
Orthodontics and External Apical Root Resorption

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External apical root resorption (EARR) is a common complication of orthodontic treatment. Many factors have been investigated to explain differences seen among individuals in their susceptibility to EARR. Our central hypothesis is that in addition to the environmental component (increased stress and strain on the teeth, surrounding periodontal ligament, and alveolar bone secondary to occlusal and orthodontic forces), genetic factors that encode proteins and pathways involved in alveolar bone and cementum maintenance underlies EARR susceptibility or resistance. It is estimated that genetic factors can explain approximately 64% of the EARR variation in humans. Current data suggest that more than one gene is involved in the disease process. The identification of genes that modulate susceptibility to EARR will allow for better understanding of the disease processes as well as the screening of individuals before treatment. (Semin Orthod 2007;13: 246-256.) © 2007 Elsevier Inc. All rights reserved.

External apical root resorption (EARR) is a common clinical complication of orthodontic treatment. It is the permanent shortening of the end of the tooth root that can be seen on routine dental radiographs.¹ Although EARR may occur in any or all teeth, it most often involves the maxillary incisors. For many orthodontic patients maxillary central incisor EARR can average 1 to 2 mm from the original (pre-treatment) tooth root length, with essentially no effect on function. In approximately 1 of 20 patients undergoing orthodontic treatment, up

to 5 mm of tooth root loss can occur,² potentially endangering the longevity of the tooth. It may also occur in the absence of orthodontic treatment.^{3,4} A total of 7% to 13% of individuals who have not had orthodontic treatment show 1 to 3 mm of EARR on radiographs.⁵

Histology of Root Resorption

When teeth are moved orthodontically, the periodontal ligament (PDL) is subjected to the mechanical forces of compression and tension. In the direction of tooth movement, the PDL becomes compressed between the moving tooth and the alveolar bone. In cases of heavy forces over long durations the PDL is injured resulting in hyalinized tissue formation. In most histological reports, the process of resorption is closely associated with the remodeling of the periodontal ligament as a result of its injury and necrosis.⁶⁻⁸ The first cells that appear in the necrotic area are macrophages.^{9,10} These cells are responsible for the initial resorption of the pre-cementum layer.⁶ It has been shown that these macrophages are later followed by multinucleated cells (odontoclasts), which attack cementum and eventually dentin.⁷ Initially the removal of the hyalinized tissue leads also to the removal

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of the cementoid layer, which is believed to be a protective layer. This process might leave a raw surface of cementum that can be readily attacked by odontoclasts. The initial penetration of cells into precementum/cementum has been shown to occur at the periphery of the hyalinized area.⁶ An increased number of multinucleated giant cells were observed adjacent to areas of root resorption.⁷ Kvam⁹ was the first to describe resorption lacunae penetrating the cementum into dentin in human premolar teeth. Barber and Sims¹¹ further observed that extensive root resorption occurs with heavy forces. Later on, Rygh¹² showed that root resorption is mainly seen near the hyalinized zone.

Histological root resorption (RR) usually presents as microscopic areas of resorption lacunae on root surfaces. Seventy-five percent of these areas show complete repair with secondary cementum.¹³ Orthodontic force applied to teeth for a short amount of time can produce resorption lacuna in the absence of radiographically visible EARR.¹⁴ An increase in duration and magnitude of orthodontic force can lead to an increased incidence of RR, resulting in the exposure of root dentin underlying the damaged cementum. This exposed dentin increases the likelihood of osteoclastic attack and EARR,¹⁵ particularly if the tooth is subjected to forces from alternating directions in a parafunctional manner (Fig 1). Permanent root resorption occurs mostly in the apical region, resulting in EARR.¹⁶ It is very important to distinguish between EARR and RR when studying incidence and prevalence. There are differences in the duration of applying active orthodontic force to express these conditions and how they are observed. EARR and RR during orthodontic tooth movement are related conditions influenced by a wide range of shared genetic, biochemical, and mechanical factors. Root resorption detectable histologically is a preliminary step toward external apical root resorption (EARR) that is permanent and detectable radiographically. It is believed that when root resorption exceeds the reparative capacity of cementum, we see EARR.

