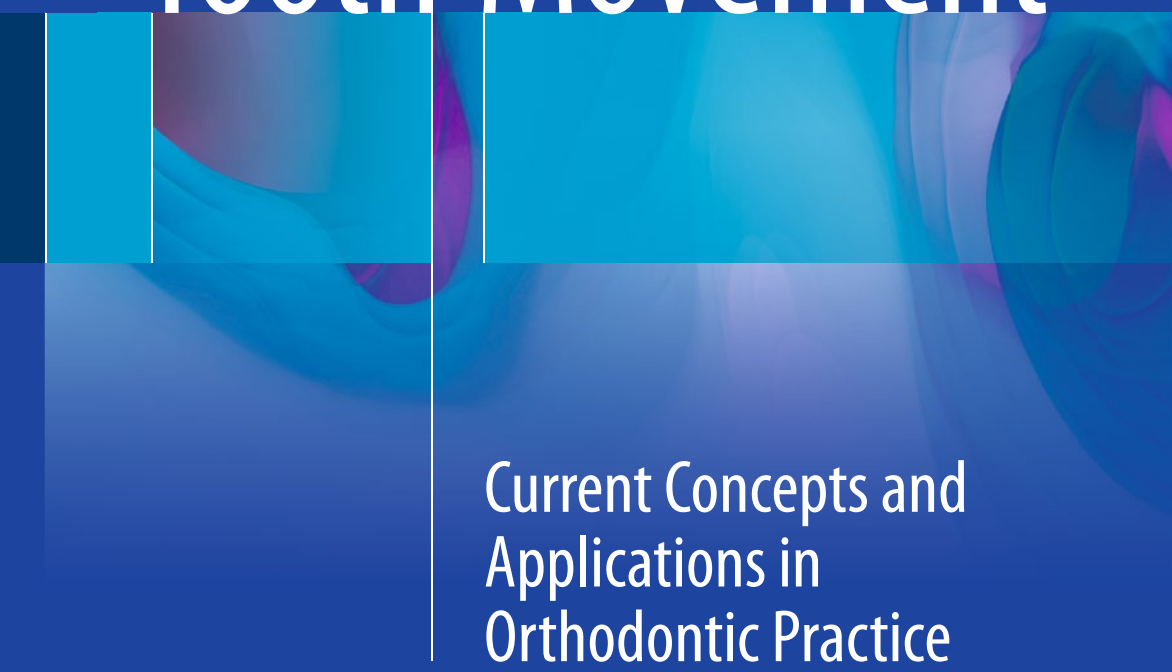
Biology of Orthodontic Tooth Movement



Current Concepts and Applications in Orthodontic Practice

Bhavna Shroff
Editor

Springer

Biology of Orthodontic Tooth Movement

Bhavna Shroff
Editor

Biology of Orthodontic Tooth Movement

Current Concepts and Applications in Orthodontic Practice

Springer

Editor
Bhavna Shroff
Department of Orthodontics
VCU School of Dentistry
Richmond, Virginia
USA

ISBN 978-3-319-26607-7 ISBN 978-3-319-26609-1 (eBook)
DOI 10.1007/978-3-319-26609-1

Library of Congress Control Number: 2016942276

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

Biology has always been an integral part of orthodontics. The biological processes behind the orthodontic movement of teeth have been a source of scientific curiosity since the early parts of the twentieth century, and visionaries like C. Sandstedt, A. Oppenheim, B. Orban, and A. H. Ketcham established a long-lasting relationship between the two fields. The controversies about the use of light or heavy forces during orthodontic tooth movement and the observations of the biological effects of such forces on teeth, periodontal ligament, and supporting bone have gradually shifted to a more profound and better understanding of the mechanisms involved in the remodeling of those tissues and cellular event associated with it. It is with gratitude that we can recognize pioneers like Reitan, Davidovitch, and Per Rygh as major contributors, who introduced new ways to study this field.

In more recent years, the interest in the biology of tooth movement has shifted to a different set of priorities. As a specialty, we started a conversation about how to use our fundamental understanding of orthodontic tooth movement to accelerate the movement of teeth through the bone. We are also using this knowledge to attempt to control, minimize, and also predict the occurrence of iatrogenic effects and, ultimately, to bring to our patients a better experience during their treatment.

This book is primarily the work of people who are passionate about the biology of orthodontic tooth movement. They have dedicated a life time to the study and the understanding of how teeth move when we treat our patients. They have been inspired by their mentors who instilled in them this scientific curiosity and the power to ask the questions discussed in this book. This book is not only an account of our current knowledge of this field but also an opportunity to look into the future and see the possibilities that will be available to the clinician to improve the treatment of the people that we serve.

