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# Orthodontitis: The Inflammation Behind Tooth Movement and Orthodontic Root Resorption

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## Abstract

This chapter summarizes, criticizes, and updates the knowledge regarding orthodontitis – the inflammation that lies behind orthodontic tooth movement and orthodontic root resorption, gathered over the years, focusing on the last decade publications that followed the ending of the Human Genome Project. Types of root resorption as well as the remodeling and (mini)modeling processes involved in the orthodontic root resorption process are described. Several well-known theories that might explain root shortening as a result of orthodontic treatment are presented. The effects of patient-related factors and treatment-related factors (orthodontic and non-orthodontic) are discussed in light of current literature. A protocol to minimize orthodontic root resorption and to avoid consequences of periodontitis during orthodontic treatment, using radiographic monitoring (standard, frequent, or intensive), is suggested.

Inflammation is the process that lies behind orthodontic tooth movement [1–5]. Further, no orthodontic tooth movement is possible without this inflammation [6, 7]. Orthodontic force application, most of the time, reduces blood flow for enough time to induce local changes in the periodontal ligament (PDL) [8]. The body reaction to this process is usually by aseptic local inflammation. Until recently, when “orthodontitis” [9] was presented to the profession, this inflammation which lies behind tooth

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movement and orthodontic root resorption (ORR) induced by orthodontic treatment was never named.

Orthodontitis, composed from the prefix which is our profession and the suffix “-itis” [10] that is used in medical terminology to describe any inflammation of an organ or a tissue. Since this inflammation involves the bone, the periodontal ligament and the tooth, the best name to fully describe the process is probably “orthodontitis.”

According to histological observations, most studies demonstrate root surface changes cemental and dentinal in all teeth that are exposed to any level of force application [11, 12]. Although the effect of orthodontitis on the alveolar bone is different on the pressure and the tension sides, the effect on roots’ surfaces is similar, but not equal, on both sides. Usually, more remodeling/modeling activity is detected on the pressure than on the tension sides.

From radiographic or clinical point of view, the manifestation of orthodontitis on the roots can be divided into two groups:

- (a) Instrumental orthodontitis (IO) – where no radiographic signs on the roots’ surfaces are evident
- (b) Instrumental-detrimental orthodontitis (IDO) – where radiographic signs on the roots’ surfaces are evident

**Instrumental Orthodontitis (IO):** IO initiates controlled bone modeling (resorption and apposition) [13], as well as bone and cemental remodeling (reversible changes) [13, 14]. IO enables tooth movement to occur due to frontal and undermining alveolar bone resorption as well as bone apposition on the pressure and the tension sides, respectively [15]. The roots next to IO areas also undergo surface resorption and apposition [16] mainly by cemental remodeling. These biological processes terminate when orthodontic force application ceases. The periodontal ligament that surrounds the roots, in most cases, is fully regenerated. IO symptoms include mild to moderate tooth mobility and/or sensitivity and pain during the first days following force application. The pain usually subsides in 1–3 days; however the mobility and some degree of sensitivity last during most time of the treatment [17]. IO clinical signs include mild to moderate tooth mobility [18] as the symptoms and minor to mild radiographic PDL (lamina dura) widening. No root shortening or other morphological changes can be detected radiographically. Signs and symptoms disappear following orthodontic force cessation. The mechanism behind the IO process is that the orthodontic force enables, in this case, almost normal blood flow but induces local electrical current and pH changes as well as release of different biological materials due to local environmental change (e.g., cytokines, prostaglandins, and others) [1, 2, 14]. These events trigger local inflammatory activity in the area surrounding the roots that are limited to the PDL, affecting the alveolar bone and cementum. The inflammation in the pressure area induces mainly bone modeling process, where the alveolar bone is resorbed, while the inflammation in the tension area induces bone modeling by the apposition process; new bone is deposited on the affected surfaces.

Surface cemental remodeling, similar to the physiological one, is induced in both areas as well. The inflammation mechanism, which is a part of a normal bone and cementum metabolism, is genetically controlled. It is activated regularly (not related to orthodontic treatment) during our lifetime and it remains behind the normal hard tissues remodeling/modeling process [13]. Regarding treatment, analgesics are sometimes prescribed during orthodontic treatment [19]. The patients/parents have to be aware of the pain, the sensitivity and the tooth mobility prior to force application, and the ability to use analgesics as well as soft diet during the period of pain and sensitivity. No further action is needed. If the pain, sensitivity, and/or tooth mobility lasts following treatment, the orthodontist should look for other reasons like dental trauma, periapical lesions, cervical resorption, or other tooth, periodontal, or endodontal pathologies.

IDO is divided into two:

1. Instrumental and Detrimental Orthodontitis Grade 1 (IDO1): The inflammation in IDO1, for yet unknown reasons, changes its character on the cemental side and the remodeling process changes its characteristics to the modeling process; the resorption process goes beyond the cementum into the dentin. It might be that during orthodontic force application, the local environmental changes, due to the decrease in the local blood supply and bone bending, induce the formation of large enough necrotic tissue. The necrotic tissue which has to be eliminated consequently releases different chemicals and biological components which encourage the inflammation activity by recruiting local and far away inflammatory cells. This time the inflammation process on the root surface goes beyond the expected and wanted remodeling into the modeling process. IDO1 produces minor to moderate root shortening [20] as well as scattered lacunae on other root surfaces. This irreversible ORR is the direct result of orthodontitis. ORR is usually diagnosed using X-rays during, close to the end, or following orthodontic treatment. The symptoms and treatment are similar to IO. When the orthodontic treatment is completed, there are only radiographic signs (root shortening or peripheral surface resorption) but no symptoms. Following treatment the patients/parents have to be informed about the morphological changes seen in the different X-rays films. No further treatment is needed. If IDO1 manifestations are diagnosed during treatment, one should follow the suggested protocol ([Appendix](#)).
2. Instrumental and Detrimental Orthodontitis Grade 2 (IDO2): IDO2 is very similar to IDO1. However, in this case, the inflammation results in severe root shortening [20]. The symptoms are tooth mobility and sensitivity during or following orthodontic treatment. The signs include tooth mobility/sensitivity and severe root shortening as viewed on X-rays. The consequences of IDO2 require treatment. The treatment for IDO2 depends on the time that it is discovered. If IDO2 is diagnosed during treatment, one should follow the suggested protocol ([Appendix](#)). However, if IDO2 is diagnosed after debonding, it is suggested that orthodontic or prosthodontic fixed retention be used to splint the affected teeth together with unaffected teeth. In rare situations, fused crowns can be a good

treatment solution. Extractions and implant replacements should be considered only in extremely rare cases if ever, since it has been demonstrated that those teeth can remain in the mouth for many years [21, 22]. The mechanism for both IDO1 and IDO2 is similar to that described for IO. However, due to personal susceptibilities, the level of the resorptive activity on the root surface is different, and it is probably individually genetically determined [23–26]. It is suggested that the physiological remodeling process, which has five steps, namely, activation, resorption, reversal, apposition, and quiescence, is being disturbed most likely in the transition between the resorption and the reversal stages [13, 14]. This coupling between resorption and apposition probably disappears or is delayed and, therefore, resorption continues into the next mineral tissue, the dentin, and it is characterized by irreversible morphological root changes that can be detected radiographically.

#### Background and terminology:

Historically, the phenomenon, we previously called orthodontically induced inflammatory root resorption (OIIRR), appeared as root absorption in the professional literature in the midst of the nineteenth century [27]; however, its significance began to receive clinical attention only in the beginning of and through the twentieth century [28, 29]. The knowledge related to OIIRR, since it was discovered, was expanded immensely, but yet, in spite of the scientific and the technological developments, most of the publications that try to uncover ways to prevent this phenomenon find difficulties in providing solutions. In almost all published data, there was a large variance between individuals in the study groups and in different teeth of the same individual. Even years after the Human Genome Project [30] ended, we do not know how to identify an individual patient with OIIRR potential or how to prevent the process.

The initial term “root absorption” [27] was replaced in the beginning of the twentieth century by the term root resorption (RR) [28]. Since then the process was defined as apical RR (ARR) [31], external ARR (EARR) [32], orthodontically induced RR (OIRR) [33], orthodontically induced inflammatory RR (OIIRR) [6, 7], and others. Only lately, the new name orthodontitis was presented to the profession [9]. This new term actually covers the depth and breadth of what lies behind the OIIRR phenomenon.

