *Oral Diseases*, Vol. 21, pp. 694–704.

Jiang, N., Guo, W., Chen, M., Zheng, Y., Zhou, J., Kim, S. G., … Mao, J. J. (2015). Periodontal Ligament and Alveolar Bone in Health and Adaptation: Tooth Movement. *Frontiers of Oral Biology*, *18*, 1–8.

Jiang, R. ping, McDonald, J. P., and Fu, M. K. (2010). Root resorption before and after orthodontic treatment: A clinical study of contributory factors. *European Journal of Orthodontics*, *32*(6), 693–697.

Jiang, R. ping, Zhang, D., and Fu, M. kui. (2003). A factors study of root resorption after orthodontic treatment. *Zhonghua Kou Qiang Yi Xue Za Zhi = Zhonghua Kouqiang Yixue Zazhi = Chinese Journal of Stomatology*, *38*(6), 455–457.

Jönsson, A., Malmgren, O., and Levander, E. (2007). Long-term follow-up of tooth mobility in maxillary incisors with orthodontically induced apical root resorption. *European Journal of Orthodontics*, *29*(5), 482–487.

Jung, Y. H., and Cho, B. H. (2011). External root resorption after orthodontic treatment: A study of contributing factors. *Imaging Science in Dentistry*, *41*(1), 17–21.

Kaley, J., and Phillips, C. (1991). Factors related to root resorption in edgewise practice. *Angle Orthodontist*, *61*(2), 125–132.

Kalra, S., Tripathi, T., and Rai, P. (2019). External Apical Root Resorption in Orthodontic Patients-Local Cause or Genetic Predisposition. *ACTA SCIENTIFIC DENTAL SCIENCES*, *3*, 2581–4893.

Kang, Y. G., Nam, J. H., Kim, K. H., and Lee, K. S. (2010). FAK pathway regulates PGE2 production in compressed periodontal ligament cells. *Journal of Dental Research*, *89*(12), 1444–1449.

Kanzaki, H., Chiba, M., Arai, K., Takahashi, I., Haruyama, N., Nishimura, M., and Mitani, H. (2006). Local RANKL gene transfer to the periodontal tissue accelerates orthodontic tooth movement. *Gene Therapy*, *13*(8), 678–685.

Katagiri, T., and Takahashi, N. (2002). Regulatory mechanisms of osteoblast and osteoclast differentiation. *Oral Diseases*, Vol. 8, pp. 147–159.

Khosla, S. (2001). Minireview: The OPG/RANKL/RANK system. *Endocrinology*, Vol. 142, pp. 5050–5055.

Killiany, D. M. (1999). Root resorption caused by orthodontic treatment: an evidence-based review of literature. *Seminars in Orthodontics*, *5*(2), 128–133.

Kim, K. W., Kim, S. J., Lee, J. Y., Choi, Y. J., Chung, C. J., Lim, H., and Kim, K. H. (2018). Apical root displacement is a critical risk factor for apical root resorption after orthodontic treatment. *Angle Orthodontist*, *88*(6), 740–747.

Kjaer, I. (1995). Morphological characteristics of dentitions developing excessive root resorption during orthodontic treatment. *European Journal of Orthodontics*, *17*(1), 25–34.

Krishnan, V. (2017). Root Resorption with Orthodontic Mechanics: Pertinent Areas Revisited. *Australian Dental Journal*, *62*, 71–77.

Krishnan, V., and Davidovitch, Z. (2006, April). Cellular, molecular, and tissue-level reactions to orthodontic force. *American Journal of Orthodontics and Dentofacial Orthopedics*, Vol. 129, pp. 469.e1-469.e32.

Kuhlberg, A., and Nanda, R. (2005). Principles of Biomechanics. In *Biomechanics and Esthetic Strategies in Clinical Orthodontics 1st ed.* (Vol. 53).