As to me, I am grateful to my family, my teachers, and mentors. They made me who I am today, and they gave me the greatest gifts of all, the curiosity to ask questions and the passion for what I do. I wish to dedicate this book to Professor Jean-Claude Kaqueler who introduced me to research and electron microscopy, Dr. Charles J. Burstone who made me love orthodontics, and to Dr. Ravindra Nanda for his unwavering support along this extraordinary journey.

You have my eternal gratitude.

Richmond, VA, USA — Bhavna Shroff

Contents

Role of Alveolar Bone in Mediating Orthodontic Tooth Movement and Relapse

1

Imad Maleeh, Jennifer Robinson, and Sunil Wadhwa

Abstract

In this chapter, we present a unique perspective on biological tooth movement, one that describes the adaptive nature of the alveolar bone in response to mechanical loading. We provide a new foundation to the classical "pressure-tension" theory of orthodontic tooth movement. The chapter describes the individual roles of the cell types of bone (osteoblasts, osteoclasts, osteocytes, osteoprogenitor cells, and bone lining cells) in response to tooth movement, largely focusing on the mechanosensing osteocytes. Also discussed are methods that possibly increase the rate of orthodontic tooth movement as well as the plausible role that osteocytes may have in mediating relapse. Finally, we conclude with an "overall model of tooth movement and relapse." This chapter attempts to present an upstream mechanism to the traditional "pressure-tension" theory based on the most recent evidence.

German anatomist and surgeon Julius Wolff was the first to describe the adaptive nature of bone in response to the mechanical loads under which it is placed. Bone mass and architecture are determined primarily by loading patterns (magnitude and direction), which cause the bone trabeculae and cortex to remodel accordingly [1].

I. Maleeh, DDS • S. Wadhwa, DDS, PhD (✉)
Division of Orthodontics, Columbia University College of Dental Medicine,
622 W. 168th Street, VC 9-219, New York, NY 10032, USA
e-mail: im2313@cumc.columbia.edu; Sw2680@cumc.columbia.edu

J. Robinson, PhD
Division of Orthodontics, Columbia University College of Dental Medicine,
622 W. 168th Street, VC 9-219, New York, NY 10032, USA

Department of Biomedical Engineering, Columbia University, New York, NY, USA
e-mail: Jlr2228@columbia.edu

B. Shroff (ed.), *Biology of Orthodontic Tooth Movement*,
DOI 10.1007/978-3-319-26609-1_1

Increases in bone mass result from increased mechanical strains, such as physical activity [2]. On the other hand, decreased strain magnitude from prolonged bed rest leads to bone loss [3]. Similar to long bones, the alveolar bone that houses the dentition acclimates to changes in occlusal loading. However, the mechanisms in which occlusal forces are transferred to the alveolar bone have the added complexity of an intervening medium, the periodontal ligament (PDL). Orthodontic tooth movement (OTM) is based on the aforementioned biological principle; intermittent or continuous forces are applied to teeth, changing the mechanical loading of the system and subsequently eliciting a cellular response that leads to bone adaptation in a new functional environment. Many theories have been described in the literature with the attempt to elucidate the mechanisms involved in biological tooth movement. Most in vivo studies have concentrated on changes occurring within the PDL; however, more recent proposals have focused on the response of the alveolar bone [4]. In this chapter, we will concentrate on the recent studies showing that tooth movement may be more heavily dictated by the alveolar bone as opposed to the PDL.

1.1 Cell Types Involved in OTM

There are five types of cells identified in the alveolar bone that respond to orthodontic tooth movement: osteoblasts, osteoclasts, osteocytes, osteoprogenitor cells, and bone lining cells [5]. Osteoblasts are of mesenchymal origin and are primarily the bone-forming cells. Osteoblasts synthesize and secrete the extracellular matrix of bone, including type 1 collagen. Several factors have been shown to influence the development of osteoblasts from mesenchymal progenitor cells in the PDL. The factors include bone morphogenetic proteins (BMPs), transforming growth factor (TGF-βI and II), insulin-like growth factor (IGF-I and II), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [6]. In addition to their bone-forming capabilities, osteoblasts lining the bony socket are now believed to respond directly to strain from orthodontic tooth movement through a process known as mechanotransduction [7].

The second type of cells are the osteoclasts, which are derived from hematopoietic stem cells. Osteoclasts are responsible for the bone resorption necessary for tooth movement. Soluble factors such as colony-stimulating factor (CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin (OPG), and bone morphogenic proteins (BMPs) regulate osteoclast differentiation [8–10]. These factors are produced by osteocytes found in the alveolar bone and osteoblasts found in the PDL [11]. CSF as well as RANKL and its receptor RANK promote differentiation of osteoclasts. OPG inhibits differentiation by acting as a decoy receptor for RANKL, thus inhibiting its binding to RANK [12].