Although the clinical relevance of orthodontitis and its manifestations and ORR are controversial, the number of studies related to this topic has significantly increased. A review of all the articles is not realistic and there are many reviews on the subject with the most recent one published in 2010 [34]. This chapter will try to describe and discuss contemporary relevant materials and innovations that were published in the last decade and to focus on the analysis of this information.

Orthodontitis is affected by both patient- and treatment-related factors. The main *patient-related factors* published lately are associated with the followings: heredity [14, 23–25, 35–43], immunology [44–46], systemic factors [12, 47–64], chronologic age [65, 66], dental age [67, 68], gender [69, 70], presence of RR before orthodontic treatment [71, 72], habits [47, 73], previously traumatized teeth [74, 75], tooth

structure/root form [70, 76–80], topography of adjacent alveolar bone [81–84], and individual tooth susceptibility [85–87]. The *treatment-related factors* should be divided into two groups: orthodontic treatment-related factors and non-orthodontic treatment-related factors. The orthodontic treatment-related factors published lately are associated with force magnitude [88–95], duration of force application [86, 88, 96–98], type of tooth movement [89, 99–101], and the treatment method [84, 86, 88, 102–118]. The non-orthodontic treatment-related factors published recently were endodontically treated teeth [42, 74, 75, 119, 120]; the use of nonsteroid anti-inflammatory drugs [50], doxycycline [51], and bisphosphonates [64]; surgical procedures (ovariectomy [62, 63], sympathectomy [121]); and the therapeutic effect of adding fluoride [58], thyroid hormone [60, 82], light-emitting diode (LED) [122], and ultrasound [123, 124] as a part of the treatment.

It is obvious that the periodical changes in the medical discourse have an important impact on the nature of the orthodontic studies and research. For example, when the influences of nutrition and metabolism on the human health were in the focus of the medical discourse, this same subject – the effect of nutrition and metabolism on orthodontitis and ORR – was studied in orthodontics as well [31, 125, 126]. When the medical literature was loaded with publications related to autoimmune diseases, the idea that there is the exposure of the dentin, tissue which is not recognized by the body's immune system, to humoral factors as an antigen appeared in the orthodontic literature as well [45].

And of course today, when the genes and associated subjects of the Human Genome Project like molecular biology and personalized medicine [127] are leading the medical discourse, we see that the number of studies relating to genetics is rapidly rising [14, 23, 25, 26, 35–41, 128, 129]. Maybe in the near future, as we see substantial amount of medical studies with good results on vaccines against factors involved in the inflammation process, like interleukins or cytokines [130], studies related to orthodontitis and ORR will be focused in that field.

The social hype and expectation raised by the Human Genome Project, initiated at the end of the last century, were enormous [131, 132], and they increased with the introduction of a private company – Celera – due to a competition with official government agencies that budget three billion USD to the project [133]. This project had short- and long-term goals [134]. Today, more than 10 years after the genome was decoded, it is clear that only a small part of the short-term goals, related primarily to mapping the human genome and to the innovative technology, have been fulfilled, while the major long-term goal is far from being achieved [30]. The ability to explain, using the knowledge obtained from the project, the differences in diversity of physiological and pathological processes between different individuals proved to be restricted [134]. Now, we further understand that the genes act in different ways in changing environment [135] (e.g., stress, fever, compression, and tension). The knowledge that no direct relationship between the genotype and the phenotype exists makes the discovery of individual characteristics challenging. The fact that each gene has a relationship in activity and expression to other nearby and even far away genes makes the statistical possible gene interactive relationships almost countless [136]. It is now clearer that genes are only

actors, among many others that play on the human biology stage or network. The current discourse in technoscience-medical world [137] discusses not only the genome but also the proteome, a new and by far more complex world than that of the genome [138, 139]. Results of the studies show that the connection of genetics and orthodontitis can provide explanations in only small percentages of the phenomenon [23, 140, 141]. This is mainly due to the large variance between individuals and even between identical twins.

Along our life span, surface root remodeling is among many other physiological processes that take place in our body [13, 142]. This remodeling is seen in all teeth, erupted or not, that serve as control in orthodontitis studies [58, 143] and is a part of the normal human body physiological turnover. This remodeling is controlled by the inflammation mechanism, and when ended, the resorbed area is fully regenerated [13, 14]. It might be that this physiological turnover process is the result of direct (e.g., chewing) as well as indirect (mesial drift) pressure acting on the jaws that is transferred to the roots of the teeth. The only microscopic sign that indicates the existence of this resorption, apart from areas where it is directly observed, is the presence of a reversal line, a sedimentation of material generated by mononuclear lining cells from the blastic cells' lineage (fibroblast, osteoblast, cementoblasts, etc.) at the very depth of the resorption area, where apposition of mineral material and the reconstruction of the resorbed area had begun [13]. The cementum covering the root is very similar to the alveolar bone structure [144], and both, like the cortical bone, experience the remodeling process which under normal circumstances is described as a coupling process that has its own precise sequence, from activation through resorption, reversal, formation, and its conclusion at the quiescence stage A-R-R-F-Q [13]. As mentioned, the process occurs at the roots of erupted teeth that are exposed to daily mechanical loads but also the roots of unerupted teeth that are exposed to indirect occlusal loads, as well as eruption forces. In most cases, this physiological resorption process takes place only at the cementum level and seldom reaches the defined boundaries of the dentin. This process is fully reversible and leaves no morphological scars that can be observed by external imaging methods. The process is a part of the normal cycle in both the apical cellular and the coronal acellular cemental layers.

Orthodontic force application changes, in minutes, the anatomical and physiological environment of the roots. All tissues involved in the system, namely, the roots, the periodontal ligament, and the bone (tooth, periodontal ligament, and bone system (TPLBS)), and sometimes areas that are far from this system, the sutures and other bones of the skull, experience those changes and react accordingly. This unexpected load stimulus that does not belong to the normal growth and development pathway demands the body to react. The reaction does not necessarily have to be in the limits of the physiological borders of the inflammation controlled remodeling process, where the TPLBS remains at the end of the process untouched, keeping the morphology and the function unchanged, as seen in most instances of force application (as described in IO). Actually in many cases, the reaction to orthodontic force application, the remodeling, goes far beyond the cementum into the dentin and actual loss of root material can be detected either

microscopically or macroscopically. These morphological changes are irreversible and can be diagnosed, using several imaging techniques, especially cone beam computerized tomography, as shortening of the involved roots horizontally and/or rarely diagonally. Usually, the resorbed root material is replaced by alveolar bone; nevertheless, normal periodontal ligament layer always separates between the two, keeping the normal function of the harmed tooth [6, 7]. Actually, if we look at the different definitions related to bone turnover and other biological processes, the changes in the root can be associated with modulation or mini-modulation that initiated as remodeling reaction to the force application, and from a yet unknown reason, the coupling of reversal from resorption to formation did not occur. It is important to emphasize that teeth that experienced mild or even severe resorption do not lose their vitality, color, or function, similarly to the nearby periodontal ligament that moved in space [13]; furthermore, their roots' surface areas, in many instances, are relatively increased by the side surface local resorption, which might increase their stability as a compensation for shortening the roots.

Many publications are trying to explain the reasons or goals for *bone remodeling*. Is the goal of the process to repair micro-fractures in the bone due to fatigue, extreme loads, or local weakness, or is it a part of mineral, especially calcium, recruitment process, since the bone is the biggest mineral reservoir of the body? Or maybe is it a process that aims to remove osteocytes or cementocytes that went through apoptosis and ended their life cycle from the bone and cellular cemental areas, respectively?