In most of the reports, resorption occurred mainly in the apical third of the root.¹⁶ Two possible explanations for the increased incidence of resorption lacuna in the apical third were:

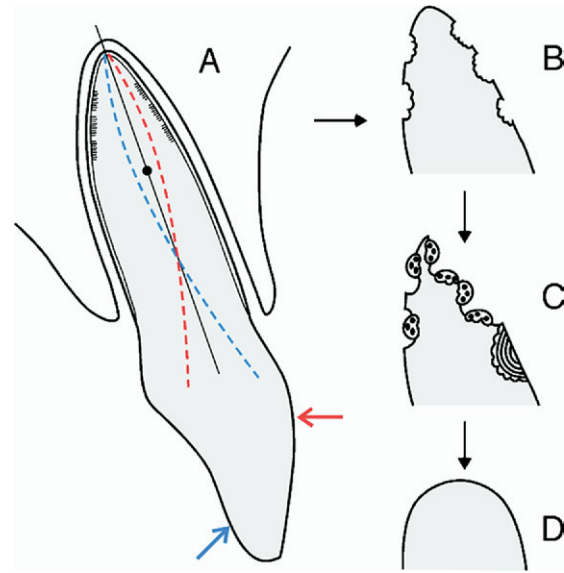


Figure 1. Root resorption lacunae that are not repaired may cause a sequestration of the apex, which when resorbed results in external apical root resorption (Roberts WE, Al-Qawasmī RA, Hartsfield JK Jr, Katona TR. Biomechanics of root resorption, in *Orthodontics Year Book '04*. Tokyo, Quintessence Publishing Company, 2004, pp 84-90). (Color version of figure is available online.)

1. The fulcrum is occlusal to the apical half of the root and the differences in the direction of the periodontal fibers could result in increased possibilities of trauma in the apical and middle thirds of the root.
2. The apical third is covered with cellular cementum while the middle and gingival thirds are covered with acellular cementum. The cellular cementum depends on more active cells, and has more supporting vasculature, which makes it more liable to trauma and cell injury reactions.

There is an increase in number of blood vessels toward the apex of the roots. Blaushild and coworkers¹⁷ assessed quantitatively the vascular system in the cementum-related periodontal ligament along the rat incisor. Blood vessels were found to occupy 47% of the PDL area in the apical half compared with 4% at the incisal end. This extensive vascularization in the apical half of the PDL is consistent with the high metabolic demands, and the need for protective cushioning, of the constantly growing dental and periodontal tissues. It has been suggested that dif-

ferences in the hardness and elastic modulus of the cementum might also be correlated with the amount of root resorption. Hardness and elastic modulus of the cementum for the human maxillary first premolar gradually decreases from the cervical to the apical regions.^{18,19}

Odontoclasts: The Cells Doing the Damage

Odontoclasts are multinucleated cells responsible for the resorption of dental hard tissues. These cells are morphologically and functionally similar to osteoclasts.^{20,21} Both odontoclasts and osteoclasts are of hemopoietic origin. Macrophage-colony stimulating factor (M-CSF) is an essential factor in the proliferation and differentiation of osteoclasts from their progenitors.^{22,23} Another factor that is also essential for osteoclast differentiation and activation is the receptor activator nuclear factor kappa B ligand (RANKL).^{24,25} Together M-CSF and RANKL are required to induce the expression of genes that are essential to the commitment of the progenitors to the osteoclast lineage. These genes include ones encoding for tartrate resistant acid phosphatase (TRAP), ca-

thepsin K, calcitonin receptor, and β_3 -integrin, leading to the development of mature osteoclasts. The presence of these markers has also been identified in odontoclasts.²⁶⁻²⁸ The receptor activator of nuclear factor kappa B (RANK) and its ligand RANKL have been localized in odontoblasts, pulp fibroblasts, periodontal ligament fibroblasts, and odontoclasts.^{29,30} Osteoclastogenesis is modulated by osteoprotegerin (OPG), a member of the TNF receptor superfamily that inhibits osteoclastogenesis by preventing RANKL from binding to its receptor RANK at the osteoclast membrane (Fig 2).