Kurol, J., and Owman-Moll, P. (1998). Hyalinization and root resorption during early orthodontic tooth movement in adolescents. *Angle Orthodontist*, *68*(2), 161–166.

Kusy, R. P., and Tulloch, J. F. (1986). Analysis of moment/force ratios in the mechanics of tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics*, *90*(2), 127–131.

Lee, R. Y., Artun, J., and Alonzo, T. A. (1999). Are dental anomalies risk factors for apical root resorption in orthodontic patients? *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *116*(2), 187–195.

Levander, E., and Malmgren, O. (1988). Evaluation of the risk of root resorption during orthodontic treatment: A study of upper incisors. *European Journal of Orthodontics*, *10*(1), 30–38.

Levander, E., Malmgren, O., and Stenback, K. (1998). Apical root resorption during orthodontic treatment of patients with multiple aplasia: A study of maxillary incisors. *European Journal of Orthodontics*, *20*(4), 427–434.

Li, Y., Jacox, L. A., Little, S. H., and Ko, C. (2018). Orthodontic tooth movement : The biology and clinical implications. *Kaohsiung Journal of Medical Sciences*, *34*(4), 207–214.

Lindskog, S., Pierce, A. M., Blomlöf, L., and Hammarström, L. (1985). The role of the necrotic periodontal membrane in cementum resorption and ankylosis. *Dental Traumatology*, *1*(3), 96–101.

Liou, E. J. W., and Chang, P. M. H. (2010). Apical root resorption in orthodontic patients with en-masse maxillary anterior retraction and intrusion with miniscrews. *American Journal of Orthodontics and Dentofacial Orthopedics*, *137*(2), 207–212.

Liu, H., Li, W., Jia, S., and Li, B. (2017). Puerarin and zinc additively prevent mandibular bone loss through inhibiting osteoclastogenesis in ovariectomized rats. *Histology and Histopathology*, *32*(8), 851–860.

Lopatiene, K., and Dumbravaite, A. (2008). Risk factors of root resorption after orthodontic treatment. In *Stomatologija, Baltic Dental and Maxillofacial Journal* (Vol. 10).

Ludlow, J. B., Timothy, R., Walker, C., Hunter, R., Benavides, E., Samuelson, D. B., and Scheske, M. J. (2015, January 1). Ffective dose of dental CBCT - A meta analysis of published data and additional data for nine CBCT units. *Dentomaxillofacial Radiology*, Vol. 44.

Luiz, G., Ribeiro, U., and Jacob, H. B. (2016). Understanding the basis of space closure in Orthodontics for a more efficient orthodontic treatment. *Dental Press J Orthod*, *21*(2), 115–140.

Makedonas, D., and Hansen, K. (2008). Diagnosis, screening and treatment of root resorption in orthodontic practices in Greece and Sweden. *Angle Orthodontist*, *78*(2), 248–253.

Makedonas, D., Lund, H., and Hansen, K. (2013). Root resorption diagnosed with cone beam computed tomography after 6 months and at the end of orthodontic treatment with fixed appliances. *Angle Orthodontist*, *83*(3), 389–393.

Makrygiannakis, M. A., Kaklamanos, E. G., and Athanasiou, A. E. (2018). Effects of systemic medication on root resorption associated with orthodontic tooth movement: a systematic review of animal studies. *European Journal of Orthodontics*, *41*(4), 346–359.

Malmgren, O., Gholdson, L., Hill, C., Orwin, A., Petrinni, L., and Lundberg, M. (1982). Root resorption after orthodontic treatment of traumatized teeth. *Am J Orthod*, *82*, 487–491.

Malyankar, U. M., Scatena, M., Suchland, K. L., Yun, T. J., Clark, E. A., and Giachelli, C. M. (2000). Osteoprotegerin is an α(v)β3-induced, NF-κB-dependent survival factor for endothelial cells. *Journal of Biological Chemistry*, *275*(28), 20959–20962.