We know that in extreme circumstances, the body sacrifices less essential tissues and organs [145]. When the TPLBS is exposed to an extreme condition, such as increased force application, the local strain increases above a certain amount for a long enough time (the threshold of the amount of force and time is individually determined). The first programmed reaction activates the physiological inflammation process. Local materials that are being released from the damaged cells initiate a process of recruiting local and far away cells in order to eliminate the and repair the initial damage. However, when the blood supply is decreased and the amount of the hyalinized necrotic tissue increases, there might be difficulties in maintaining the normal coupling process, even by accelerating it or by increasing the areas of the resorption on the cementum surface [94, 97]. Thus the remodeling process experiences insufficiency. The expression of this insufficiency, while still reversible, is detected first only by using the microscope and when it continues and the damage to the roots is large enough and goes beyond the cementum into the dentin. The initially reversible process turns into an irreversible one that can be detected even by using external imaging techniques. We do not know yet whether the reaction to the insufficiency remains within the boundaries of the known inflammation mechanism or activates a new, yet unknown, pre-programmed destructive reaction aimed to protect the surrounding alveolar bone and periodontal ligament by scarifying the roots. Further, we definitely should ask the questions: Why in most IDO1 and IDO2 cases the roots are being replaced by bone tissue and not, for example, by connective tissue? And moreover, how come the periodontal ligament and adjacent bone



are fully regenerated while only the roots are being changed and resorbed? Are the bone and the periodontal tissue placed higher than the roots in the hierarchy of tissue importance (if it exists) (Fig. 4.1)?

Another theory can be suggested. This one is based on the well-known evolutionary phenomenon called the Butler’s field theory [146]. This theory tries to explain the reason for the disappearance of the last tooth in each field of the dentition (lateral incisors, second premolars, and third molars) during evolution [147]. It might be speculated that when the TPLBS is exposed to an extreme condition, in which the local blood supply stops and necrotic tissue appears, the body activates hidden genetic mechanisms which normally are used to decrease the number of teeth, however in this instance only partially.

The “self-defense mechanism” is another theological possibility that might explain this irreversible root shortening. It may well be that by activating the IDO1 and IDO2, the body intends to prevent itself from reoccurrence of similar events in the future. Since force application increases the inside pressure in the TPLBS, the body initially utilizes physical and later biological mechanisms in trying to do their best to reduce the entropy (the disorder) immediately, with implication to the future. It might be that by reducing the root length, the disrupting local pressure is decreased, and future similar threat is prevented. The publication that found less root shortening in patients with a history of earlier orthodontic treatment compared to the remaining patients [148] supports this theory. There were early reports that recognized the overall protective function of the root’s outer layer, the cementoid, or the precementum [8], but there are no explanations why the roots are more protected in the second orthodontic round. According to our proposed theory, the root shortening by itself can prevent a future pressure around the apex from being raised. In Figs. 4.2 and 4.3, we can see the effect of root shortening on the amount

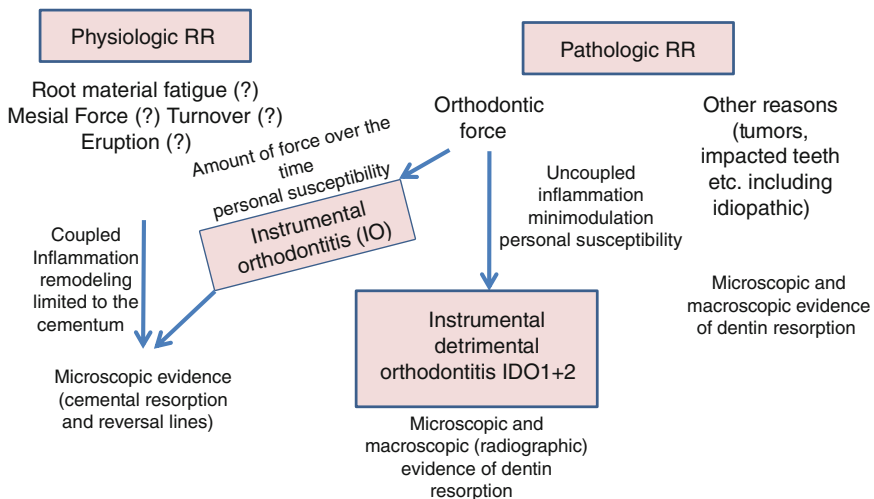
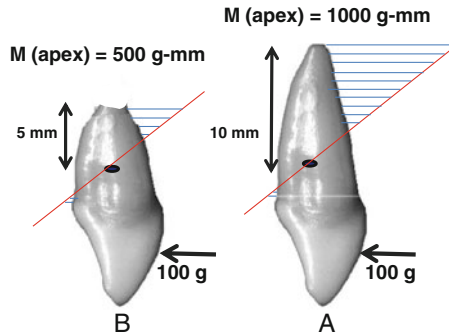


Fig. 4.1 Types of root resorption (RR)

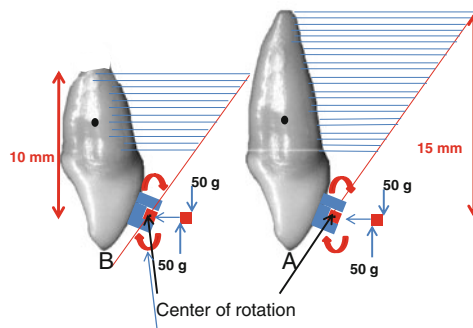




**Fig. 4.2** Stress, force, and moments and the self-defense mechanism theory in uncontrolled force application. If an uncontrolled 100 g of force is applied to tooth A, the center of rotation is close to the center of resistance, and the stress distribution on the root surface is depicted by the horizontal lines. Note the minimal stress line next to both the center of rotation and the gingival area of the root. If the same force is applied to tooth B with a shorter resorbed root, the amount of stress developed in the apical area is much lower than that on tooth A with the longer root (see text)

of stress developed in the apical zone due to similar uncontrolled and torque force applications. Figures 4.2 and 4.3 graphics depict the issue [149]:

The strain and of course the stress developed in the TPLBS following orthodontic force application are dependent on mechanical factors like the amount of the force applied, point of application, the resultant vector of force and moment, the location of the center of resistance, and others, as well as biological factors, like the root shape and form, the number of roots, the biological and physical properties of the cementum, periodontal ligament and bone, and more. It is clear that mostly genetics determines the major biological factor, related to the potential reaction to the strain. It determines the degree of the inflammatory reaction and the degree of the resistance or



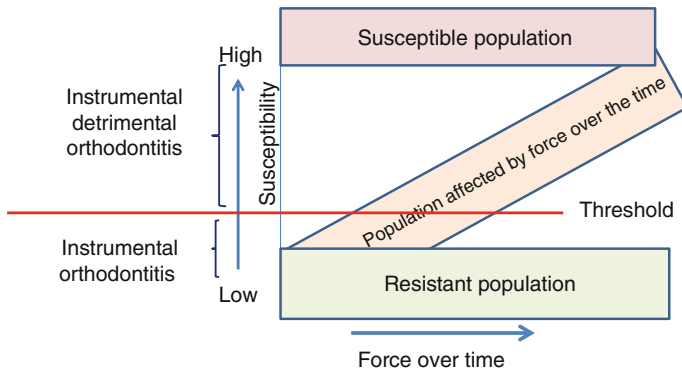
**Fig. 4.3** Stress, force, and moments and the self-defense mechanism theory in torque application. In order to move the root of tooth A and tooth B buccally, torque is needed. The center of rotation in this movement is in the bracket, which is away from the center of resistance. Using similar forces on both teeth, the amount of developed stress in the apical zone of tooth A is much bigger than the one developed in the tooth with shorter root B (see text)

the vulnerability of the individual to orthodontitis. Genetics, epigenetics, and environmental factors determine the general health condition of the individual and his/her ability to react to the force. It is well known that even identical twins, whose genome is equal, react in different ways, due to environmental influences [150] and even hybrids mice do not always react exactly the same in identical conditions. Individual variances are always there. A major factor that should not be forgotten, associated to the reaction of the body to orthodontic force, is time. Roughly we can divide the population into three categories related to their susceptibility to orthodontitis:

- (a) Those that are not susceptible at all and will never show any macroscopic signs (signs that can be detected by X-rays) during the whole treatment, whether light, medium, or heavy forces will be applied for short, medium, or long term. Those patients own a high threshold level to force over the time and will react always by developing only IO as a reaction to the applied forces.
- (b) Those who will always show macroscopic signs of root shortening, in any orthodontic treatment, when light, medium, or heavy forces will be used for short, medium, or long term. Those patients own a low threshold level to force over the time and will develop manifestations of IDO1 and occasionally IDO2 as a reaction to the applied forces.
- (c) Those whose genetic-environmental complex reaction or threshold is sensitive to the amount of force and/or duration of treatment time. For example, when using low levels of force for a short treatment time, both or the mutual combination of force and time is under the threshold of activating IDO (1 OR 2) (the actual amount of force level and time length are yet not known). This will prevent the appearance of macroscopic root shortening, however, if the force will be above their threshold or the time will be long enough or there will be a mutual combination, namely, low force but long treatment time or high force but a short treatment time; macroscopic root shortening as a result of IDO [1, 2] will be evident (see Fig. 4.4).