The OPG/RANKL/RANK system is a key mediator in osteoclastogenesis. OPG, RANKL and RANK have also been identified in odontoclasts activated during resorption of deciduous teeth.^{29,31} Other cytokines that regulate osteoclast activity and function include transforming growth factor-alpha (TGF- α), interleukin-1beta (IL-1 β), and interleukin-6 (IL-6). These three proinflammatory cytokines are capable of increasing RANKL activity leading to upregulation of osteoclastogenesis.³²⁻³⁴ TNF- α , IL-1 β , and IL-6 are also capable of regulating osteoclastogenesis independent of RANKL by directly acting on osteoclasts.³⁴⁻³⁸

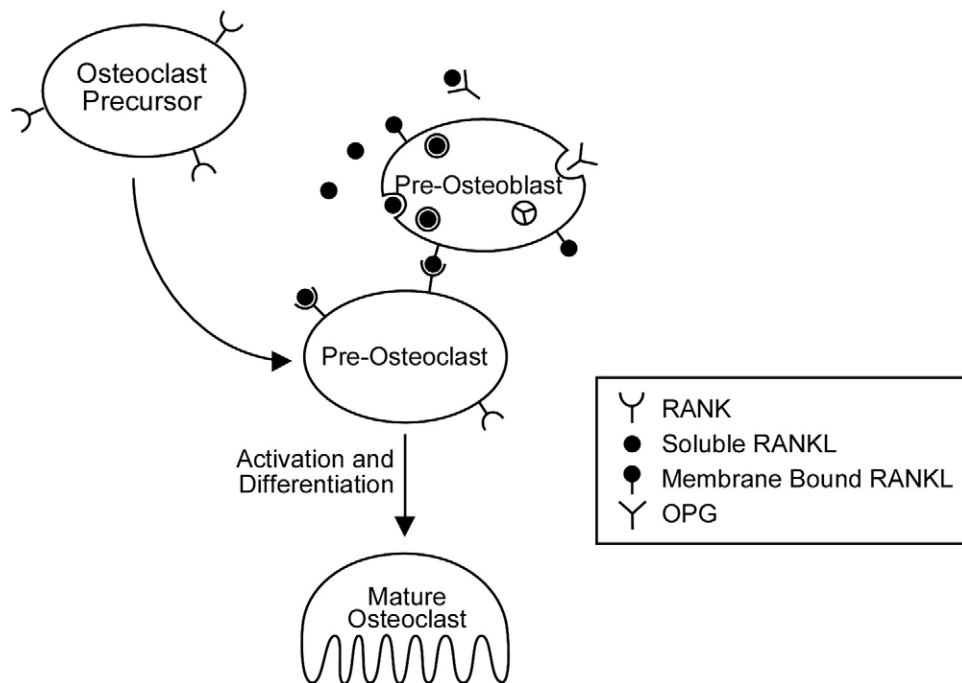


Figure 2. Osteoclastogenesis/odontoclastogenesis is promoted through the binding of RANKL to RANK receptors. The amount of RANKL available to bind to RANK is mediated by the binding of RANKL to OPG.