Marinescu, I. R., Bănică, A. C., Mercuţ, V., Gheorghe, A. G., Drăghici, E. C., Cojocaru, M. O., Popescu, S. M. (2019). Root Resorption Diagnostic: Role of Digital Panoramic Radiography. *Current Health Sciences Journal*, *45*(2), 156–166.

Marques, L. S., Ramos-Jorge, M. L., Rey, A. C., Armond, M. C., and de Oliveira Ruellas, A. C. (2010). Severe root resorption in orthodontic patients treated with the edgewise method: Prevalence and predictive factors. *American Journal of Orthodontics and Dentofacial Orthopedics*, *137*(3), 384–388.

Martin, C. K., Dirksen, W. P., Carlton, M. M., Lanigan, L. G., Pillai, S. P., Werbeck, J. L., Rosol, T. J. (2015). Combined zoledronic acid and meloxicam reduced bone loss and tumour growth in an orthotopic mouse model of bone-invasive oral squamous cell carcinoma. *Veterinary and Comparative Oncology*, *13*(3), 203–217.

Martins, D. R., Tibola, D., Janson, G., and Torres Maria, F. R. (2011). Effects of intrusion combined with anterior retraction on apical root resorption. *European Journal of Orthodontics*, *34*(2), 170–175.

Martins, D. R., Tibola, D., Janson, G., and Torres Maria, F. R. (2012). Effects of intrusion combined with anterior retraction on apical root resorption. *European Journal of Orthodontics*, *34*(2), 170–175.

Masella, R. S., and Meister, M. (2006). Current concepts in the biology of orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics, 129*(4), 458–468.

Mauès, C. P. R., do Nascimento, R. R., and Vilella, O. de V. (2015). Severe root resorption resulting from orthodontic treatment: Prevalence and risk factors. *Dental Press Journal of Orthodontics*, *20*(1), 52–58.

McFadden, W., Engstrom, C., Engstrom, H., and Anholm, J. (1989). A study of the relationship between incisor intrusion and root shortening. *Am J Orthod Dentofac Orthop*, *96*, 390–396.

Meeran, N. A. (2013, January). Cellular response within the periodontal ligament on application of orthodontic forces. *Journal of Indian Society of Periodontology*, Vol. 17, pp. 16–20.

Mehta, S. A., Deshmukh, S. V., Sable, R. B., and Patil, A. S. (2017). Comparison of 4 and 6 weeks of rest period for repair of root resorption. *Progress in Orthodontics*, *18*(1), 18.

Miedzik, M., and Syryńska, M. (2007). Cephalometric imaging in the assessment of facial growth direction; literature review. *Polish Journal of Radiology*, *72*(2), 82–87.

Mirabella, A. D., and Artun, J. (1995). Prevalence and severity of apical root resorption of maxillary anterior teeth in adult orthodontic patients. *European Journal of Orthodontics*, *17*(2), 93–99.

Mirabella, A. D., and Årtun, J. (1995). Risk factors for apical root resorption of maxillary anterior teeth in adult orthodontic patients. *American Journal of Orthodontics and Dentofacial Orthopedics*, *108*(1), 48–55.

Miresmaeili, A., Mollaei, N., Azar, R., Farhadian, N., and Mani Kashani, K. (2015). Effect of Dietary Vitamin C on Orthodontic Tooth Movement in Rats. *Journal of Dentistry (Tehran, Iran)*, *12*(6), 409–413.

Mirhashemi, A. H., Ahmad Akhoundi, M. S., Sheikhzadeh, S., Momeni, N., Dehpour, A., Alaeddini, M., … Ansari, E. (2015). Effect of Fluoxetine Consumption on Orthodontic Tooth Movement in Rats. *Journal of Dentistry (Tehran, Iran)*, *12*(12), 882–889.