During our lifetime there might be shifting from one group to another. It depends on health condition, nutrition, metabolism, mental state, and of course other unknown yet genetic and/or environmental variables.

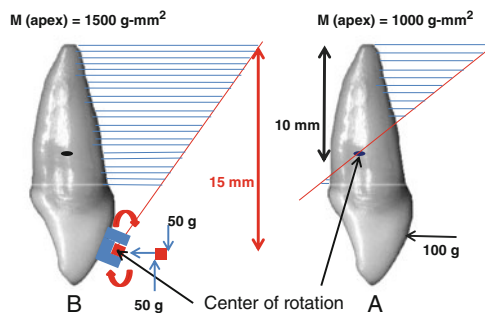
It is well known that all the abovementioned biological- and treatment-related factors change with time and actually all the time, even during the orthodontic treatment or experiments. Therefore, our abilities to in-depth study the subject are limited, and drawing conclusion from those studies should be taken with utmost care. Most of the clinical studies, dealing with orthodontitis, are retrospective, and therefore we can only compare the final state with the initial one or to a 6–9-month periapical X-ray of the upper incisors, suggested by Malmgren [20], if it was taken [151, 152]. We do not have the ability to follow or to know from those studies the exact time root changes had happened. Is it at the beginning, midterm, or final stages of the treatment? Was it a short-term event or did it last slowly through the whole treatment time? From Malmgren [20] publication, it is clear that the number of teeth suffers from IDO



**Fig. 4.4** Population susceptibility categories

increases with treatment time. We can speculate that during the last period of treatment, the ability to involve torque movements in the treatment is increased. Torque, unlike uncontrolled movements, moves the center of rotation, away from the center of resistance, toward the bracket and by that increases the distance from the apical region. The direct result of this movement, the torque, is the heavily increased moment developed in the apical region relative to an uncontrolled movement, which might affect the local stress and further the activation of the destructive consequence (Fig. 4.5).

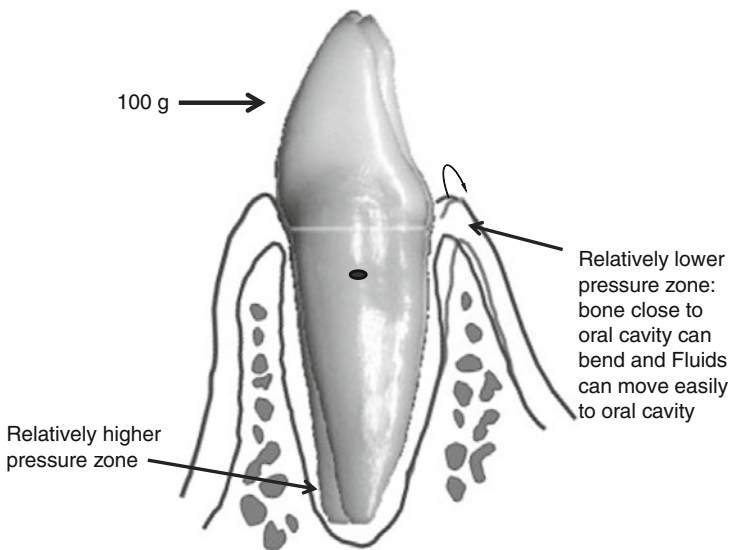
We know the gender and age of the patients, the treatment durations, the appliances used, whether it was an extraction or non-extraction case, and some other general socioeconomic and demographic parameters. We know that in most cases when we detect, following treatment, root length changes, they always appear in the apical region. It can be either full root shortening or diagonal one that is diagnosed



**Fig. 4.5** The difference in stress distribution of uncontrolled force and torque on the apex. If an uncontrolled 100 g of force is applied to tooth A, the center of rotation is close to the center of resistance, and the stress distribution on the root surface is depicted by the horizontal lines. Note the minimal stress next to both the center of rotation and the gingival area of the root. In order to move the root of tooth B buccally, torque is needed. Since the center of rotation in this movement is in the bracket, which is away from the center of resistance, for the same force, the stress distribution on the root surface is much higher especially in the apical zone

using cone beam computerized tomography (CBCT) [153], an imaging tool that became, in recent years, very popular in dentistry.

How come in most short-term experimental in vivo clinical studies, following a few weeks or months of treatment [89, 95], morphological root changes can be detected in the extracted teeth in the pressure and tension surfaces surrounding the roots, but never as apical root shortening, while in long-term clinical studies in which teeth are not extracted, apical root shortening is detected following 6 and more months of treatment? This disparity was never explained. Does the presence of cellular cementum in the apical region increase the vulnerability of the roots to orthodontic forces in this region compared to areas where acellular cementum is present? Does the fact that the coronary areas of the root, surrounded with very thin alveolar bone, having the ability to bend and absorb part of the pressure developed due to the force applied to the teeth defend those areas of the roots from the damage of orthodontitis (IDO)? Does the fact that the coronal root area is open to the oral cavity, and the different fluids, i.e., extracellular, intracellular, and blood, can easily move outside the scene and by that decrease the pressure developed, compared to the apical areas, where the bone is much thicker and the area is almost blocked to fast fluid movement, from higher to lower pressure zones, explain why we see mainly apical root shortening compared to less coronal root damage, or is it due to the fact that the stress distribution levels in most movements are higher in the apical region compared to the coronal region if the pressure level is the main factor initiating the IDO process (Fig. 4.6)?



**Fig. 4.6** High and low pressure along the root surface. When 100 g of force is applied to the crown, the root moves accordingly. Crestal bone can bend (decrease the pressure), while the apical bone cannot. Fluids from the crestal zone can easily move into the oral cavity (decrease the pressure) compared to the fluid in the apical zone. In most movements the stress in the apical zone exceeds the one on the gingival zone. Thus the pressure in the crestal zone can actually be decreased or is much lower than in the apical zone, and therefore it is rare to see the signs of root resorption in the gingival zone

Knowledge achieved from animal experiments, in which the researches were trying to imitate clinical human conditions, is important. However, there is always a risk of drawing conclusions from those experiments to humans. Human orthodontitis clinical studies are unfortunately short term in nature and usually examine the first premolars. Drawing clinical conclusions from 4- to 12-week studies on the behavior of the TPLBS exposed to 24 or more months of treatment is questionable. Moreover, the teeth that are examined in those studies, the first premolars, are usually the teeth that are not very susceptible and vulnerable to present signs of IDO. Further, we do not recall any short-term study where actual root shortening was reported. Therefore, it might be summarized that drawing long-term clinical conclusions from many laboratory studies is far from being accurate. We believe that similar attitude has to be toward studies using computer programs that simulate the actual conditions of the TPLBS. The finite element model (FEM) is the most popular one in this context [14, 79, 80, 154]. Although this engineering program accepts numerous physical properties' variables of the biological components, again, drawing conclusions on the human TPLBS is limited and has to be taken very carefully since it is impossible to follow the changes in time and of course to consider the individual variations in the reaction to force application.

This part of the review will present and discuss orthodontitis and the effect of different patient-related factors published in the last decade:

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## 4.1 Genetic Factors

The present concept in the professional literature is that *bone* remodeling is controlled by inflammation process. The current assumption says that normal bone remodeling is a reaction to probably local micro-fractures or local fatigue areas of the bone. This process is genetically controlled [13]. The term “bone remodeling” means that at the end of the precise timing process, a full regeneration (functional and morphological) of the remodeled part is completed. Since the cementum is very comparable to the alveolar bone, the implication of the remodeling process from the bone to the cementum is logical, especially since it was shown that alveolar bone remodeling and physiological cemental remodeling are alike [155]. As mentioned before it might be that the cemental remodeling process is the outcome of IO; however in IDO the process goes beyond the cementum borders into the dentin to become irreversible minimodeling process (morphological root changes). Most of the current genetic research of the physiological (the one that is limited to the cementum) and the pathological (the one that damages the dentine) orthodontitis (IO and IDO) deals with parameters that are well known from the medical literature for being responsible to the inflammation process. Humoral and cell parameters like RANK, RANKL, OPG, P2X7R, cytokines, interleukins, prostaglandins, etc., and of course genetic expressions such as genotype, phenotype, polymorphism, and others are the main actors of the many research projects currently studying thoroughly the full extent of orthodontitis [14, 23–26, 35–41, 43, 128, 129].

