Chapter

Biology and Mechanobiology of the Tooth Movement during the Orthodontic Treatment

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Abstract

Orthodontic treatment usually lasts from 2 to 3 years and some intractable cases may require even longer, so the duration of treatment not only leaves the patient dissatisfied, but is also the main reason why many patients reject or refuse orthodontic treatment; Therefore, various areas of research, hand in hand with the needs of orthodontists, have been developing methods to accelerate tooth movement and reduce the duration of orthodontic treatment, in such a context, the biology of tooth movement is a fascinating field of study that focuses on understanding the biological and biomechanical processes involved in tooth movement; thus, through research and scientific advances, it has been possible to obtain greater knowledge about this phenomenon and its application in clinical practice through the expression of RANKL/OPG. On the other hand, in addition to bone remodeling, the biology of tooth movement also focuses on other biological factors that influence the process of inflammatory response, cellular response and soft tissue response, these factors would play a crucial role in the adaptation of alveolar and periodontal tissues to the forces applied during orthopedic/orthodontic treatment of the cranio-cervical maxillofacial region.

Keywords: orthodontic tooth movement, RANK, RANK-L, OPG, accelerated tooth movement, tooth movement techniques, bone biology

1. Introduction

Orthodontic tooth movement (OTM) is the result of a constant process of remodeling of the alveolar bone stimulated by mechanical forces applied to the teeth; these induce bone resorption on the compression side and bone formation on the tension side, thus making possible the reorganization of the teeth in ideal positions to achieve esthetics and physiological function of the stomatognathic system [1]. Thus, it is possible to reorganize the teeth in ideal positions to achieve esthetics and physiological function of the stomatognathic system, so an orthodontic treatment can be

a very variable journey time between the orthodontist and the patient in which they will live many experiences, depending on a good diagnosis that would be more positive than negative [2]. Thus, the average orthodontic treatment time is 23 months, and complicated cases can last more than 25 months. Currently, there have been several studies that seek to cut the duration of orthodontic treatment by accelerating tooth movement, and even more during the last 3 decades have included treatments such as corticotomy, dentoalveolar distraction, low-level laser therapy, and pharmacological action, among others. Therefore, we will try to show the necessary update from a very general to a very specific view of the biology and mechano-biology of tooth movement [1, 3].

2. Principles of tooth movement

The general principles of tooth movement are fundamental concepts that govern both the natural movement of teeth in the oral cavity and orthodontic procedures to correct tooth position. These principles are essential to understanding how tooth positions can be modified in a comfortable, safe, and controlled manner, and from the multidisciplinary view of all dental specialties and their clinical limits of action where it leads to the limits of the insertion periodontium and the protective periodontium, it is possible to suggest that the general principles of tooth movement could be (**Figure 1**) [4]:

2.1 Assessment and planning

Before initiating any tooth movement procedure, it is essential to perform a detailed assessment and treatment plan, including an accurate diagnosis with 2D and 3D imaging, dental model studies, and bite analysis, allowing for proper planning according to the treatment objectives.

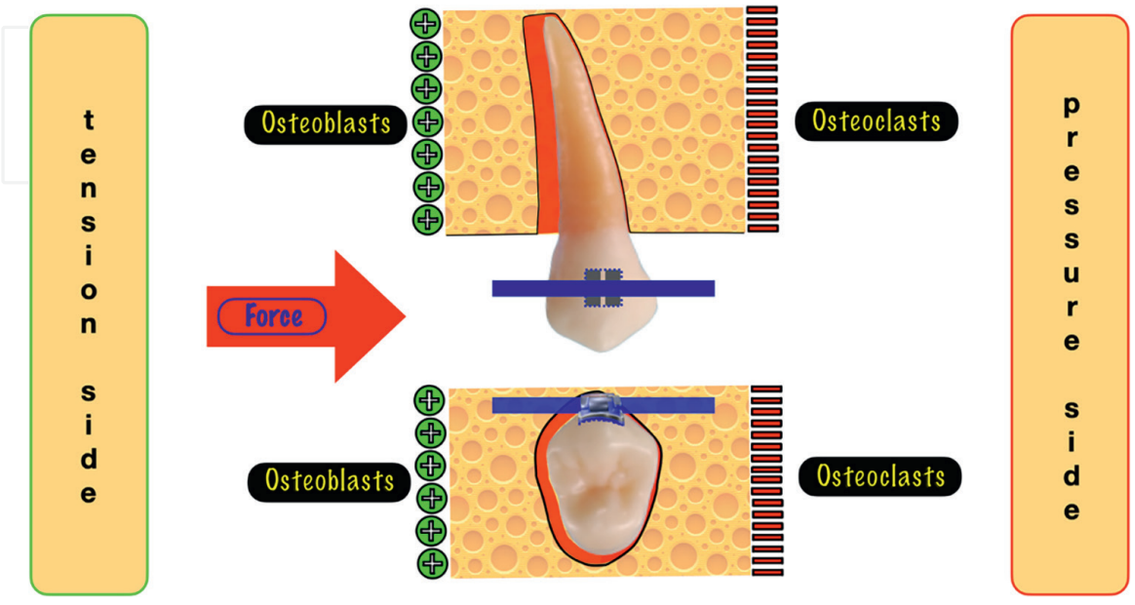

Figure 1.
Principles of tooth movement represented by the pressure/tension diagram in tooth movement.