The third type of cell is the osteocyte, which is believed to be a terminally differentiated osteoblast that is surrounded by the bone matrix and whose function is primarily proprioceptive and responsive [13]. Osteocytes communicate with neighboring osteocytes and osteoblasts on the bone surface via long cytoplasmic extensions, in which direct exchange of ions occurs through connections called gap

junctions. The osteocytes reside within the bone in a space called a lacuna, and their cytoplasmic processes are housed within small canals called canaliculi. They are thought to be the mechanosensory cells of bone that play a pivotal role in functional adaptation to changing loading patterns [14].

The fourth cell type is the bone lining cell, which is also thought to be a terminally differentiated osteoblast. Lining cells are involved in bone protection and maintenance of bone fluids [15]. They may also be involved in the propagation of the activation signal that initiates bone resorption and bone remodeling [15]. Lastly, osteoprogenitor cells are the stem cell population tasked with generating osteoblasts and are situated in the vicinity of blood vessels of the PDL [16].

Orthodontic tooth movement occurs as a result of a complex sequence of events that involves cell-cell and cell-matrix interactions as well as a conglomeration of systemic hormones, cytokines, and growth factors. Recent research has pointed to osteocytes and osteoblasts lining the alveolar within the PDL as key cells regulating orthodontic tooth movement.

1.2 Osteocytes May Be Responsible for Mediating Orthodontic Tooth Movement Resorption

Orthodontic tooth movement was historically described by the "pressure-tension theory." This theory was first developed through classic histologic studies and led researchers to postulate that within the bony socket, "pressure" and "tension" sides were generated after force application [17–19]. The theory hypothesizes the side that the tooth is moving toward causes pressure/compression of the PDL (also named the "compression" side). Compression of the PDL is then believed to cause constriction of the blood vessels within the PDL causing a lack of nutrient flow and subsequent hyalinization and cell death. Osteoclasts from within the PDL (frontal resorption) or from the adjacent bone marrow (undermining resorption) invade the area and resorb the hyalinized PDL and adjacent alveolar bone causing the tooth to move [20]. On the contralateral side of the socket, namely, the "tension side," PDL fibers are stretched leading to stimulation of bone deposition. This theory simplifies tooth movement to a 2-dimensional process, namely, the mesial and distal ends. More recently, studies have described resorptive patches localized more lingually or buccally of the moving teeth. This is likely a consequence of irregularities in the periodontal and bone morphology, which illuminates the 3-dimensional nature of tooth movement [21]. Due to the presence of the PDL fibers between the tooth and the bone, the terminology of this theory is confounding. The "pressure or compression" side suggests loading of the bone, when in actuality the PDL fibers develop laxity and thus are unloaded or could be under tension [22]. On the "tension" side, stretched PDL fibers are seen, causing the loading of bone and bony matrix deposition. For the sake of clarity, we will therefore eliminate the use of compression and tension and refer to the compression side as the direction in which the tooth is moving and tension as the direction opposite to the direction of tooth movement (Fig. 1.1).

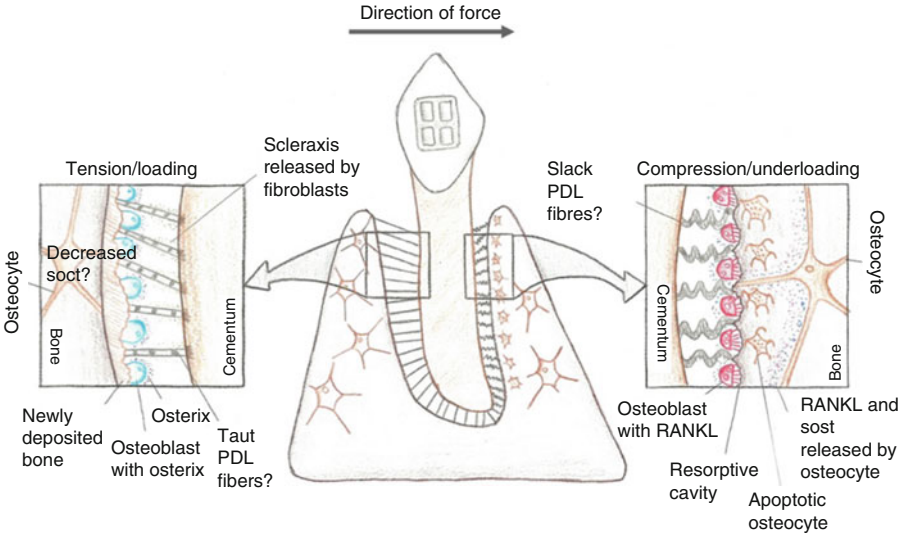


Fig. 1.1 Model of orthodontic tooth movement. On the direction the tooth is moving, orthodontic force causes an increase in apoptotic osteocytes and increase in the production of RankL. On the side opposite to the direction of tooth movement, orthodontic force causes an increase in the production of scleraxis in PDL fibroblasts and an increase in osterix in the PDL alveolar lining cells