Risk Factors for EARR

Individuals vary in their susceptibility to EARR. Many factors have been examined to explain this variability. These included factors related to patients or treatments such as the type of malocclusion,³⁹⁻⁴³ appliance used,⁴⁴ the nature of force,⁴⁵⁻⁴⁷ duration of treatment,^{48,49} missing teeth,^{48,50,51} role of trauma,^{43,52-54} systemic factors,⁵⁵⁻⁵⁷ habits,^{43,58-60} and gender.^{39,44,49,50,53,59-64} None of these factors could entirely explain increased susceptibility to EARR among certain individuals. It has been proposed that this variability can be due to an innate or systemic predisposition to resorption in permanent and primary teeth.⁶⁵⁻⁶⁷ Also when extreme susceptibility exists, EARR can occur in the absence of any causative factors.⁶⁰ Harris and coworkers⁴ reported that individuals with root resorption in one tooth also tend to exhibit resorption in other teeth. Kurol and coworkers⁷³ concluded that individual variations were considerable regarding both extension and depth of root resorption within individuals, and these were not correlated to the magnitude of tooth movement achieved. Later, Owman-Moll and coworkers⁶⁹ showed that individual variation overshadowed the force magnitude and the force type in defining the susceptibility to root resorption associated with orthodontic force (RRAOF). Sameshima and Sinclair⁴⁹ analyzed the records of 868 patients who were treated with full, fixed edgewise appliances from 6 private offices and found that Asian patients experience significantly less root resorption than white or Hispanic patients. While this may infer an ethnic difference based on genetic factors, environmental or cultural factors may also be important. The familial clustering of EARR has been reported in a number of studies, although no single specific pattern of inheritance was identified.^{59,70,71} It is likely that the pattern of inheritance for individual susceptibility to EARR is polygenic (complex), with a complicated interaction of a number of proteins coded for by a number of genes that interact with some number of environmental factors, of which orthodontic force may be one (Fig 3).

Since mechanical forces and other environmental factors do not adequately explain the variation seen among individual expressions of EARR, an increased interest has focused on the

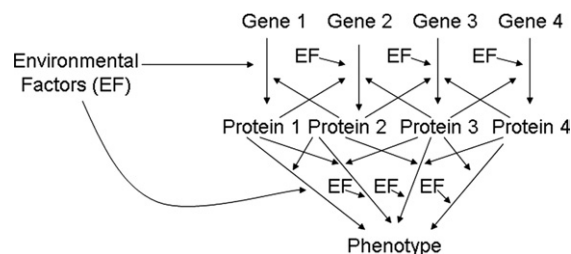


Figure 3. Polygenic (complex) traits have a variable number of influencing genetic factors, some of which may have more influence than the others, but none are capable of producing the trait by itself. The potential relationship between various genes and the environmental factors is complex as denoted by the arrows.

role of genetic factors influencing the susceptibility to EARR. It appears that the reaction to orthodontic force can differ depending on the individual's genetic background. These genetic factors could be related to proteins that govern cementum resorption and repair during the application of force. Analysis of sib-pair models for their susceptibility to EARR have shown a heritability estimate of 0.8 for the maxillary central incisors.⁶⁸ This genetic variation accounts for approximately 64% of the total phenotypic (clinical) variation, which likely represents the effect of some combination of genetic and environmental factors.⁴⁹ A more recent retrospective twin study on EARR showed that the concordance scores for monozygotic twins were approximately twice those of dizygotic twins, indicating a strong genetic component of EARR, although since the concordance for the monozygotic twins was much less than 100%, there is also evidence for environmental factors.⁷²

Al-Qawasmi and coworkers⁷³ used the candidate gene approach to identify the evidence of genetic linkage in 38 pedigrees. In their study they found suggestive evidence of linkage between EARR in maxillary central incisor and a polymorphic marker *D18S64* (LOD score 2.51). This polymorphism marker lies close to *TNFRSF11A* gene, suggesting that this locus or a closely linked one contributes to the susceptibility to EARR. The *TNFRSF11A* gene codes for RANK, an essential signaling molecule in osteoclast differentiation and function, as already noted.⁷⁴ Furthermore, significant evidence of linkage disequilibrium for an *IL-1B* polymorphism with EARR was reported.⁷³ The analysis of 35 families indicated that the *IL-1B*

polymorphism accounts for 15% of the total variation seen for maxillary central incisor EARR seen in their sample. The potential for effect of the IL-1 β protein on root resorption was confirmed in an IL-1 β knockout mouse model.⁷⁵