2.2 Application of forces

Tooth movement is achieved by applying forces to the teeth. These forces can be natural, such as those resulting from chewing and tooth eruption, or induced by orthodontic treatments, such as the use of brackets, wires, and orthopedic devices for stimulation or correction in the jaws. In this sense, the magnitude, direction, and duration of these forces are critical in determining how tooth movement will be achieved, but this will be dealt with separately later in the chapter.

2.3 Biological response

The teeth and surrounding tissues respond to the forces applied to the periodontal ligament and alveolar bone. In a general or macro view, these are the main tissues involved in the biological response to tooth movement because the periodontal ligament allows controlled tooth mobility while the alveolar bone remodels in response to the applied forces.

2.4 Bone resorption and bone formation

During dental movement, a balance is produced between bone resorption (elimination of bone tissue) and bone formation (creation of new bone tissue). This process of bone remodeling allows the teeth to move gradually and in a controlled manner to their new positions. In this process, the osteoclastic cells that break down the bone on the resorption side and the osteoblastic cells that generate new bone on the formation side participate from a cellular macro-vision; in addition to these, nowadays osteocytes have been mentioned; these have gained importance in this process and allow a better explanation of the RANKL-RANK/OPG phenomenon during OTM.

2.5 Treatment sequence

In orthodontic procedures, a careful treatment sequence is planned to move teeth effectively. This involves the use of wires and brackets to apply forces in stages, allowing the teeth to adjust and the bone to gradually adapt to the new positions, with important considerations of the biological limits of tooth movement through the alveolar bone.

2.6 Long-term stability

The stability of the long-term result is fundamental because, after orthodontic treatment is completed or when there is a natural change in the position of the teeth (such as the eruption of permanent teeth in childhood), it is important that the teeth maintain their new position. For this reason, the use of retainers and the continuous follow-up of periodical check-ups with the orthodontist are essential to ensuring the retention of the results.

2.7 Periodontal and dental health

Changes in tooth position may affect oral hygiene, which could increase the risk of periodontal disease and tooth decay. Therefore, special attention should be paid to oral hygiene and gum health during and after treatment.

These general principles of tooth movement are essential for successful orthodontic treatment, understanding how teeth move naturally in the oral cavity, and providing a solid foundation for ensuring the long-term health and stability of the dentition.

3. Knowing in a friendly way the osteoblasts, osteocytes, and osteoclasts

Osteoblasts and osteoclasts are specialized cells that play a fundamental role in the process of tooth movement, especially in the bone remodeling that occurs during this process. Bone-forming cells derive from mesenchymal cells (stem cells), initially progenitors of others that are called pre-osteoblasts, secondarily becoming mature osteoblasts, and from there becoming osteocytes or linear cells; on the other hand, those that do not transform into either of these two types are destroyed by apoptosis; therefore, it has been mentioned in various studies that the origin of osteocytes comes from osteoblasts [5, 6].

3.1 Osteoblasts

They are large (20–30 m) mononuclear cells with a large nucleus that has a pyriform aspect (morphology) of polyhedral shape, basophilic cytoplasm, and a highly developed Golgi apparatus. They also have a large rough endoplasmic reticulum with abundant mitochondria. Likewise, they are very active cells and producers of the elements of the organic fraction of bone tissue, especially collagen. In addition, they produce alkaline phosphatases and non-collagenous proteins that initiate the process of bone resorption [6].

The half-life of human osteoblasts is long (from 1 to 10 weeks); later, they disappear by apoptosis mechanisms and are transformed into cell types with more advanced stages of maturation called bone lining cells, or osteocytes (15%). Limiting cells are elongated, flat cells with a spindle-shaped nucleus, usually without organelles that can express osteoblastic markers such as Bone sialoprotein, osteopontin, osteonectin, and alkaline phosphatase, as well as the parathormone receptor (PTH), and remain along the endosteal surface, constituting with the endosteum a protective layer of the bone surface, which plays an important role in the activation of bone remodeling [1].