We see the Harris et al. [141] and Al-Qawasami et al. [23] publications as the two milestones related to hereditary and orthodontitis. Harris' clinical research studied the meaning of patients' susceptibility to EARR. The conclusion of this article says: "Even when the nature of the malocclusion, the treatment plan, the appliance and the practitioner appear to be held constant there is a considerable range among patients, in the occurrence and the extent of EARR. One interpretation of these differences is that the person's genotype modulates his or her susceptibility to EARR: some people appear to be intrinsically endowed with resistance to apical resorption under the stress of mechanotherapy, and some, at the other extreme, are prone to experience severe resorption under the same regimen." This conclusion was challenged by the group from Indiana University who conducted their genetic-related studies for the last decade. The 2003 epic publication by this group was the first one to report on a genetic marker that identifies people who are susceptible to ORR before the beginning of orthodontic treatment. This research found association of EARR and IL-1 $\beta$  polymorphism suggesting a role of this cytokine in the pathogenesis of EARR. One of the conclusions of this article suggested that potential orthodontic patients can be screened for IL-1 $\beta$  genotype by analyzing the DNA from a simple cheek swab or mouthwash taken during initial examination to identify those who carry 2 copies of the high-risk allele (allele 1 of IL-1 $\beta$ ). As of today, almost 10 years after this study was published, we are not aware of any clinic that does this test, nor did we read any prospective study that found potential orthodontic patients who carry two copies of this allele, and their susceptibility to EARR was evaluated during and following treatment. Further, another retrospective study [37] found that the allele and the genotype distribution of the IL-1 $\beta$  polymorphism in patients and control cohorts revealed no indication of a predisposition to EARR, and another group [26] found, with much higher logarithmic odds (LOD) score than the Al-Qawasami et al. group [23], that variations in the interleukin 1-RN (IL-1 receptor antagonist) gene and not only in the IL-1 $\beta$  gene are determinants of a predisposition to postorthodontic EARR. The debate on the role of genetic polymorphism as well as different biologic agents like interleukins, prostaglandins, RANK and RANKL, osteoprotegerin (OPG) [40], TNF $\alpha$ , TNFRSF11A, TNSALP [35, 39], and others on the susceptibility to EARR is ongoing, and we hope that in the future it will be cleared and solved.

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## 4.2 Immune System Factors

Surprisingly, the number of publications discussing role of the immune system in orthodontitis, in the last 20 years, is minute relative to the overwhelming number of publications related to genetics of the inflammation process and orthodontitis. As mentioned previously, this might be the effect of the shift of the current medical discourse to the genome role in physiological and pathological conditions.

It is well known that the immune reaction itself and the modulation of different lymphocytes response go mutually with the components of the inflammatory process [156, 157]. Therefore it might be just a question of time that this issue will

become again a part of the medical discourse and the dental discourse as well. Years ago it was hypothesized that susceptibility to detrimental orthodontitis may be associated with autoimmune response to dentine matrix proteins [45, 158]. This was based on the evidence that anti-dentine antibodies could be detected in experimental root lesions in mice. The recent paper by Ramos et al. [46] concludes with two important issues that should get more attention:

- (a) Each individual carries antibodies against the dentin matrix, which might not be recognized as a self-structure by the human immunologic system (probably from the time of the physiological exposure of the material during the replacement of the deciduous dentition). These antibodies may become active upon exposure of the dentin during the hyalinization that leads to damage of the cementum layer and dentine exposure. The level of these antibodies decreases during orthodontic treatment especially in patients who suffer from more extensive IDO [159].
- (b) Relatively high levels of anti-human-dentine-extract (HDE) secretory IgA (sIgA) are simple indicators for patient's susceptibility to IDO. This antibody is the main line of defense of the oral cavity and the upper respiratory tract surfaces and is secreted in large amounts into the saliva by the salivary glands [128].

This study further suggests to analyze the level of this antibody (sIgA) before initiating orthodontic treatment in order to learn about the susceptibility of the patient to IDO, in a similar way to the study of Al-Qawasmy et al. [23], who suggested the DNA examination for two copies of allele 1 of IL-1 $\beta$  in new orthodontic patients.

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### 4.3 Other Systemic Factors

The patient's systemic condition in relation to IDO continues to be investigated and is focused on two main issues. One is the spontaneous systemic state and the other one is the systemic status derived from influences of external factors: substances such as drugs, food supplements, hormones, and other materials and therapeutic procedures such as surgical. The systemic condition that involves no dispute regarding its influence on IDO is *allergy* including asthma.

Owman-Moll and Kurol [47] selected fifty adolescents and divided them into two equal groups: the high-risk group based on measurements of the most severe IDO, namely, IOD2 expression, and the low-risk group based on measurements of mild or no changes in root morphology IO and IDO1 expression. After a preliminary screening of possible risk factors regarding IDO, only subjects with allergy showed an increased risk of root resorption, but *this was without statistical significance*.

In 2006, Nishioka et al. [48] studied retrospectively the association between IDO2 expression and immune system factors in 60 Japanese orthodontic patients. The pretreatment records revealed that the incidence of allergy was significantly higher in the IDO2 group. The incidence of asthma also tended to be higher in this



group. From these results, they concluded that allergy and asthma may be high-risk factors for the development of excessive root shortening during orthodontic tooth movement in Japanese patients.

*Periodontitis* was suggested to influence orthodontitis in a similar way to allergy and asthma as the number of inflammatory cells in the tissues adjacent to the roots of the teeth increases; however this issue was never studied or verified directly, and no conclusion related to ORR can be drawn. For example, experimental periodontitis was induced in rats by placing a cotton ligature around the cervix of the first upper molars for 48 h. An increase in the percentage of resorption areas and in the number of odontoclasts following orthodontic force application was found. These histomorphometric values were reduced once the inflammatory reaction had subsided. The results suggest delaying orthodontic treatment in patients with periodontal disease until the inflammatory signs have subsided [49]. Can we draw clinical conclusions from this 2-day rat experiment on the effect of periodontitis in conjunction with orthodontic force application to humans especially related to apical root shortening?

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#### 4.4 Chronologic Age

As most studies in previous decades found no significant correlation between the age of the orthodontic patients and the incidence and severity of IDO expression, it was quite surprising to find different results in recent studies. The results of a study in rats [65] revealed that adult rats (9–12 months old) had increased incidence and severity of root shortening with prolonged tooth movement compared to young rats (6 weeks old). In both groups, the middle part of the root had the highest incidence and severity of resorption. A clinical study by Jiang et al. [66] on 96 patients between 9 and 34 years treated by fixed appliances for at least 1 year found that patient age correlated with RR of the upper incisors before treatment and after treatment according to panoramic radiographs. It may be speculated that more ORR occurred in adults due to the presence of resorbed roots before treatment. However, the inaccuracy of analyzing the exact amount of ORR on panoramic radiographs is a well-known phenomenon [160, 161].

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#### 4.5 Dental Age

There is a consensus in the professional literature that ORR is related to the process of root development and that there is an advantage of moving teeth with incomplete root development regarding prevention of root shortening. However, while Hendrix et al. [47] found that teeth with incomplete root formation at the onset of orthodontic treatment continue to develop roots during treatment, but the roots reach somewhat less than their expected root length potential, Mavragani et al. [68] found no significant difference in the extent of root lengthening between the roots that elongated during treatment and the normal root lengthening in age-matched untreated individuals. They

also found that roots that were incompletely developed before treatment reached a significantly greater length than those that were fully developed at the start of treatment. The differences between the two publications might be the result of the way the teeth were X-rayed and the roots' length was measured [159, 160].

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## 4.6 Gender

All recent studies found no association between gender and IDO expression. No difference in either the incidence or severity of ORR between male and female patients was found in a study by Sameshima and Sinclair [69] who used periapical radiographs of 868 patients who were treated with full, fixed edgewise appliances. No statistically significant differences in ORR were found in relation to gender in a group of 96 subjects treated using fixed appliances for at least 1 year and who had panoramic radiographs at two time points [66]. “Even” the CBCT did not reveal a significant association between IDO and the gender of orthodontic patients [70].