Montazerolghaem, M., Rasmusson, A., Melhus, H., Engqvist, H., and Karlsson Ott, M. (2016). Simvastatin-doped pre-mixed calcium phosphate cement inhibits osteoclast differentiation and resorption. *Journal of Materials Science: Materials in Medicine*, *27*(5), 83.

Motokawa, M., Sasamoto, T., Kaku, M., Kawata, T., Matsuda, Y., Terao, A., and Tanne, K. (2012). Association between root resorption incident to orthodontic treatment and treatment factors. *European Journal of Orthodontics*, *34*(3), 350–356.

Nanekrungsan, K., Patanaporn, V., Janhom, A., and Korwanich, N. (2012). External apical root resorption in maxillary incisors in orthodontic patients: Associated factors and radiographic evaluation. *Imaging Science in Dentistry*, *42*(3), 147–154.

Nieto-Nieto, N., Solano, J. E., and Yañez-Vico, R. (2017, May 19). External apical root resorption concurrent with orthodontic forces: the genetic influence. *Acta Odontologica Scandinavica*, Vol. 75, pp. 280–287.

Nishijima, Y., Yamaguchi, M., Kojima, T., Aihara, N., Nakajima, R., and Kasai, K. (2006). Levels of RANKL and opg in gingival crevicular fluid during orthodontic tooth movement and effect of compression force on releases from periodontal ligament cells in vitro. *Orthodontics and Craniofacial Research*, *9*(2), 63–70.

Oshiro, T., Shiotani, A., Shibasaki, Y., and Sasaki, T. (2002). Osteoclast induction in periodontal tissue during experimental movement of incisors in osteoprotegerin-deficient mice. *Anatomical Record*, *266*(4), 218–225.

Otsuka, E., Kato, Y., Hirose, S., and Hagiwara, H. (2000). Role of ascorbic acid in the osteoclast formation: Induction of osteoclast differentiation factor with formation of the extracellular collagen matrix. *Endocrinology*, *141*(8), 3006–3011.

Owman-Moll, P. (1995). Orthodontic tooth movement and root resorption with special reference to force magnitude and duration. A clinical and histological investigation in adolescents. *Swedish Dental Journal. Supplement*, Vol. 105, pp. 1–45.

Owman-Moll, P., Kurol, J., and Lundgren, D. (1995). Repair of orthodontically induced root resorption in adolescents. *The Angle Orthodontist*, *65*(6).

Owman-Moll, Py, and Kurol, J. (1998). The early reparative process of orthodontically induced root resorption in adolescents - Location and type of tissue. *European Journal of Orthodontics*, *20*(6), 727–732.

Owman-Moll, Py, Kurol, J., and Lundgren, D. (1996). The effects of a four-fold increased orthodontic force magnitude on tooth movement and root resorptions. An intra-individual study in adolescents. *European Journal of Orthodontics*, *18*(3), 287–294.

Pamukçu, H., Polat-Özsoy, Ö., Gülşahi, A., and Özemre, M. Ö. (2020). External apical root resorption after nonextraction orthodontic treatment with labial vs. lingual fixed appliances. *Journal of Orofacial Orthopedics*, *81*(1), 41–51.

Parker, R. J., and Harris, E. F. (1998). Directions of orthodontic tooth movements associated with external apical root resorption of the maxillary central incisor. *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *114*(6), 677–683.

Pastro, J. D. V., Nogueira, A. C. A., Salvatore de Freitas, K. M., Valarelli, F. P., Cançado, R. H., de Oliveira, R. C. G. R. C. G., and de Oliveira, R. C. G. R. C. G. (2018). Factors Associated to Apical Root Resorption after Orthodontic Treatment. *The Open Dentistry Journal*, *12*(1), 331–339.

Patel, S., and Ford, T. P. (2007). Is the resorption external or internal? *Dental Update*, *34*(4), 218–229.

Phillips, J. (1955). Apical root resorption under orthodontic therapy. *Angle Orthod*, *25*, 1–12.