In the direction in which the tooth is moving, osteoclasts are required to resorb the alveolar bone in order to allow for orthodontic tooth movement. The exact mechanism for the recruitment of the osteoclasts remains unknown. However, recent evidence points to osteocytes controlling alveolar bone resorption. Evidence that osteocytes are responsible for osteoclast bone resorption during orthodontic tooth movement comes from a study in transgenic mice in which the osteocytes were ablated. These mice express the receptor for diphtheria toxin on the cell surfaces of osteocytes. Therefore, an injection of diphtheria toxin caused osteocyte cell death. It was found that orthodontic tooth movement in the later phase was significantly reduced in transgenic mice with osteocyte cell death. Further, the number of osteoclasts and the quantity of eroded bone surface were significantly reduced in the transgenic mice injected with diphtheria toxin than in control mice [23].

It is established that osteocytes are the mechanosensing cells within the bone [24]. Osteocytes form a lacunar-canalicular network that allows their communication with other osteocyte, osteoblast, and osteoclast progenitors [24]. Mechanical loading-induced fluid flow through the lacunar-canalicular network provides nutrients to osteocytes and the upregulation of anabolic factors [25]. In contrast, loss of loading causes a decrease in fluid flow and increased osteocyte apoptosis. Birte Melsen was one of the first to posit that the resorption seen in orthodontic tooth movement is associated with alveolar bone underloading [26]. Meikle followed her study and used Frost's principle of a "mechanostat" to help support her findings. The fundamental idea of this principle is that for each bone in the skeleton, there is

a functional adapted state within the boundaries of which normal bone mass is maintained [27]. It was found that the use of an orthodontic appliance (cross-arch spring bonded to the teeth) changes the dynamics of the stimuli received by the bone and has a negative effect on bone mass. A bonded appliance, whether active or passive, was sufficient to alter the loading dynamics of the teeth, shielding some areas of bone from stress and leading to bone loss and osteopenia [4]. This osteopenia resulted from stress shielding of the interradicular bone by the appliance and a consequent reduction in occlusal loading below the critical threshold required for maintaining normal osseous architecture.

Osteocytes cause increased bone resorption during an underloading state by releasing RANKL and undergoing apoptosis. RANKL is the key molecule involved in the maturation of osteoclasts. In bone, osteocytes are the major producers of RANKL and cause an increase in osteoclastogenesis by releasing soluble RANKL through the lacunar-canalicular network. This promotes its interaction with osteoclast precursors to stimulate their differentiation and activation [28]. Therefore, the increase in orthodontic tooth movement-induced RANKL expression may result from osteocytes within the alveolar bone. This may explain why tooth movement in mice in which the osteocytes are ablated has a decrease in osteoclastic bone resorption [23].

We and others have found that orthodontic tooth movement causes a significant increase in osteocyte apoptosis within 1 or 2 days [29]. We also found that osteoclast recruitment occurred after 72 h and was particularly evident at day 7 after the initiation of orthodontic force. This suggests that osteoclastogenesis commences later than the peak of osteocyte apoptosis, suggesting that it is a downstream effect [29]. Apoptotic osteocytic bodies have been shown to release potent factors that cause an increase in osteoclasts [30–32]. It may seem paradoxical that osteocyte apoptosis causes an increase in osteoclast resorption, whereas osteocyte ablation causes an inhibition of osteoclast bone resorption. These confounding results may be explained by the type of cell death and/or the amount of cell death. In osteocyte ablation, it is presumed that osteocyte cell death occurs via necrosis [33], which may cause a differential response for osteoclastogenesis as compared to osteocyte apoptosis. Further it may also be possible that cell death of a finite number of osteocytes causes bone resorption, whereas cell death of all the alveolar bone osteocytes causes inhibition of osteoclast resorption. Future studies on the role of OTM-induced osteocyte apoptosis on osteoclast resorption are needed in order to clarify this issue.

1.3 Osteoblast Progenitors Within the PDL and Alveolar Bone Lining Cells Mediate New Bone Formation

The periodontal ligament is composed of alveolar bone lining osteoblastic cells and fibroblastic PDL cells. In the direction opposite to which the tooth is moving, upregulation of osterix within the alveolar bone lining cells and scleraxis within the periodontal fibroblasts occurs [34]. Osterix is an osteoblast differentiation factor,

and its upregulation is associated with new bone formation. In mice that are deficient in osterix, no bone formation occurs [35]. In contrast, scleraxis upregulation is associated with tendon formation and has been shown to cause downregulation of osteoblast differentiation [34]. Therefore, the upregulation of scleraxis with the PDL fibroblasts prevents its calcification and maintains its patency, whereas upregulation of osterix on the alveolar bone lining osteoblasts causes deposition of new bone on its surface. We have also found the upregulation of the bone maturation marker bone sialoprotein (BSP) in alveolar bone lining cells on the side opposite the direction of tooth movement [36]. BSP is also associated with matrix calcification [37]. Taken together, the results suggest that the OTM process, on the side opposite the direction of tooth movement, causes osteoblast differentiation of the osteoblast lining cells of the periodontal ligament.