Analysis of inbred mice and their offspring have shown that inbred mice of different strains differ in their susceptibility to histologically analyzed RRAOF.⁷⁶ This indicated that genotype is an influencing factor on RRAOF. Mice were grouped into resistant (A/J, C57BL/6J, and SJL/J), intermediate (C3H/HeJ and AKR/J), and susceptible (BALB/cJ, DBA/2J, and 129P3/J) strains. That study identified a 7-fold difference in susceptibility between the DBA/2J (susceptible) and A/J (resistant) mouse strains. Furthermore, analysis of the mode of the inheritance of the susceptibility to RRAOF was studied in a cross between A/J mice (resistant) and either DBA/2J or BALB/cJ mice (both susceptible strains). Results from these crossings showed that RRAOF is a traceable trait in mice. The mode of inheritance seems to be polygenic in these mice.

Data from mice studies have shown that increased susceptibility to histological RRAOF is always associated with an increase in the number of TRAP-positive cells in the pressure area of the root surface. Immunohistological analysis has indicated that mice susceptible to RRAOF (DBA/2J) express increased levels of RANKL adjacent to tooth subjected to orthodontic force compared with mice resistant to RRAOF (A/J).⁷⁷ The level of OPG is increased in the tissues surrounding the roots of the resistant mice compared with the susceptible mice.⁷⁷ Thus the genes that code for RANKL and OPG are also candidates for analysis of key mediators of osteoclast function. A clinical study has shown ($P = 0.003$) that the G1181C polymorphism in OPG is associated with EARR, accounting for approximately 8% of the clinical variation seen in that sample (unpublished data). As with the data for IL-1 β , this is another gene in which variation may influence EARR in combination with other factors. It appears that differential expression of molecules that govern osteoclasts/odontoclasts function play a role in determining the susceptibility to root resorption during orthodontic force application. This might imply that certain individuals might react with an exaggerated odontoclastic response to orthodontic treatment

leading to EARR. The identification of susceptibility genes will provide a clear understanding of the molecular mechanisms underlying EARR and specifically how orthodontic force affects the expression of genes that encode proteins and pathways critical in tooth movement, cementum resorption, and maintenance/repair.

Barriers Against Cementum Resorption

Both bone and cementum are susceptible to resorption under orthodontic force although cementum shows a greater resistance against resorption.¹² Cementum, unlike bone, is not involved in the metabolic process of calcium homeostasis.⁷⁸ Bone is regarded as a mineral reservoir that can be induced to release calcium on need. Cementum, on the other hand, is a mineralized tissue that typically does not release minerals under physiological conditions. Bone is a well-vascularized tissue while cementum is not. The anastomoses and canaliculi between cementocytes and the periodontal ligament are scarce, which makes cementum less sensitive to its environment than bone tissue. The closeness of blood supply to mineralized tissues is a critical factor in their response to metabolic needs.⁷⁹ The bone side of the PDL contains more blood vessels than the cementum side of the PDL. Furthermore, osteoclasts are a part of normal bone structure, but odontoclasts are rarely seen on cementum under physiological conditions. The cementoid (unmineralized precementum) layer is 3 to 5 μm thick in acellular cementum and even thicker in cellular cementum. This layer is continuously deposited and thus always present. This unmineralized layer is poorly resorbed by odontoclasts⁸⁰ and plays a role in retarding the resorption process.⁸¹