Picanço, G. V., Freitas, K. M. S. de, Cançado, R. H., Valarelli, F. P., Picanço, P. R. B., and Feijão, C. P. (2013). Predisposing factors to severe external root resorption associated to orthodontic treatment. In *Dental Press Journal of Orthodontics* (Vol. 18).

Proffit, W. R., Fields, H. W., and Sarver, D. M. (2007). *Contemporary orthodontics*.St. Louis, Mo.: Mosby Elsevier.

Quintanilha, L., Fernandes, P., Couto Figueiredo, N., Cristina, C., Antonucci, M., Maria, E.,Chairman, J. (2019). *Predisposing factors for external apical root resorption associated with orthodontic treatment*.

Rafiei, M., Sadeghian, S., Torabinia, N., and Hajhashemi, V. (2015). Systemic effects of fluoxetine on the amount of tooth movement, root resorption, and alveolar bone remodeling during orthodontic force application in rat. *Dental Research Journal*, *12*(5), 482–487.

Ramanathan, C., and Hofman, Z. (2009). Root resorption during orthodontic tooth movements. *European Journal of Orthodontics*, *31*(6), 578–583.

Rego, M. V. N. Do, Thiesen, G., Marchioro, E. M., Berthold, T., and Bandeira, E. (2004). Reabsorção Radicular e Tratamento Ortodôntico : Mitos e Evidências Científicas. *J Bras Ortodon Ortop Facial*, *9*(51), 292–309.

Ren, H., Chen, J., Deng, F., Zheng, L., Liu, X., and Dong, Y. (2013). Comparison of cone-beam computed tomography and periapical radiography for detecting simulated apical root resorption. *Angle Orthodontist*, *83*(2), 189–195.

Retrouvey, J. M., Goldberg, M., and Schwartz, S. A. (2012). Dental Development and Maturation, From the Dental Crypt to the Final Occlusion. In *Pediatric Bone* (pp. 83–108).

Ruellas, A. C. de O., Pithon, M. M., and Santos, R. L. dos. (2013). Maxillary incisor retraction: evaluation of different mechanisms. *Dental Press Journal of Orthodontics*, *18*(2), 101–107.

Samandara, A., Papageorgiou, S. N., Ioannidou-Marathiotou, I., Kavvadia-Tsatala, S., and Papadopoulos, M. A. (2019). Evaluation of orthodontically induced external root resorption following orthodontic treatment using cone beam computed tomography (CBCT): A systematic review and meta-analysis. *European Journal of Orthodontics*, *41*(1), 67–79.

Sameshima, G. T., and Asgarifar, K. O. (2001). Assessment of Root Resorption and Root Shape: Periapical vs Panoramic Films. *Angle Orthodontist*, *71*(3), 185–189.

Sameshima, G. T., and Sinclair, P. M. (2001a). Predicting and preventing root resorption: Part I. Diagnostic factors. In *American Journal of Orthodontics and Dentofacial Orthopedics* (Vol. 119). Mosby Inc.

Sameshima, G. T., and Sinclair, P. M. (2001b). Predicting and preventing root resorption: Part II. Treatment factors. *American Journal of Orthodontics and Dentofacial Orthopedics*, *119*(5), 511–515.

Sameshima, G. T., and Sinclair, P. M. (2004). Characteristics of patients with severe root resorption. *Orthodontics and Craniofacial Research*, *7*(2), 108–114.

Sarver, D. M., and Weissman, S. M. (1995). Nonsurgical treatment of open bite in nongrowing patients. *American Journal of Orthodontics and Dentofacial Orthopedics*, *108*(6), 651–659.

Saygin, N. E., Tokiyasu, Y., Giannobile, W. V., and Somerman, M. J. (2000). Growth Factors Regulate Expression of Mineral Associated Genes in Cementoblasts. *Journal of*

*Periodontology*, *71*(10), 1591–1600.