The osteoblasts are located above the bone surface, producing a soft substance called osteoid. In addition, some of them can be included or trapped in the mineralized bone; this cell that is included will become an osteocyte. In the same way, the younger ones are surrounded by a halo of lower density, preserving the rounded aspect; the older ones are those that would be in the deepest area of the mineralized bone tissue and keep an elongated aspect with prolongations in all its periphery, emitting cytoplasmic processes towards the cellular matrix, which serve as a link between them and the neighboring cells. Allowing communication between them by transmembrane proteins or integrins, which act as a link between cells or between a cell and the extracellular matrix, allowing the passage of messengers such as calcium, cytokines, or prostaglandins [6].

3.2 The osteocytes

They are deposited in osteocyte cavities, or osteoplasts, with extensions in calcophore ducts. Only a small proportion of osteoblasts (30%) become osteocytes;

the remaining osteoblasts eventually die by apoptosis. The function of osteocytes is mineral homeostasis; they have poorly developed organelles [7].

3.3 The osteoclasts

They are giant cells (100 m), multinucleated (2–30 nuclei), motile, rich in mitochondria and vacuoles, capable of removing calcified matrix from bone, with the qualities of resorbing and remodeling bone by removing calcified matrix from bone. They are the protagonists of the sensitive task of dissolving calcium phosphate crystals and digesting collagen from bone cells through highly specialized structures. They are formed by the fusion of several mononuclear cells derived from the blood stem cells of the bone marrow. Osteoclasts comprise 1–2% of the bone cells in the human body, so their population is scarce; they have a half-life of 2 weeks to die later by apoptosis; they are located under the periosteum, specifically in the inner edge of Havers tunnels of cortical bone, in trabeculae of diameter greater than 200 microns, and in the outer wall of the bones; likewise, it is possible to find potential precursors in the peripheral blood, spleen, and bone marrow. They are cells that present an irregular or rough edge in the form of a brush or similar (the more irregular or sharp, the greater the cellular capacity); their main characteristic is the destructive effect of the bone that is observed when the cell encounters it; because of this, there remain certain osteoclastic cavities, also called Howship's lacunae [7, 8].

Lately, researchers worldwide have been dedicated to identifying the complex resorptive machinery and the exponential form of the biology of tooth movement, obtaining great advances in the study of genetic diseases, the phenotypes observed with the detected dysfunction, experimental studies in animal models, and the obtaining of precursors and mature cells in culture, with the detailed observation of the responses to mechanical, biological, and pharmacological stimuli [8].

Together, osteoblasts and osteoclasts work in dynamic equilibrium during tooth movement; while osteoblasts build new bone on the side opposite the side to which the tooth is moving, osteoclasts resorb bone on the side to which it is moving. This balance between bone resorption and bone formation is critical to allowing teeth to move in a controlled manner and maintaining the integrity of the surrounding alveolar bone. Knowledge of these biological processes is essential to understanding how tooth movement is achieved and how orthodontic techniques are effectively applied to correct tooth position [9].

4. Interaction between osteoclasts (resorption) and osteoblasts (replenishment) during the OTM

The dental organs are located inside the maxillary alveolar bone through its dental root, giving a fixation advantage to the alveolar bone; however, they are separated from the bone by the parodont, from which we can identify the protection parodont and the fixation parodont. The element of fixation of the tooth to the bone is the periodontal ligament (PDL), whose main component is a network of parallel collagen fibers inserted in the root cementum of the dental organ at one end and at the other end in the hard lamina of the bone. This collagen of the PDL is constantly remodeled under normal operating conditions, and it is possible to mention two components of great importance [10]:

- Cellular elements, which include mesenchymal cells in the form of fibroblasts and osteoblasts, osteoclasts, and osteocytes, as well as vascular and neural elements present in the PDL,

- Histic fluids, which act as the internal environment of the cells, play an important role in normal function and enable orthodontic movements of the teeth.

Thus, to meet the objectives of orthodontic treatment, it requires major microscopic and macroscopic changes of the dental and peridental tissues, including the dental pulp, periodontal ligament, alveolar bone, and gingiva, through the controlled use of biological forces.

The biological basis of OTM is given by inflammatory reactions in the paradental tissues of the periodontium and a specific stress distributed around the periodontal ligament and alveolar bone, associated with a process of bone remodeling in response to mechanical forces applied during orthodontic treatment. Likewise, by the variety of cellular components, there are several factors that could interfere in bone remodeling; more specifically, there are three types of cells with significant involvement in tooth movement: osteoblasts, osteocytes, and osteoclasts (**Figure 2**) [7, 9].

There are many theories proposed to explain tooth movement as a physiological adaptive movement to mechanical stimulation induced by orthodontic forces in which osteoblasts rebuild the bone destruction produced by osteoclasts in the old bone; however, it could also be considered an acute aseptic inflammatory response with an early release of chemokines by local cells, facilitating molecular adhesion in blood vessels, and stimulating inflammatory cell recruitment of precursor cells into the extravascular space. Prostaglandins and neuropeptides are also released during pressure or tension as inflammatory mediating agents that increase vascular permeability and cell adhesion, as well as transmit pain signals, regulate tone, and modulate vascular permeability [8].