Effect of Pharmacological Agents on Root Resorption

Several pharmacological agents have been explored to prevent or minimize the incidence of root resorption associated with orthodontic force application. Molecules that affect osteoclast activity negatively such as bisphosphonates have the potential to reduce root resorption, but also reduce tooth movement. Igarashi and co-workers^{82,83} reported a significant dose-dependent inhibition of root resorption in rats admin-

istered with bisphosphonates after orthodontic force application. On the other hand, Alatlí and Hammarström⁸⁴ and Alatlí and coworkers^{85,86} found that the injections of bisphosphonates in rats induces a cementum surface alteration leading to increased surface vulnerability of the root surface to resorption during orthodontic tooth. A recent study has suggested that the local injection of clodronate is found to cause a decrease in the number of osteoclasts and inhibit root resorption associated with tooth movement.⁸⁷ Any consideration of the clinical application of bisphosphonates to suppress root resorption should take into account the recent concern about their association with osteonecrosis of the jaw, especially in some cancer patients who are receiving intravenous bisphosphonate therapy, and also with some patients who are receiving oral bisphosphonates, for example, to treat osteoporosis.⁸⁸

The administration of echistatin, an arginine-glycine-aspartate acid (RGD)-containing peptide was found to be effective in reducing root resorption during tooth movement in rats.⁸⁹ Echistatin affects clastic cell function by targeting the $\alpha\beta_3$ -integrin receptor, expressed by odontoclasts and osteoclasts. This disrupts the tight seal formation and the actin microfilament ring that depends on the adhesion of the $\alpha\beta_3$ -integrin to the substrate.⁹⁰ This mechanism may also affect tooth movement.

The administration of corticosteroids in doses of 15 mg/kg to rats during orthodontic treatment increased root resorption,⁹¹ whereas low doses of 1 mg/kg decreased root resorption. Paradoxically, Ong and coworkers⁹² stated that steroid treatment suppressed clastic activity in the rat. Doxycycline, a potent collagenase inhibitor, is capable of reducing the number of osteoclasts and preventing root resorption and alveolar bone loss following mucoperiosteal flap surgery in rats.^{93,94} Systemic administration of doxycycline has shown to significantly reduce root resorption, the number of odontoclasts, osteoclasts, mononuclear cells on the root surface, and TRAP-positive cells on the root and bone in rats.⁹⁵

The administration of high doses (50 mg/kg) of Celebrex, a cyclooxygenase-2 inhibitor, during the application of orthodontic forces was reported to reduce root resorption in rats without interfering with the rate of tooth movement.

Cox-2 inhibitors block the pathways essential for prostaglandin formation.⁹⁶ Similar findings were reported by Kameyama and coworkers⁹⁷ where they showed that aspirin suppresses root resorption induced by mechanical injury of the periodontal soft tissues. Recently reports of increased cardiovascular morbidity and mortality forced the withdrawal of a Cox-2 inhibitor (Vioxx) from the market, while others had restrictions placed on their use.⁹⁸ The administration of very low doses of L-thyroxine was shown to decrease RRAOF in both rats and human studies.⁹⁹⁻¹⁰¹ Vazquez-Landaverde and coworkers have shown that the hormone can achieve its effect at a local level.⁸⁷ It is assumed thyroxine either increases the resistance of the cementum and dentin to clastic activity or increases the rate of alveolar bone resorption. It is well documented that thyroid hormone exerts a biphasic effect on bone formation and resorption. At lower doses it may increase bone formation, whereas at larger doses bone resorption is enhanced.¹⁰²

Repair of Root Resorption

The idea that roots of permanent teeth are repaired after mechanical damage was first introduced into literature by Bridgman in 1862.¹⁰³ Later, Black¹⁰⁴ had demonstrated that the roots are repaired by formation of cementum. A detailed histological picture of repair was first reported by Fletcher in 1911.¹⁰⁵ Brudvik and Rygh¹⁰⁶ have shown that resorptive areas are repaired by deposition of cementum and further reestablishment of the periodontal ligament. In a study on human premolars using light microscopy and scanning electron microscopy, Langford and Sims¹⁰⁷ have shown that repair occurs entirely with cellular cementum. They have also shown the presence of Sharpey fiber holes in the new cementum, indicative of principal periodontal fiber insertion and PDL reestablishment at that site. Although it has been proposed that small areas of resorbed cementum will typically be repaired, if the resorption exceeds reparative capacity at the apical end of the tooth, the root is shortened.¹⁰⁸ It has been shown that initial human cementum repair takes place at the bottom of the resorption cavity.^{11,109} This pattern of repair was different from the one been shown previously in animal studies where repair by sec-