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## 4.7 Presence of RR Before and During Orthodontic Treatment

Confirmation to the positive correlation that was found in the past between the severity of ORR at the end of orthodontic treatment and the presence of ORR before treatment was given in the clinical study by Jiang et al. [66]. This correlation, obtained by evaluation of panoramic radiographs, was found especially for the anterior teeth.

Another correlation that was confirmed during the last decade by Artun et al. [71] is the positive correlation between the presence and severity of ORR during the initial stages of treatment and the severity of the resorption present at later stages, as evaluated on periapical radiographs for the maxillary central and lateral incisors. They found that patients with detectable ORR during the first 6 months of active treatment are more likely to experience resorption in the following 6-month period than those without. In a later study Artun et al. [72] found the amount of the resorption at the end of treatment to be highly correlated to that found after 6 and after 12 months of treatment.

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## 4.8 Habits

Contrary to articles published in the past, the last published studies on the association between habits or parafunction on orthodontitis found no association. Owman-Moll and Kurol [47] checked the nail biting habit histologically on teeth that were moved orthodontically before their extractions, while Makedonas et al. [73] related to nail biting, nail biting history, finger sucking, and finger sucking history and used CBCT to evaluate the severity of resorption after 6 months of active treatment. They found no impact of the habits or past habits on the amount of the resorption.

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## 4.9 Previously Traumatized Teeth

The only study in the last decade concerning OIRR in relation to previous trauma is the one by Makedonas et al. [73] who diagnosed ORR with CBCT after 6 months of orthodontic treatment with fixed appliances. The results of the study indicated that trauma before treatment did not have any impact on the amount of resorption after 6 months of active treatment.

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## 4.10 Tooth Structure/Root Form

The different effect of the orthodontic force on teeth with different root forms is still in controversy. Some of the studies found root morphology as not being a risk factor for IDO [47, 70, 73, 76, 77]. Mavragani et al. [76] studied mild dental invagination and Van Parys et al. [77] pipette-shaped roots, and according to Lund et al. [70], root length at baseline was not associated with the degree of resorption. However, other studies reached different results. Smale et al. [78] report on long roots, narrow roots, and deviated root form as risk factors for EARR of the central incisors and on normal root form and wide roots as preventive factors. Nishioka et al. [48] found root morphology abnormality (shortened, blunt, eroded, pointed, bent, bottle shaped) significantly higher in the ORR group of orthodontically treated patients. Finite element model [79, 80] found various root morphologies affecting stress distribution of forces along the roots. Oyama et al. [79] applied forces in a vertical (intrusive) and horizontal (lingual) direction to the tooth axis and observed stress concentration in the root of the models with short, bent, and pipette-shaped roots. In the models with a bent or pipette-shaped root, significant stress was concentrated at the root apex. In the short-root model, significant stress was concentrated at the middle of the root, while the blunt-shaped root model showed no significant stress concentration at the root. Kamble et al. [80] applied orthodontic forces in various directions (intrusion, extrusion, tipping, and rotational) on maxillary central incisors and found significantly increased stress at the apex of the root with dilacerated morphology and at the cervical one-third region of the tooth with the short root. Increased stress was observed at the middle one-third region in the tooth with the pipette-shaped root during intrusion and extrusion. They conclude that the stress distribution pattern indicates that the maxillary central incisors with deviated root morphology are at higher risk of RR.

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## 4.11 Topography of Adjacent Alveolar Bone

The bone factor regarding orthodontitis has been studied for decades. A study on tooth movement through regenerated bone created after distraction osteogenesis on beagles [81] found less resorption of the roots when the teeth were moved in mature, well-organized and mineralized bone created after 12 weeks of consolidation compared with immature, fibrous, and less-mineralized bone after 2 weeks of

consolidation; however the amount of tooth movement was greater when the teeth were moved to immature bone although with more tipping. The effect of bone turnover rate on tooth movement and RR in rats was studied by inducing secondary hypo- and hyperthyroidism [82]. The different metabolic rates were created by this induction. It was found that low bone turnover induces a significantly larger amount of resorption on roots that are not submitted to mechanical loading. However the amount of RR induced by the orthodontic force was not influenced by the metabolic rate. The high bone turnover in the hyperthyroidism group increased the amount of orthodontic tooth movement but did not decrease the amount of IDO. It has to be noted again that administration of low doses of thyroid hormone (TH) was found to have a protective role on the root surface during orthodontic treatment [60]. Controversial reports on the association between alveolar bone density and orthodontitis appear in the literature [11]. Bone structure effect on orthodontitis of lower incisors was studied on pre- and posttreatment cephalometric radiographs of orthodontic patients by Otis [84]. No significant correlation was found between the extent of the IDO and the amount of alveolar bone around the root, the thickness of cortical bone, and the density of the trabecular network. Motokawa et al. [84] hypothesized that a movement of the maxillary central incisor near the cortical bone of the alveolus and incisive canal might cause severe RR.

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## 4.12 Individual Tooth Susceptibility

All teeth may suffer from RR induced by the inflammation created by the orthodontic movement [11]; however several studies indicate that some of the teeth are more vulnerable to IDO than others. Apajalahti and Peltola [85] report that according to their study that used panoramic radiographs pre- and posttreatment, the most severe resorption was seen in the maxillary incisors and premolars. However according to most studies, the maxillary incisors are the most affected by RR during orthodontic treatment. This might be due to the greater movement of these teeth compared to other teeth during orthodontic treatment in order to achieve greater esthetic and functional demands [11] Mohandesan et al. [86] who studied the roots of maxillary incisors on periapical radiographs before and 6 and 12 months after the start of treatment found more shortening of the roots of the lateral incisors compared to those of the central incisors and that clinically significant resorption was found at a higher rate for the laterals compared to the centrals.

Opposite results were obtained recently by Jung and Cho [87] who report that according to their study on panoramic radiographs, maxillary central incisors were found to be the most resorbed teeth, followed by the maxillary lateral incisor. They found that the latter teeth are followed by the mandibular central incisors and the mandibular lateral incisors regarding vulnerability to IDO.

This part of the review will present and discuss the treatment-related factors affecting OIIRR published in the last decade:

## 4.13 Orthodontic Treatment-Related Factors

### 4.13.1 Force Magnitude

There is no orthodontic tooth movement without force application; therefore, the force level is the immediate or usual suspect blamed for IDO1 and IDO2. In the last decade, Darendeliler and his group in Sydney, Australia, published results of several researches using microcomputed tomography, scanning electron microscopy, and laser microscopy, discussing the force magnitude effect on orthodontitis [89–95]. In these studies, it was found that the volume of the resorption craters at least in certain areas of the roots (in human premolars and rats molars) was directly proportional to the force magnitude exerted for intrusion, extrusion, rotation, tipping, and bodily movements. Only one similar study, conducted by a group from the Netherlands [88] on mandibular premolars of dogs, that measured the dimensions of the lacunae found the effect of force magnitude on the severity of root resorption to be statistically insignificant. According to a recently published study by Darendeliler's group, when extremely heavy forces were applied on rats' molars, root resorption increased; however the amount of tooth movement decreased [89].

All those studies, which contributed tremendously to our understanding of the orthodontitis process, have to be taken with utmost care. Orthodontics human studies that involve extractions of teeth are usually short term. The average study length is a few months, while orthodontic treatment lasts usually 20–24 months. Moreover, the premolars which are the common teeth involved in those studies are not the ones that suffer from IDO1 and IDO2 as, for example, the upper incisors and none of the extracted teeth demonstrated apical RR. Again, we can learn a lot from animal studies; however the implication from those studies on human beings is not always correct and exact.

### 4.13.2 Duration of Force Application

No study to date contradicted the direct correlation found between the duration of force application and the severity and incidence/prevalence of the resorption that occurs during treatment, whether those studies were clinical [86, 96] or histological [88, 97, 98]. It is more than reasonable to assume that long-term exposure of the roots to orthodontitis might eventually lead to IDO1 or even to IDO2 expression. As we previously mentioned, genes and their products and the proteins act differently in changing environment; therefore, the longer the treatment, the chances of the environment to change increases.

### 4.13.3 Orthodontic Type of Movement

Teeth are probably more vulnerable to intrusion. It was found that applying intrusive 100 cN of continuous force to maxillary first human premolar teeth for 8 weeks

prior to their extractions produced about four times more root resorption than similar extrusive force [99].