However, the big question that invades is the importance of osteocytes, or rather, what is their architectural role in the formation of new bone; therefore, experimental and clinical studies continue to be carried out in search of methods of application of internal or external agents that allow dental movement in a simple way for the patient in search of more efficient results and without sequels to the tissues of the stomatognathic system [8, 9].

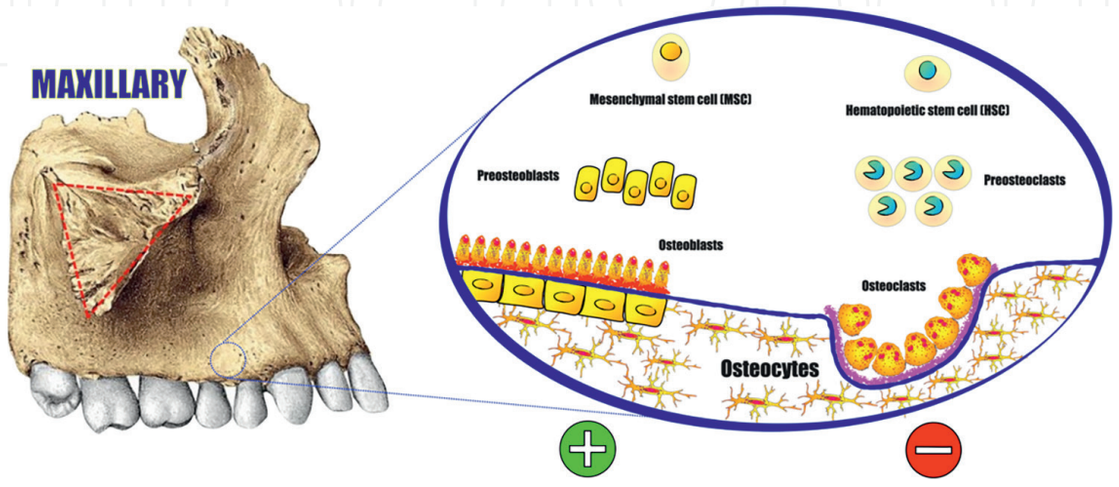

Figure 2.
Differentiation of the bone cells involved in tooth movement.

5. What are the biological limits of the OTM?

In OTM, mechanical forces that can be intermittent or continuous can stimulate this bone remodeling cascade in the alveolar bone, and this occurs differently depending on whether the perspective is from the pressure or tension side of the tooth involved in OTM; therefore, the pressure side is characterized by bone resorption, while on the tension side, bone formation occurs when the forces are within a healthy biological range. This biological response to force is governed by two predominant control mechanisms [9, 11]:

- The bioelectrical theory is because changes in bone metabolism come from electrical signals that occur when alveolar bone is bent or stimulated by various means. Thus, researchers have supported the idea that the changes that occur in alveolar bone during OTM are likely due to a piezo-electric effect; thus, mechanically induced deformation of collagen crystals would produce a stress-generated potential (SGP). However, although the presence of piezoelectricity is believed to explain the electrical signals that in turn lead to the maintenance of the bony skeleton, the correlation with OTM is less clear since orthodontic movement occurs because of a sustained force versus the type of intermittent forces that cause SGP [11].

- The pressure-tension theory is based on chemical messengers being responsible for cellular changes during OTM; specifically, the tooth would shift in the alveolus in response to the orthodontic force propagating through the periodontal ligament (PDL). As blood flow within the PDL decreases where the PDL is compressed and increases where the PDL is stretched, the chemical environment is concomitantly altered to stimulate second messengers such as cyclic adenosine monophosphate (cAMP) and activation of cells responsible for OTM. Briefly, the resulting elevation of cAMP activates cell differentiation and proliferation through kinase activity in the nucleus of each cell; in addition to cAMP, inositol phosphates and intracellular calcium respond to mechanical forces by elevating their biological levels, having an effect in which calcium entry into the cell could come from G protein-controlled ion channels or by the release of calcium from internal cellular stores. This pressure-tension theory is widely accepted as the classical OTM theory, although biological electricity still stands out for its importance in bone homeostasis [12].

It is also important to reason the affection of orthodontic treatment approaches and outcomes within the considerations of the mechanisms governing OTM; put another way, there are several frequently asked questions from practitioners interacting with tooth movement, which might include:

What are the biological limits of OTM?

Is it possible to maintain symmetrical control over OTM?

What is the biologically safe, effective OTM speed?