ondary cementum starts at the periphery of the resorption lacunae.^{106,110,111} Henery and Weimann¹⁶ were the first to show that 72% of the resorption areas show repair. Later, Owman-Moll and Kuroi¹⁰⁹ reported that areas of repair can reach to 82% after 6 to 7 weeks of force cessation and retention.

Impact and Management

The American Association of Orthodontists (AAO; St Louis, MO) estimated that in the year 2000 there were 4.5 million people being treated by its members. Extrapolation estimates that 90,000 to 225,000 patients undergoing orthodontic treatment during 2000 may develop EARR of more than 5 mm. This number of possible affected individuals does not include those treated by orthodontists that are not AAO members and by nonorthodontists. This estimate of EARR incidence indicates the extent of this problem for patients who undergo orthodontic treatment. It also underlies the need for informed consent and an understanding by the patient about the possibility of EARR. When EARR occurs, it is frustrating to the patient and practitioner. When EARR is recognized radiographically, it is permanent and irreversible. Stopping the orthodontic force will generally stop the resorption process as long as other forces (including occlusion and other forces on the teeth) allow the reparative process to stop further resorption. An interesting clinical study found that low-intensity pulsed ultrasound (LIPUS) application to a maxillary first premolar on one side of a group of 12 patients' mouths before extraction resulted in a histological hypercementosis and fewer resorption lacunae analyzed by scanning electron microscopy (SEM) compared with the untreated contralateral first premolar.¹¹² Although the authors referred to this as a repair, the LIPUS may have actually prevented the resorption lacunae from initially forming, as opposed to secondarily repairing them. The use of pharmaceutical or ultrasound agents to stop the process is still under investigation. Most of the pharmaceutical agents target odontoclast function and affect osteoclast function, which negatively affects tooth movement.

To stop treatment and allow time for the resorptive process to stop, the process must be

recognized. Thus pretreatment, progress, and post-treatment radiographs are recommended. Progress radiographs approximately 6 to 12 months after the initiation of treatment not only allow for a check on root angulation during treatment, but on the status of any root resorption as well. If resorption is recognized, then the patient and his referring dentist must be informed, and active treatment stopped for at least 3 to 4 months. During this time it is also important to assure that there are no parafunctional or other occlusal forces on the teeth that may be contributing to root resorption. If treatment is to be continued, then radiographic monitoring on a routine basis should be used. It may be necessary to stop treatment short of achieving the original treatment objectives and goals. It is reassuring that anecdotally most cases of EARR do not result in tooth loss or a diminution in function or esthetics.

Genetic factors explain about 64% of the variation seen in EARR associated with orthodontic treatment. This makes certain individuals more susceptible to EARR. The identification of genes that modulate susceptibility to EARR may allow for screening of individuals before treatment and thereby modulating the treatment plan accordingly. In addition, recognition of and accounting for the genetic factors that influence part of the variation in EARR associated with orthodontic treatment is also important to help uncover environmental factors that may be influential. Investigation in an out-bred population such as that found in a typical clinical study of a trait whose variation is strongly correlated with genetic variation must take that genetic variation into account. If this is not done, then a significant (both in a statistical and real sense) unexplained source of variation that may alter or even cover up the perceived effect of other factors on the trait will be ignored.

However, the current data suggest that there are multiple genes that may be involved, and that each may only play a relatively small role, although together they can have a significant clinical effect. Thus, more research is needed to understand the genes that are involved, and how their protein products interact with occlusal and orthodontic forces resulting in EARR.

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