However, whether the increase in bone formation is due to changes in the mechanical loading environment of the osteoblast lining cells within the PDL or instead caused by soluble factors released by osteocytes within the alveolar bone remains unknown. Evidence that it may be from osteocytes comes from a classical study by Heller and Nanda in which they gave a lathrytic agent that caused disruption of the collagen fibers within the PDL. In this study, they found that OTM caused an increase in new bone formation on the side opposite of tooth movement in animals treated with control and the lathrytic agent. From these results, the authors concluded that the PDL-induced fiber tension on the alveolar osteoblast lining cells may not be absolutely necessary to stimulate bone formation during OTM. Instead distortion of the alveolus bone related to force application may be a more important factor initiating the new bone formation [38]. It has also been shown that osteocyte production of sclerostin was reduced on the side opposite to the tooth movement [39]. Sclerostin is mainly produced by osteocytes and inhibits the Wnt signaling pathway, and its downregulation is associated with new bone formation [40]. Therefore, the new bone formation seen on the side opposite to which the tooth is moving may be due to osteocytic decrease in soluble Sost, which is a known Wnt signaling inhibitor. The net effect is an increase in Wnt signaling within the alveolar bone lining cells, an increase in osterix and BSP expression, and new bone formation. Future studies examining new bone formation on the side opposite to the tooth movement in transgenic mice with alteration in Sost signaling are needed to clarify this issue.

1.4 Methods to Increase the Rate of Orthodontic Tooth Movement

Several approaches to accelerate orthodontic tooth movement by altering bone biology have been proposed. Currently, two main methods exist for accelerating tooth movement by altering bone biology: (1) induced local bone damage, i.e., corticotomy-assisted orthodontics, piezocision-aided orthodontics, and corticision, and (2) mechanical loading-induced remodeling, i.e., vibration. Local bone damage-assisted OTM is performed by perforating the cortical bone or by making local

incisions around the cortical bone. The biological basis for this modality is that local bone damage (i.e., microcracks) has been shown to cause an increase in osteoclast activity and bone remodeling [41]. Case reports in the literature and small clinical trials have demonstrated a modest increase in the rate of initial OTM by these methods [42–44]. However, this effect was not seen in the long term. In addition, we have performed a recent study in which we evaluated the effect of applied force with and without corticision. We found no differences in the rate of tooth movement and osteoclastic bone resorption between animals that received the corticision procedure versus those who did not in a rat model [45]. Taken together, the results suggest that corticotomy, corticision, and/or piezocision results in a modest change in the rate of initial orthodontic tooth movement. This may be due to the fact that the resorption seen in the later phases in OTM is due to underloading of osteocytes in the alveolar bone, which is not affected by local bone damage procedures. In support, osteocyte ablation caused a decrease only in the later phases of tooth movement [23]. Also, OTM-associated microcracks are seen in both directions in which the tooth is moving and not limited only to the resorption side [46]. The early increase in OTM seen in bone damage-associated tooth movement may be associated with the fact that osteoclast recruitment does not occur immediately after the application of orthodontic force, but rather 3–7 days later [29]. Therefore, the increase in the initial phase of tooth movement by local bone damage may be due to an earlier recruitment of osteoclasts.

Recently, the use of resonance vibration has been developed as a new treatment modality for accelerating tooth movement. This idea contradicts the traditional use of vibration for increasing bone mass. Whole body vibration has demonstrated significant increases in bone mineral density and structure due to the mechanosensory functions of osteocytes [24, 47, 48]. Therefore, the anabolic effect provided by vibration would theoretically inhibit tooth movement by preventing OTM-associated osteocyte underloading. In fact, Kalajzic et al. showed that vibration in rats decreased the rate of tooth movement [49]. Moreover, Woodhouse et al. found no evidence that supplemental vibration force increased the rate of initial tooth alignment or reduced the time required to achieve complete alignment [50]. Taken together, the results suggest that the effects of vibration on accelerating orthodontic tooth movement are not due to a biological response. On the contrary, the effects may have more to do with frictional sliding forces.