On the other hand, the osteocyte could also be involved as an active cell within the biological factors of OTM in the framework of canonical bone remodeling therapies and not only in the mention that the osteocyte is in charge of maintaining bone shape and architecture, thus allowing the possibility of an extended hypothesis that includes the osteocyte as a dynamic or active regulatory cell of bone remodeling, being very well structured in murine studies in somatic bone remodeling episodes and in the OTM.

6. Molecular approach to osteocytes during OTM

Current molecular biology studies have been instrumental in establishing the elemental role of osteocytes in bone remodeling; thus, there may be a direct osteocyte mechanism that could improve orthodontic clinical outcomes or act in the opposite manner. The cellular and molecular underpinnings of bone biology related to OTM are based on human and dog studies and argue for several main precepts, such as duration, magnitude, type, or direction of movement; however, clinical scenarios have allowed us to observe that the correct interplay of these precepts would allow for adequate blood flow and in turn facilitate OTM (**Figure 3**) [11].

In other words, if force levels are too high, blood flow decreases with the possibility of being blocked by compaction in the compressed PDL; subsequently, osteoclasts are recruited from the bone adjacent to the compressed PDL and from the bloodstream in compression, and it is possible to observe necrosis and undermining resorption of the PDL. Thus, it would increase the time required to move the tooth through the alveolar bone (from 2 days under normal circumstances to 7–14 days), which is observed under extreme movement conditions with the consideration of extreme mobility [11].

In reality, OTM is characterized by the rate of bone turnover and the site and type of bone remodeling, which are different from what would occur in other clinical bone situations, such that the rate of cortical bone turnover is 2–10% per year and the rate of trabecular bone turnover is 30–35% per year, while the rate of alveolar bone turnover is considered to be approximately 15–30% per year under natural, biological conditions and/or when not under the influence of OTM.

Since osteocytes constitute 90–95% of bone cells, it is currently believed that osteocytes are the main mechanosensory cell, completely insensitive to shock in bone; thus, osteocytes could exert control over osteoblasts and osteoclasts through signaling

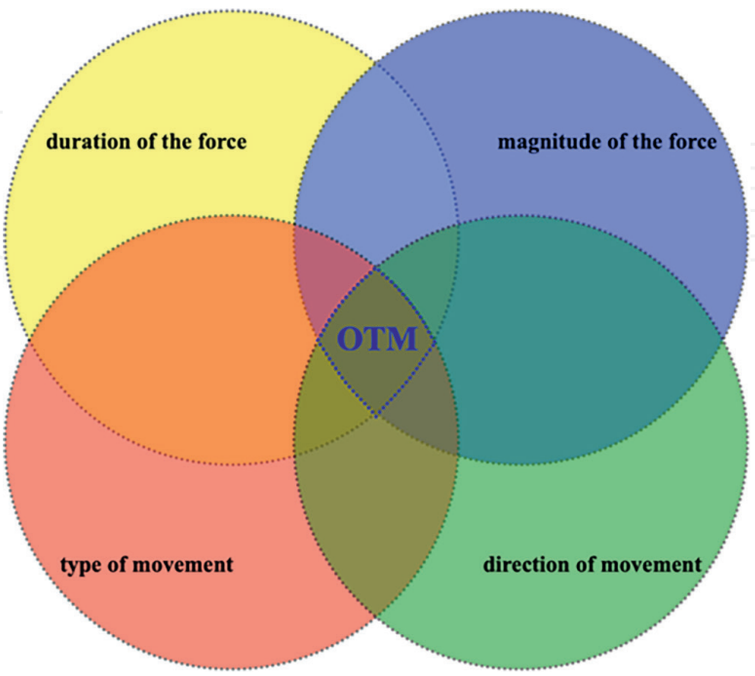

Figure 3.
Cellular and molecular underpinnings of bone biology related to OTM.

pathways such as receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), and nitric oxide (NO); in addition, the number and location of osteocytes and their interactions with surrounding cells and tissues make them logical biological candidates in the OTM [13].

7. Molecular approach to osteocytes during OTM

To date, various cellular and molecular studies have allowed us to know the changes in the tissues surrounding the dental root during OTM. The main case-control studies in animals have shown that the subtraction of osteocytes during OTM impeded the correct osteoblast/osteoclast interaction in the bone borders that are related to the PDL. Thus, in the results of the control group, good osteocyte cell activity was observed in the osteoblast/osteoclast cell interaction and, consequently, evident tooth movement [14].

Another important element to consider is cell apoptosis, which is important during tooth movement since the osteocytes reach their maximum point 24 hours after initiating OTM. This opens an enormous amount of controversy and debate since the formation of osteoclasts occurs 72 hours after tooth stimulation; therefore, the osteocytes would be present long before the formation of osteoclasts begins during OTM. This could be explained by the fact that NO increases rapidly in osteocytes after mechanical stress, being observed as a constant and pulsating flow like an intermittent hydrostatic compression; that is, when NO levels increase, there would be a strong protection of osteocytes against cell apoptosis, allowing a decrease in bone resorption and an increase in bone formation [2, 11, 15].