Scarfe, W. C., Farman, A. G., and Sukovic, P. (2006, February). Clinical applications of cone-beam computed tomography in dental practice. *Journal of the Canadian Dental Association*, Vol. 72, pp. 75–80.

Schoppet, M., Preissner, K. T., and Hofbauer, L. C. (2002). RANK ligand and osteoprotegerin: paracrine regulators of bone metabolism and vascular function. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *22*(4), 549–553.

Schroeder, H. E. (1992). Biological problems of regenerative cementogenesis: synthesis and attachment of collagenous matrices on growing and established root surfaces. *International Review of Cytology*, *142*, 1–59.

Schroeder, H. E. (1993). Human cellular mixed stratified cementum: a tissue with alternating layers of acellular extrinsic- and cellular intrinsic fiber cementum. *Schweizer Monatsschrift Fur Zahnmedizin = Revue Mensuelle Suisse d''odonto-Stomatologie = Rivista Mensile Svizzera Di Odontologia e Stomatologia / SSO*, *103*(5), 550–560.

Segal, G. R., Schiffman, P. H., and Tuncay, O. C. (2004). Meta analysis of the treatment-related factors of external apical root resorption. *Orthodontics and Craniofacial Research*, *7*(2), 71–78.

Seifi, M., Hamedi, R., and Khavandegar, Z. (2015). The Effect of Thyroid Hormone, Prostaglandin E2, and Calcium Gluconate on Orthodontic Tooth Movement and Root Resorption in Rats. *Journal of Dentistry (Shiraz, Iran)*, *16*(1 Suppl), 35–42.

Shoji-Matsunaga, A., Ono, T., Hayashi, M., Takayanagi, H., Moriyama, K., and Nakashima, T. (2017). Osteocyte regulation of orthodontic force-mediated tooth movement via RANKL expression. *Scientific Reports*, *7*(1).

Sicher, H., and Weinmann, J. P. (1944). Bone growth and physiologic tooth movement. *American Journal of Orthodontics and Oral Surgery*, *30*(3), C109–C132.

Sringkarnboriboon, S., Matsumoto, Y., and Soma, K. (2003). Root resorption related to hypofunctional periodontium in experimental tooth movement. *Journal of Dental*

*Research*, *82*(6), 486–490.

Taddei, S. R. D. A., Madeira, M. F. M., Lima, I. L. D. A., Queiroz-Junior, C. M., Moura, A. P., Oliveira, D. D., … Da Silva, T. A. (2014). Effect of Lithothamnium sp and calcium supplements in strain- and infection-induced bone resorption. *Angle Orthodontist*, *84*(6), 980–988.

Thilander, B., Rygh, P., and Reitan, K. (2011). Tissue reactions in orthodontics. *Orthodontics: Current Principles and Techniques. Elsevier, Philadelphia, PA*, 247–286.

Tian, Y., Wang, K., Wang, J., Liu, F., and Piao, M. (2013). Root resorption after orthodontic treatment: a study of age factor and prevalence in anterior teeth. *Shanghai kou qiang yi xue = Shanghai journal of stomatology*, *22*(2), 224–227.

Topkara, A., Karaman, A. I., and Kau, C. H. (2012). *Apical root resorption caused by orthodontic forces: A brief review and a long-term observation* (Vol. 6).

Torlakovic, L., and Færøvig, E. (2011). Age-related changes of the soft tissue profile from the second to the fourth decades of life. *Angle Orthodontist*, *81*(1), 52–59.

Tronstad, L. (1988). Root resorption - etiology, terminology and clinical manifestations. *Dental Traumatology*, *4*(6), 241–252.

Tyrovola, J. B., Spyropoulos, M. N., Makou, M., and Perrea, D. (2008). Root resorption and the OPG/RANKL/RANK system: a mini review. *Journal of Oral Science*, Vol. 50, pp. 367–376.

Upadhyay, M., and Nanda, R. (2015). Biomechanics in Orthodontics. In *Esthetics and Biomechanics in Orthodontics 2nd. ed.* (Vol. 53, pp. 74–89).