1.5 Retention

One of the most pressing issues in orthodontic treatment is tooth relapse. Relapse is defined as the tendency of teeth to return toward their pretreatment positions [51]. Specifically, its occurrence renders treatment failure for both the orthodontist and the patient. Instability of orthodontically aligned teeth occurs to some extent in almost every patient [52]. The etiologic factors that drive relapse are still unclear; however, several causes have been proposed. Relapse is believed to be complex and

multifactorial, including factors such as inter-canine width [53], mandibular growth rotation [54], facial growth [55, 56], third molar eruption [57], influence of stretched gingival and connective tissue fibers [58–62], treatment modalities [63], uncooperative patients, imbalance in muscle and soft tissue pressure [64, 65], arch dimensions [66], and ongoing bone turnover [67]. However, it is now becoming clear that orthodontic tooth movement and relapse occur via the same biological mechanisms, regardless of the initial force applied.

Similar to orthodontic tooth movement, orthodontic relapse is associated with increased osteoclast activity and apoptosis on the side in which the tooth is moving [68]. One of the big differences between OTM and relapse is that relapse is associated with an increase in alveolar bone density, whereas OTM is associated with a decrease. For example, Franzen et al. demonstrated that after appliance removal, tissue mineral density and bone volume percentage gradually increased as the course of relapse progressed, attaining control levels after 3 days [69]. The return of bone density back to the levels of pre-orthodontic tooth movement during relapse leads one to speculate that changes in osteocyte mechanical loading environment may also mediate relapse. This is consistent with the findings of increased osteoclasts and an increase in apoptosis during orthodontic relapse. However, studies with osteocyte ablation and relapse are needed in order to further investigate this hypothesis.

1.6 Overall Model of Tooth Movement and Relapse

In our working model, we posit that when an orthodontic force is applied to the teeth, it causes a change in the mechanical loading environment of the osteocytes within the adjacent alveolar bone. In the direction in which the tooth is moving, there is an underloading state causing osteocytes to release factors (RANKL) and undergo apoptosis, both of which promote osteoclastic bone resorption. On the side opposite to direction of tooth movement, osteocytes undergo an increased loading response causing them to inhibit their release of Sost which promotes new bone formation from osteoblasts lining the alveolar bone. The net effect of OTM is an overall reduction in alveolar bone density due to increased bone resorption relative to new bone formation.

After the cessation of OTM and removal of the forces applied to alveolar bone from braces, a portion of the alveolar bone may be in an underloading state. This causes osteocytes to release RANKL and undergo apoptosis causing bone and tooth remodeling. The net effect is the return of alveolar bone density baseline levels and repositioning of the teeth close to their original position. Efforts to accelerate the rate of orthodontic tooth movement may occur by further reducing the underloading-induced bone remodeling state. Furthermore, retention strategies should be aimed at increasing alveolar bone density after the cessation of orthodontic tooth movement. Reducing the underloading remodeling state to accelerate orthodontic tooth movement is difficult to achieve. This may explain the modest effects experienced over the past century. On the other hand, trying to increase bone density after the

cessation of tooth movement to prevent relapse may be easier to achieve. For example, externally applied vibration in conjunction with retainer wear may further enhance tooth stability [70].

Conclusion

Traditionally, orthodontic tooth movement was believed to occur by causing necrosis of the PDL, causing the recruitment of osteoclasts and subsequent resorption and tooth movement. However, recent studies have now suggested that tooth movement may be due to alterations in the mechanical loading state of alveolar bone osteocytes. On the side in which the tooth is moving, there may be an underloading state causing osteocytes to release RANKL which increases bone resorption. On the other side, an increased loading state in which the osteocytes decrease their release of Sost resulting in an increase in bone formation may exist. Because these two theories are not mutually exclusive, it is possible that a combination of the two is occurring. It is now evident that the traditional idea that OTM solely occurs by necrosis and hyalinization of the PDL is a misconception.

References

1. Frost HM. Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians. Angle Orthod. 1994;64:175–88.
2. Nilsson BE, Westlin NE. Bone density in athletes. Clin Orthop Relat Res. 1971;77:179–82.
3. Donaldson CL, et al. Effects of prolonged bed rest on bone mineral. Metabolism. 1970;19:1071–84.
4. Milne TJ, et al. Induction of osteopenia during experimental tooth movement in the rat: alveolar bone remodeling and the mechanostat theory. Eur J Orthod. 2009;31:221–31.
5. Patil AK, et al. Understanding the advances in biology of orthodontic tooth movement for improved ortho-perio interdisciplinary approach. J Indian Soc Perio. 2013;17:309–18.
6. Harada S, Rodan GA. Control of osteoblast function and regulation of bone mass. Nature. 2003;423:349–55.
7. Sandy JR, et al. Recent advances in understanding mechanically induced bone remodeling and their relevance to orthodontic theory and practice. Am J Orthod Dentofacial Orthop. 1993;103:212–22.
8. Nomura S, Takano-Yamamoto T. Molecular events caused by mechanical stress in bone. Matrix Biol. 2000;19:91–6.
9. Zhao S, et al. MLO-Y4 osteocyte-like cells support osteoclast formation and activation. J Bone Miner Res. 2002;17:2068–79.
10. Kurata K, et al. Bone marrow cell differentiation induced by mechanically damaged osteocytes in 3D gel-embedded culture. J Bone Miner Res. 2006;21:616–25.
11. Oshiro T, et al. Osteoclast induction in periodontal tissue during experimental movement of incisors in osteoprotegerin-deficient mice. Anat Rec. 2002;266:218–25.
12. Theoleyre S, et al. The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. Cytokine Growth F R. 2004;15:457–75.
13. Weinbaum S, et al. A model for the excitation of osteocytes by mechanical loading-induced bone fluid shear stresses. J Biomech. 1994;27:339–60.
14. Aarden EM, et al. Function of osteocytes in bone. J Cell Biochem. 1994;55(3):287–99.