Similarly, it is important to mention that endothelial nitric oxide synthase (eNOS) is the main source of NO in osteocytes; this eNOS is expressed at its highest level at 24 hours on the compression and tension sides during OTM; furthermore, inducible nitric oxide synthase (iNOS) increases to its highest level at 6 hours after starting OTM; thus, the highest NO levels are observed at the beginning of OTM. At present, it is not entirely clear whether this is due to a lack of mechanodetection or by-products associated with osteocyte apoptosis, and further research is needed to identify the benefits in clinical practice [7].

Despite the above, in the last 20 years, the function of osteocytes during OTM has been studied and questioned; therefore, other specific components present in OTM, such as:

- extracellular matrix phosphoglucoprotein (EMPE)
- connective tissue growth factor (CTGF)
- osteopontin (OPN)

Alveolar osteocytes have a high level of MEPE that decreases dramatically on day one and then reaches maximum expression on day three of OTM due to cleavage of the mature protein. Therefore, MEPE could have dual functions depending on its proteolytic processing, and this could accelerate or inhibit mineralization due to fluid dynamics within the canaliculi, potentially transforming the way it receives and responds to mechanical stimulation during (**Figure 4**) OTM.

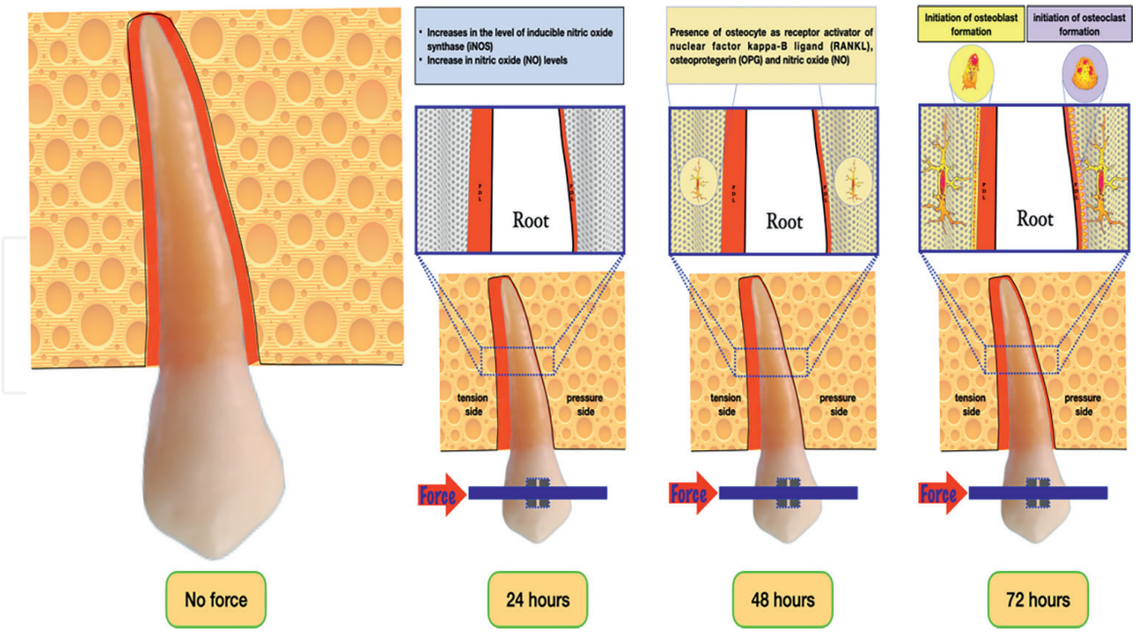

Figure 4.
Presence of osteocytes and the onset of osteoblast and osteoclast aggregation during OTM.

8. RANK/RANKL/OPG during OTM

At present, the knowledge of the OTM is fundamental for the diagnostic interpretation, clinical planning, and therapeutic projection of most of the treatments of the stomatognathic system that involve modifications of the cranio-cervical maxillofacial region; therefore, according to interdisciplinary criteria, the OTM could be categorized as the transversal axis of a correct clinical therapeutic projection. Therefore, to understand how to correct dental and/or skeletal malocclusion and its relationship with the soft tissue structures of the head and neck, knowledge of the biological and mechanical principles of the OTM is fundamental. The scientific literature has provided a substantial basis for dissecting the mechanisms that control and/or facilitate OTM, in which the core of this process is made up of several cell types, among them osteoclasts, known for bone resorption, osteoblasts that build bone, and finally, osteocytes, which notably are the harmonic structure of biological remodeling during OTM [16, 17].