Moreover, other [100, 101] clinical studies found that movements combined with intrusion are more detrimental to the roots (IDO1 and IDO2) than nonintrusive mechanics.

These findings match others who found that significant resorption occurs more in compression areas compared to tension areas and can explain the findings that IDO1 and IDO2 expressions following tipping movement are more pronounced than that resulting from bodily movement as the pressure is dispersed along the roots in the last mentioned type of movement [89]. Unfortunately the effect of torque per se on the IDO1 and IDO2 expression was not studied in the last decade.

#### 4.13.4 The Treatment Method

There is evidence that IDO1 and IDO2 manifestations are present in all forms and methods of treatment. The use of *removable thermoplastic appliances* does not prevent this side effect. Krieger E et al. [103] found that all 100 patients included in their study that were treated to resolve anterior crowding by aligners had a reduction of the pretreatment root length. According to a previous microcomputed tomography study by Barbagallo et al., clear removable thermoplastic appliances have, in a short term, in vivo experiment similar effects on root cementum as light (25 g) orthodontic forces derived from fixed appliances [104].

Also the use of *self-ligating brackets* does not reduce the incidence and severity of root uptake compared to the use of conventional brackets [105–107].

All the studies from the last decade that dealt with the effect of treatment involving extractions on IDO expression compared to treatment without extractions found that the first one resulted statistically significant higher prevalence of severe root resorption [84, 86, 108, 109] probably due to the distance of teeth and roots moved during treatment.

However, no difference was found in root resorption between two-step and en masse space closure procedures [110]. Even though the use of super-elastic heat-activated arch wires was not found to significantly increase the severity of root resorption, compared to conventional multi-stranded stainless steel arch wires during the leveling stage of treatment [111], most studies found that intermittent forces cause less severe root resorption than continuous forces [88, 112–114]. However there might be clinical importance to the timing of reactivation according to the last mentioned study.

A recent study found that more root resorption in patients is treated by the *straight-wire* method and less in the *standard edgewise* technique. The authors suggest that it may be attributed to more root movement in the pre-adjusted MBT technique that was used to represent the straight-wire method [115].

*Corticotomy-facilitated orthodontics* (CFO) in adults to relieve moderate crowding of the lower anterior teeth was found to reduce the total time of treatment significantly from  $17.5 \pm 2.8$  weeks in the CFO group to  $49 \pm 12.3$  weeks in the

conventional orthodontic therapy group and decreasing the root length lost ( $0.02 \pm 0.10$  mm compared to  $1.4 \pm 0.8$  mm) with no statistical significance [116]. No difference in the amount of resorption between the *Fränkel and eruption guidance appliance* groups was found [117].

The use of *magnets* for orthodontic tooth movements in rats by gradually increasing the force applied induced effective tooth movement with no pathological changes, such as root resorption [118]. However, this method has not been developed enough for clinical use.

A study by Brin et al. [162] that compared *1- versus 2-phase treatment* of class II malocclusion found the proportion of incisors with moderate to severe ORR to be slightly greater in the 1-phase treatment group.

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## 4.14 Non-orthodontic Treatment-Related Factors

### 4.14.1 Endodontically Treated Teeth

Although in the past there was disagreement over the correlation between endodontically treated teeth and ORR [11], recent studies on periapical or panoramic radiographs indicate no significant difference in the amount or severity of RR during orthodontic treatment between root-filled teeth and teeth with vital pulps [74, 75, 120]. However a recent study found that genetic variations in the interleukin-1 $\beta$  gene predispose root-filled teeth to EARR for matched pairs, secondary to orthodontic treatment in a different way from their control teeth with vital pulps in subjects homozygous for allele 2 [2/2(TT)] [42].

*Nonsteroid anti-inflammatory drugs* (NSAID) are sometimes used to relieve pain during orthodontic tooth movement. Nabumetone given to orthodontic patients was found to be useful in reducing IDO manifestations, pulpitis, and pain caused by intrusive orthodontic movement, without altering tooth movement in response to the application of orthodontic force [50]. These results strengthen the inflammation base of orthodontitis.

*Doxycycline* is one of the tetracycline antibiotics group and is commonly used to treat a variety of infections including chronic ones. Mavragani et al. [51] investigated the effect of systemic administration of low-dose doxycycline on ORR in rats and found a significant reduction in ORR, in the number of odontoclasts, osteoclasts, mononuclear cells on the root surface, and TRAP-positive cells on the root and bone for the doxycycline-administered group. The effect of the doxycycline may be at least partly similar to that of the NSAIDs.

*Bisphosphonates*, known to be inhibitors of bone resorption, continued to be studied in relation to orthodontic tooth movement in the last decade probably due their vast use in treatment for bone metabolism disorders such as osteoporosis, Paget's disease, and bone metastases. While in the past there was a dispute over the effect of bisphosphonates on the roots during orthodontic movement, according to the studies of the last decade, these agents reduce ORR. The bisphosphonates inhibit the ability of osteoclasts to resorb bone by mechanisms that interfere with



cytoskeletal organization and formation of the ruffled border, and this leads to cell death by apoptosis [52, 53]. Fujimura et al. [54] found in their study on mice that bisphosphonates reduced the amount of tooth movement and the number of osteoclasts. In addition, they also reduced ORR on the pressure side. Thus they concluded that bisphosphonates inhibit orthodontic tooth movement and prevent RR during orthodontic tooth movement in mice. Similar results were obtained earlier by Liu et al. [55] and later by Choi et al. [56], who found dose-dependent effect of the clodronate, a non-N-containing bisphosphonate or first-generation bisphosphonate, in rats. Their conclusion was that although clodronate might decrease RR related to orthodontic tooth movement, patients should be informed about a possible decrease in the amount of tooth movement and a prolonged period of orthodontic treatment.

According to a systematic review on the influence of bisphosphonates in orthodontic therapy that was published in 2010 [57], no data are available on the effect of longer than 21 days of bisphosphonates treatment, which is an important issue given the well-known side effects of this type of drug, which include maxillary osteonecrosis.

The apoptosis of osteoclasts that leads to reduction in bone and RR is in contradiction to the theory that reduced bone resorption increases RR [23].

*Ovariectomy* causes reduced estrogen levels resulting increased osteoclastogenesis [61]. Ovariectomy of female rats, performed to mimic postmenopausal patients, was found to affect tooth movement and orthodontitis. Tooth movement in the ovariectomy group was found to be more rapid and the amount of root shortening was more severe than in a control group [62]. A recent study [63] found that treatment of ovariectomized rats by systemic zoledronic acid, a potent and novel bisphosphonate that is used for the treatment of osteoporosis, inhibits orthodontic tooth movement and also reduces the risk of IDO2 expression in the ovariectomized rats. The mechanisms of action and the pharmacologic properties of the zoledronic acid directly involve the induction of osteoclast apoptosis [64]. These studies, albeit in rats, raise the awareness of the differences we may expect in treating orthodontically postmenopausal women.

#### 4.14.2 Sympathectomy

Haug et al. [121] found that sympathectomized (SCGx) rats had significantly more RR and substance P-immunoreactive fibers in the compressed periodontal ligament following orthodontic tooth movement compared with control rats. This publication demonstrates that there might be a direct connection between orthodontitis and the nervous system, in this case the sympathetic one. We hope that the research of those relationships will be studied in the future.

#### 4.14.3 Fluoride

The effects of fluoride intake on the roots during orthodontic tooth movement began to be explored on rats by Australian groups led by Darendeliler in the last decade. In 2007 it was reported that fluoride reduces the size of resorption craters, but the effect

is variable and not statistically significant ( $P > .05$ ) [58]. In 2011 the findings were that RR lesions of the group exposed to fluoride were significantly reduced in length and depth ( $P < 0.01$ ) [12]. The mineral content of the RR craters of the fluoride group had higher concentrations of fluorine and zinc ( $P < 0.01$ ). There was less calcium in the craters of the no-fluoride group compared with the fluoride group ( $P < 0.05$ ). The conclusion was that cementum quality (influenced by systemic fluoride exposure) might impact the extent of orthodontically induced resorptive defects. Another study of the group [59] found that fluoride reduced the depth, volume, and roughness of the resorption craters in the experimental groups. Regarding the duration of fluoride intake, it was found that the longer fluoride was administered via drinking water to the rats since their birth, the smaller the amount of tooth movement observed. Their conclusion was that fluoride in drinking water from birth reduced the severity of OIRR, but the amount of tooth movement was also decreased. The author's hypotheses as to the action of fluoride are that fluoride could suppress RR by similar mechanisms present in caries: acid resistance, enhancement of remineralization, and suppression of odontoclasts. However, according to the last study of the group regarding fluoride effect on roots of patients, a high fluoride intake from public water did not have a beneficial effect on the severity of root resorption after a 4-week orthodontic force application and 12 weeks of passive retention [163].