15. Miller SC, et al. Bone lining cells: structure and function. Scanning Microsc. 1989;3:953–60.
16. Agata H, et al. Effective bone engineering with periosteum-derived cells. J Dent Res. 2007;86:79–83.
17. Sandstedt C. Einige beitrage zur theorie der zahnregulierung. Nord Tandlaeg Tidskr. 1904;5:236–56.
18. Oppenheim A. Tissue changes, particularly of the bone, incident to tooth movement. Am J Orthod. 1911;3:57–67.
19. Schwarz AM. Tissue changes incident to orthodontic tooth movement. Int J Orthod. 1932;18:331–52.
20. Reitan K. Some factors determining the evaluation of force in orthodontics. Am J Orthod. 1957;43:32–45.
21. Bohl MV, et al. Focal hyalinization during experimental tooth movement in beagle dogs. Am J Orthod Dentofacial Orthop. 2004;125:615–23.
22. Jiang F, et al. Mechanical environment change in root, periodontal ligament, and alveolar bone in response to two canine retraction treatment strategies. Orthod Craniofac Res. 2015;18 Suppl 1:29–38.
23. Matsumoto T, et al. The role of osteocytes in bone resorption during orthodontic tooth movement. J Dent Res. 2013;92(4):340–5.
24. Bonewald LF. The amazing osteocyte. J Bone Miner Res. 2011;26(2):229–38.
25. Qin YX, Hu M. Mechanotransduction in musculoskeletal tissue regeneration: effects of fluid flow, loading, and cellular-molecular pathways. Biomed Res Int. 2014;863421(12).
26. Melsen B. Tissue reaction to orthodontic tooth movement–a new paradigm. Eur J Orthod. 2001;23(6):671–81.
27. Frost HM. Bone 'mass' and the 'mechanostat': a proposal. Anat Rec. 1987;219:1–9.
28. Nakashima T, et al. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nat Med. 2011;17(10):1231–4.
29. Moin S, et al. Osteocyte death during orthodontic tooth movement in mice. Angle Orthod. 2014;84(6):1086–92.
30. Mori S, Burr DB. Increased intracortical remodeling following fatigue damage. Bone. 1993;14:103–9.
31. Taylor D, Lee TC. Microdamage and mechanical behavior: predicting failure and remodeling in compact bone. J Anat. 2003;203:203–11.
32. Noble B. Microdamage and apoptosis. Eur J Morphol. 2005;42:91–8.
33. Komori T. Mouse models for the evaluation of osteocyte functions. J Bone Metab. 2014;21(1):55–60.
34. Takimoto A, et al. Scleraxis and osterix antagonistically regulate tensile force-responsive remodeling of the periodontal ligament and alveolar bone. Development. 2015;142(4):787–96.
35. Sinha KM, Zhou X. Genetic and molecular control of osterix in skeletal formation. J Cell Biochem. 2013;114(5):975–84.
36. Olson C, et al. Orthodontic tooth movement causes decreased promoter expression of collagen type 1, bone sialoprotein and alpha-smooth muscle actin in the periodontal ligament. Orthod Craniofac Res. 2012;15(1):52–61.
37. Kruger TE, Miller AH, Wang J. Collagen scaffolds in bone sialoprotein-mediated bone regeneration. Scientific World J. 2013;812718(6).
38. Heller IJ, Nanda R. Effect of metabolic alteration of periodontal fibers on orthodontic tooth movement. An experimental study. Am J Orthod. 1979;75(3):239–58.
39. Nishiyama Y, et al. Changes in the spatial distribution of sclerostin in the osteocytic lacunocanalicular system in alveolar bone due to orthodontic forces, as detected on multimodal confocal fluorescence imaging analyses. Arch Oral Biol. 2015;60(1):45–54.
40. Compton JT, Lee FY. A review of osteocyte function and the emerging importance of sclerostin. J Bone Joint Surg Am. 2014;96(19):1659–68.