To begin with, the classical cascade of bone remodeling seeks to explain how osteoclast precursor cells are attracted from the bloodstream to the area of injury or stimulation; thus, through this first phenomenon, localized bone resorption occurs; subsequently, a coupling of osteoblasts in the area of injury with increased blood flow is also remarkable, producing in parallel bone regeneration, which could be called a formation of new bone (immature but new) [16].

Then, the first thing that should be known is who the participants of the molecular vision of the OTM are (**Figure 5**):

8.1 Receptor activating receptor for nuclear factor kappa-B (RANK)

It is a trans-membrane protein expressed by osteoblasts and mesenchymal cells, which interacts between members of the basic multicellular unit (BMU), is homotrimetric type I, and is composed of an average amount of 317 to 616 amino

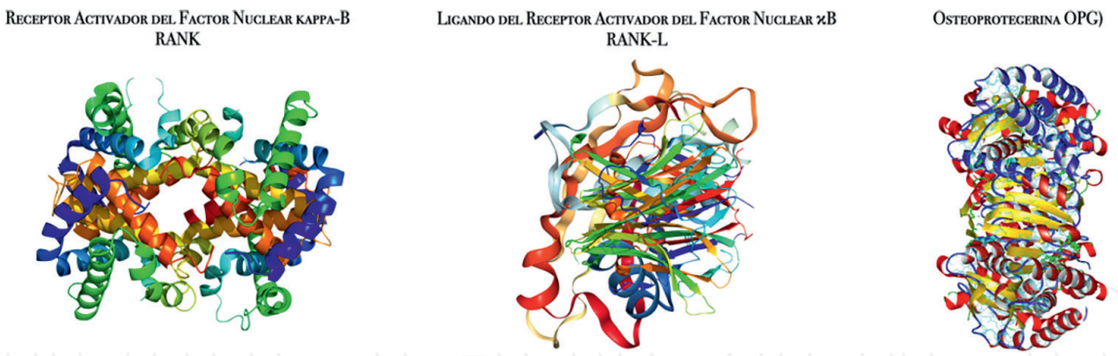

Figure 5.
Proteins involved in the molecular vision of OTM.

acids. It also induces osteoclast or osteoblast differentiation and activation, balancing hormone levels in the remodeling cycle between bone formation or resorption and is categorized as part of the tumor necrosis factor (TNF) receptor family, expressed on the membrane of osteoclasts and on the membrane surface of B and T lymphocytes, dendritic cells, and fibroblasts [18].

8.2 Receptor activator of nuclear factor B receptor ligand (RANK-L)

It is a homotrimeric transmembrane protein regulator of osteoclast formation and activation, expressed by osteoblasts and mesenchymal cells, is responsible for regulating the transcription of genes involved in a wide variety of bone processes, and is composed of about 317 amino acids; moreover, like the receptor, it belongs to the TNF receptor family [17, 19].

8.3 Osteoprotegerin (OPG)

It is a homodimeric protein secreted by osteoblasts and bone marrow cells, has about 401 amino acids, and serves as a decoy receptor known as an osteoclast differentiation inhibitory factor [19, 20].

Osteoblasts are found on the bone surface, and when stimulated by vitamin D and parathormone (PTH), they can release macrophage colony stimulating factor (M-CSF). This M-CSF has the particularity of differentiating stem cells into osteoclast precursor cells; in turn, if PTH continues its stimulus on osteoblasts, these will release RANK-L in the different processes of bone remodeling [17].

RANK-L can bind to two types of receptors:

- RANK: This receptor is found on the surface of osteoclastic precursors, and when osteoclastic precursors are stimulated, they differentiate into osteoclasts, which in turn bind to the bone surface, forming BMU to produce bone resorption. When the PTH estimate obviously decreases in RANK-L, the osteoclastic cells also separate from the bone and die.

- OPG: RANK-L can bind to OPG; the function of OPG is to prevent RANK-L from binding to the RANK receptor and thus prevent osteoclast precursor cells from being stimulated, preventing bone resorption. This is very important since there must always be a balance between the levels of RANK-L and the levels of OPG, since it has been observed that in cases of osteoporosis due to both estrogen