Wainwright, M. (1973). Facial lingual tooth movement. Its influence on the root and cortical plate. *Am J Orthod*, *64*, 278–302.

Walsh, M. C., and Choi, Y. (2014). Biology of the RANKL-RANK-OPG system in immunity, bone, and beyond. *Frontiers in Immunology*, Vol. 5, p. 511.

Wang, J., Rousso, C., Christensen, B. I., Li, P., Kau, C. H., MacDougall, M., and Lamani, E. (2019). Ethnic differences in the root to crown ratios of the permanent dentition. *Orthodontics and Craniofacial Research*, *22*(2), 99–104.

Wedenberg, C., and Zetterqvist, L. (1987). Internal resorption in human teeth-a histological, scanning electron microscopic, and enzyme histochemical study. *Journal of Endodontics*, *13*(6), 255–259.

Weltman, B., Vig, K. W. L., Fields, H. W., Shanker, S., and Kaizar, E. E. (2010). Root resorption associated with orthodontic tooth movement: A systematic review. *American Journal of Orthodontics and Dentofacial Orthopedics*, *137*(4), 462–476.

White, T. C., Gardiner, J. H., and Leighton, B. C. (1976). Orthodontics for Dental Students. In *Orthodontics for Dental Students*. Macmillan Education UK.

Will, L. A. (2015). Orthodontic Tooth Movement: A Historic Prospective. *Frontiers of Oral Biology*, Vol. 18, pp. 46–55.

Xiao, W., Wang, Y., Pacios, S., Li, S., and Graves, D. T. (2015). Cellular and Molecular Aspects of Bone Remodeling. *Frontiers of Oral Biology*, *18*, 9–16.

Yamaguchi, M., Aihara, N., Kojima, T., and Kasai, K. (2006). RANKL increase in compressed periodontal ligament cells from root resorption. *Journal of Dental Research*, *85*(8), 751–756.

Yamaguchi, Masayoshi, Mochizuki, A., and Okada, S. (1982). Stimulatory effect of zinc on bone growth in weanling rats. *Journal of Pharmacobio-Dynamics*, *5*(8), 619–626.

Yamamoto, T., Hasegawa, T., Yamamoto, T., Hongo, H., and Amizuka, N. (2016, August 1). Histology of human cementum: Its structure, function, and development. *Japanese Dental Science Review*, Vol. 52, pp. 63–74.

Yan, Y., Liu, F., Kou, X., Liu, D., Yang, R., Wang, X., … Zhou, Y. (2015). T cells are required for Orthodontic tooth movement. *Journal of Dental Research*, *94*(10), 1463–1470.

Yoo, H. S., Kim, G. J., Song, D. H., Chung, K. H., Lee, K. J., Kim, D. H., and An, J. H. (2017). Calcium supplement derived from Gallus gallus domesticus promotes BMP-2/RUNX2/SMAD5 and suppresses TRAP/RANK expression through MAPK signaling activation. *Nutrients*, *9*(5).

Yumoto, H., Hirao, K., Hosokawa, Y., Kuramoto, H., Takegawa, D., Nakanishi, T., and Matsuo, T. (2018, August 1). The roles of odontoblasts in dental pulp innate immunity. *Japanese Dental Science Review*, Vol. 54, pp. 105–117.

Zaslansky, P. (2008). Dentin. In *Collagen: Structure and Mechanics* (pp. 421–446).

Zhou, Y., Wang, Y., Wang, X. Y., Volière, G., and Hu, R. D. (2014). The impact of orthodontic treatment on the quality of life a systematic review. *BMC Oral Health*, *14*(1), 66.

Zupan, J., Jeras, M., and Marc, J. (2013). Osteoimmunology and the influence of pro-inflammatory cytokines on osteoclasts. *Biochemia Medica*, Vol. 23, pp. 43–63.