41. Huang H, et al. Accelerated orthodontic tooth movement: molecular mechanisms. Am J Orthod Dentofacial Orthop. 2014;146:620–32.
42. Dibart S, et al. Piezocision: a minimally invasive, periodontally accelerated orthodontic tooth movement procedure. Compend Contin Educ Dent. 2009;30:342–4, 46, 48–50.
43. Dibart S, et al. Rapid treatment of class II malocclusion with piezocision: two case reports. Int J Periodontics Restorative Dent. 2010;30:487–93.
44. Keser EL, Dibart S. Piezocision-assisted Invisalign treatment. Compend Contin Educ Dent. 2011;32:46–8, 50–51.
45. Murphy CA, et al. Effect of corticision and different force magnitudes on orthodontic tooth movement in a rat model. Am J Orthod Dentofacial Orthop. 2014;146(1):55–66.
46. Prager TM, et al. Microdamage in the alveolar process of rat maxillae after orthodontic tooth movement. J Orofac Orthop. 2015;76(1):41–50.
47. Rubin C, et al. Low mechanical signals strengthen long bones. Nature. 2001;412:603–4.
48. Prisby RD, et al. Effects of whole body vibration on the skeleton and other organ systems in man and animal models: what we know and what we need to know. Ageing Res Rev. 2008;7:319–29.
49. Kalajzic Z, et al. Effect of cyclical forces on the periodontal ligament and alveolar bone remodeling during orthodontic tooth movement. Angle Orthod. 2014;84(2):297–303.
50. Woodhouse NR, et al. Supplemental vibrational force during orthodontic alignment: a randomized trial. J Dent Res. 2015;94:682–9.
51. Dyer KC, et al. Relapse revisited- again. Am J Orthod Dentofacial Orthop. 2012;142:221–7.
52. Joondeph DR. Retention and relapse. In: Graber TM, Vanarsdall RL, Vig KWL, editors. Orthodontics: Current Principles and Techniques. St Louis: Elsevier Mosby; 2005. p. 1123–51.
53. Rossouw PE, et al. A longitudinal evaluation of the anterior border of the dentition. Am J Orthod Dentofacial Orthop. 1993;104:146–52.
54. Fudalej P, et al. Mandibular growth rotation effects on postretention stability of mandibular incisor alignment. Angle Orthod. 2007;77:199–205.
55. Driscoll-Gilliland J, et al. An evaluation of growth and stability in untreated and treated subjects. Am J Orthod Dentofac Orthop. 2001;120:588–97.
56. Sinclair PM, et al. Maturation of untreated normal occlusions. Am J Orthod. 1983;83:114–23.
57. Harradine NW, et al. The effect of extraction of third molars on late lower incisor crowding: a randomized controlled trial. Br J Orthod. 1998;25:117–22.
58. Edwards JG. A long-term prospective evaluation of the circumferential supracrestal fiberotomy in alleviating orthodontic relapse. Am J Orthod Dentofacial Orthop. 1988;93:380–7.
59. Bergstrom K, et al. The effect of superior labial frenectomy in cases with midline diastema. Am J Orthod. 1973;63:633–8.
60. Reitan K. The initial tissue reaction incident to orthodontic tooth movement as related to the influence of function: an experimental histologic study on animal and human material. Acta Odontol Scand Suppl. 1951;6:1–240.
61. Reitan K, et al. Tissue rearrangement during retention of orthodontically rotated teeth. Angle Orthod. 1959;29:105–13.
62. Reitan K. Principles of retention and avoidance of posttreatment relapse. Am J Orthod. 1969;55:776–90.
63. Little RM, et al. Serial extraction of first premolars-postretention evaluation of stability and relapse. Angle Orthod. 1990;60:255–62.
64. Brodie AG. Consideration of musculature in diagnosis, treatment, and retention. Am J Orthod. 1952;38:823–35.
65. Proffit WR. Equilibrium theory revisited: factors influencing position of the teeth. Angle Orthod. 1978;48:175–86.
66. Strang RHW. The fallacy of denture expansion as a treatment procedure. Angle Orthod. 1949;19:12–22.

67. King GJ, et al. Alveolar bone turnover and tooth movement in male rats after removal of orthodontic appliances. Am J Orthod Dentofac Orthop. 1997;111:266–75.
68. McManus A, et al. Evaluation of BSP expression and apoptosis in the periodontal ligament during orthodontic relapse: a preliminary study. Orthod Craniofac Res. 2014;17(4):239–48.
69. Franzen TJ, et al. Expression of bone markers and micro-CT analysis of alveolar bone during orthodontic relapse. Orthod Craniofac Res. 2014;17(4):249–58.
70. Yadav S, et al. The effect of low-frequency mechanical vibration on retention in an orthodontic relapse model. Eur J Orthod. 2015;38(1):44–50.