#### 4.14.4 Thyroid Hormone

The protective effect of thyroid hormone administration was confirmed by Vázquez-Landaverde et al. [60] who studied the effect of thyroid hormone-treated rats (intraperitoneal and oral) during orthodontic tooth movement. Circulating T3 levels, systemic alkaline phosphatase (APase) activity, and 5'deiodinase (5'D) activity were evaluated in the periodontal area. The results showed that TH-treated animals (intraperitoneal or oral) had significantly less force-induced root resorptive lesions compared with a control group, without apparent changes in T3 or alkaline phosphatase levels, and that periodontal remodeling was accompanied by a significant increase in local T3 generation as a result of T4 deiodination. This 5'D activity was higher in those animals that received exogenous TH. These results suggest that this protective TH mechanism may be achieved at a local level and that administration of low doses of TH may play a protective role on the root surface.

#### 4.14.5 Light-Emitting Diode (LED) Therapy

The effects of light-emitting diode (LED) therapy at 940 nm on inflammatory RR were studied in rats. Animals submitted to orthodontic force plus LED therapy presented significantly fewer osteoclasts and inflammatory cells and more blood vessels and fibroblasts in the periodontal ligament than the non-irradiated animals. The results led the authors to suggest that LED therapy may improve periodontal tissue repair and decrease inflammation and RR after the application of orthodontic force [122].

#### 4.14.6 Ultrasound

El-Bialy et al. [124] evaluated the effect of low-intensity pulsed ultrasound (LIPUS) known to enhance healing of traumatized connective tissues with IDO expression in humans. Histological examination revealed healing of the resorbed root surface by hypercementosis, and the scanning electron microscopy (SEM) study showed a statistically significant decrease in the areas of resorption and the number of resorption lacunae in the LIPUS-exposed premolars.

A study on rats found that LIPUS enhances repair of IDO damages by decreasing the number of osteoclasts and their level of activity probably as a result of increasing the ratio osteoprotegerin (OPT) to the receptor activator of nuclear factor kappa-B ligand (RANKL). Reparative cementum was found in the LIPUS-treated samples of rats by means of high-power SEM [123].

Similar results were obtained by a recent study [164] that expects LIPUS to be applicable to clinical use in the near future.

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#### 4.15 In Summary

Orthodontitis is the inflammation that involves the periodontal ligament, bone, cementum, and many times the dentine. It is the direct result of orthodontic force application that initiates a sequential genetic-environmental cellular process. This inflammation is the biological process that is behind every tooth movement and might lead to minor (IO) up to severe manifestations of root resorption (IDO1 or IDO2). We know exactly how and when it evokes, but until today, we are unable to predict its overall outcome that goes beyond the desirable tooth movement into unwanted resorption of the roots (IDO1 and IDO2 expression). The intensity and the length of the inflammatory process depend on many factors. Some of them are genetically related (*patient related*, personal vulnerability, or personal susceptibility), while others are *treatment related* (orthodontic and non-orthodontic), and most of them are still, even after the human genome was decoded, beyond our knowledge. This inflammation is physiologically or normally responsible for bone as well as cemental remodeling; however, for yet unknown reasons there might be a failure in the coupling process, which let the resorption continue beyond the borders of the cementum into the dentin. Unfortunately, this tissue cannot regenerate since the dentinoblasts are in the pulp and not in the dentino-cemental junction. When the damage is large enough, the morphological changes can be detected using external imaging techniques. From the three tissues involved in orthodontitis, the periodontal ligament and the bone, both are fully regenerated, while the root is not.

This review presents the readers a new term – orthodontitis – and also suggests three theories to the understanding of the process:

- (a) Reaction of the body to unrecognized extreme new conditions
- (b) Hidden part of the evolutionary process – the tissue hierarchy theory
- (c) Orthodontitis as a self-defense mechanism

Most of the publications quoted in this review draw their legitimacy from knowledge extracted out of evidence-based dentistry studies; however some publications can be defined as “expectation-based dentistry,” since their outcome has not been challenged yet.

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## Appendix

Suggested protocol to minimize orthodontic root resorption (ORR) and to avoid periodontitis consequences during orthodontic treatment (OT) for new and earlier orthodontic-treated patients. Orthodontitis and its consequences should be a part of any orthodontic treatment informed consent (Brezniak and Wasserstein 2016):

Orthodontitis and its unwanted ORR results as well as different types of periodontitis must be discussed with the patients/parents/guardians prior to the treatment and when positive findings were revealed during and following OT. This protocol is only a general suggestion or general guidelines and it does not replace the orthodontist’s professional medical discretion/judgment and responsibility of the consequences during and following OT.

### Definitions

Monitoring: PA X-ray of the upper incisors

Standard Monitoring (SM): Monitoring following 9–12 months of force application to the incisors and at least once a year in a lengthy treatment

Frequent Monitoring (FM): Monitoring every 6–9 months following force activation on the incisors

Intensive Monitoring (IM): Monitoring every 4–6 months following force activation on the incisors

- I. General health – Does the patient suffer from allergy<sup>1</sup>? If yes use FM protocol.
- II. Dental health – Does the patient suffer from periodontitis? If yes send the patient to the periodontist to discuss further related treatment considerations. When treatment lasts, use IM protocol adding bitewing X-ray every 4–6 months.
  - A. New patient before treatment:
    1. Does the patient have signs of RR (idiopathic, tooth related, etc.)? Go to 3b.
    2. Does the patient demonstrate any periodontal problem (loss of bone support, cervical resorption, etc.)? If yes, go to II.
    3. Was a close family member of the patient orthodontically treated in the past?

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<sup>1</sup>Allergy symbolizes many other systemic medical conditions that most of them including allergy have controversial relationship to orthodontitis and its manifestations.

- (a) Was ORR detected? If not use SM protocol.
  - (b) Is the amount of ORR on PA film:
    1. Less than 2 mm? Use SM during treatment.
    2. More than 2 mm but less than 1/3 of the root? Use FM protocol during treatment. Initiate treatment without extraction if needed, and decide only following 4–6 months in treatment.
    3. More than 1/3 of the root? Use 3b2 protocol; however use IM protocol during treatment.
- B. An earlier treated orthodontic patient or a transfer patient:
1. Does the patient have signs of ORR on a mandatory incisors' PA film? If not use SM; otherwise use 3b protocol.
  2. Does the patient have signs of periodontal disease on mandatory incisors' PA film and/or bitewing X-rays? If yes send the patient to the periodontist to discuss further related treatment considerations. Use FM protocol as well as bitewing X-rays every 4–6 months.
- C. Monitoring findings during treatment:
1. Does the patient have signs of ORR? If not continue to use SM; otherwise:
    - (a) Less than 2 mm? Use FM during further treatment.
    - (b) More than 2 mm but less than 1/3 of the root? Pause the treatment for 2–3 months. Take a new radiograph following 3 months in re-treatment to re-evaluate treatment continuation.
    - (c) More than 1/3 of the root? Pause the treatment for 2–3 months. Further treatment procedures depend on the current conditions:
      1. If close to the finish – Do as much as you can to finish treatment in a short time with compromises if needed. Try to avoid torque movements as much as you can. Use IM during treatment.
      2. If more than a year estimated to finish – Change treatment goals; change treatment modalities like using TADS as anchorage; evaluate surgical procedures; consider implants in extraction spaces if possible and if needed; avoid using resorbed teeth as anchored ones; don't use rectangular wires and avoid torque movements. Use IM during treatment.
  2. Does the patient have signs of periodontal disease on PA or bitewing X-ray? If yes go to II.
- D. Findings following treatment:
1. Any type of ORR and/or periodontal disease should be discussed thoroughly with the patients/parents/guardians.
  2. Teeth with mild or even severe ORR should rarely if ever be extracted. Fixed retention (sometimes double retention) attached to non-damaged teeth or fused bridges are the best long-term solution suggested for extreme cases.

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