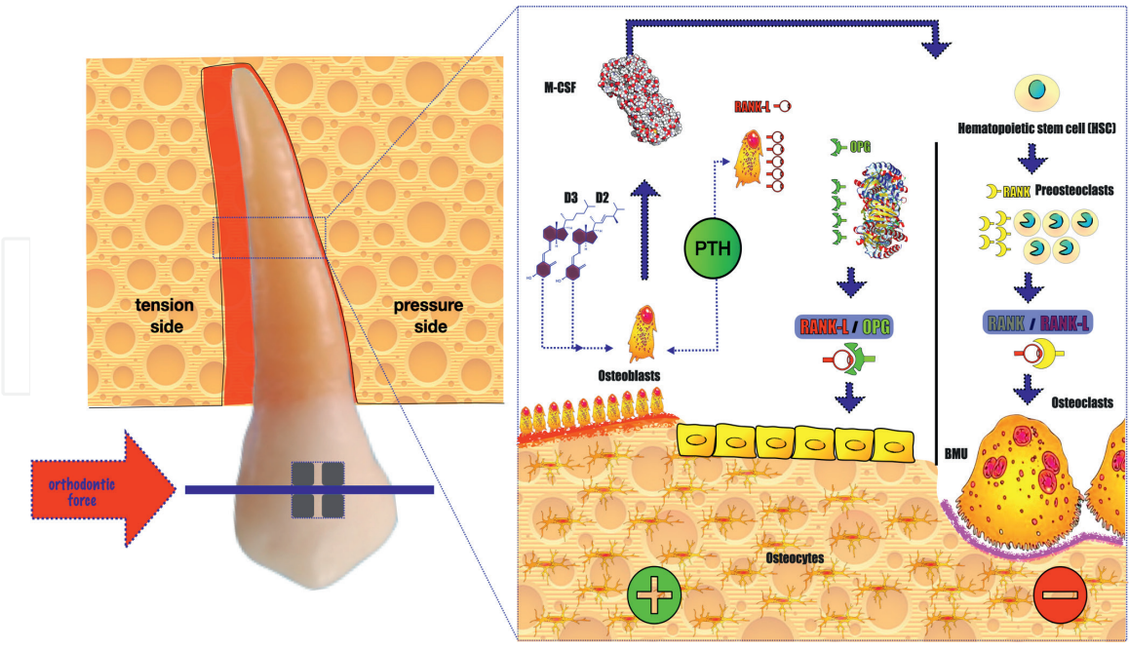

Figure 6.
Cascade of RANK/RANK-L/OPG molecular events during OTM.

deficiency and corticoid excess, there is always an increase in RANK-L and a decrease in OPG. Likewise, it is known that the constant renewal and remodeling of bone could be related to tumor necrosis factor (TNF), RANK-L, and its receptors RANK and OPG (**Figure 6**).

Various experiments have been carried out with and without animals, and experiments and clinical studies are being carried out to accelerate dental movement, which include connotations such as: local or systemic administration of drugs (vitamin D, corticosteroids, prostaglandins, and interleukins; the administration of drugs are not specific); reduction of friction between brackets and arches; osteogenic distraction, among others; however, many of the drugs presented long-term negative side effects in the human system.

Nowadays, this is becoming more important due to the increase in orthodontic consultation by patients of all ages, opening a range of clinical treatment possibilities enhanced by intelligent orthodontic mechanics, biomechanics, and mechanotherapy that allow the use of resources that accelerate the OTM while maintaining safe limits of the tooth root within the bone. For this reason, the following is a general overview of the most important positive and negative options proposed in OTM to date:

9. Micro-osteoperforations (MOP) and the regional acceleratory phenomenon (RAP)

Surgical acceleration of tooth movement can be explained by RAP since bone injury results in temporary demineralization or remineralization of the affected bony areas; thus, OTM is accelerated as the resistance offered by the dense cortical bone is removed. Among the available RAP modalities, corticotomy is the most effective because it induces RAP and stimulates tooth movement on the buccal side. In

addition, less invasive techniques, such as piezocision, corticision, and MOP without flap elevation, have also been reported to be effective [15, 21–23].

On the other hand, it is suggested that a vertical MOP cut could be an effective tool to improve OTM, especially with distalization movements, straightening, and protraction of molars in an edentulous area.

10. Root resorption and RANK/RANK-L/OPG

There is a great deal of debate among orthodontists due to the onset of external apical root resorption (EARR), which is an unavoidable iatrogenic disorder that occurs unpredictably during orthodontic treatment and whose etiology involves the dental roots and bone tissues, the mechanical forces applied, the surrounding matrix cells, and certain biological messengers known to date.

Several authors state that EARR greater than 3 mm occurs frequently in 30% of the average patient population, while in 5% of patients EARR is greater than 5 mm. On the other hand, it is possible to expect certain different tendencies depending on external factors such as sex, age, severity of malocclusion, and type of biomechanics, among others [24–26].

11. Use of 6-Shogaol to accelerate orthodontic tooth movement through the JNK-NFATc1 signaling axis

Shogaols are a group of bioactive phytochemicals in ginger found mainly in the dried and heat-treated roots. This traditional herbal medicine, which is about 2000 years old, has been widely studied for its therapeutic impact on tumor diseases because it suppresses growth and induces autophagy in cancer cells. Recently, its pharmacological activity has received great attention because in vivo and in vitro results have demonstrated the potential to attenuate certain neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease.

Specifically, 6-shogaol has antioxidant, anticancer, and neuroprotective properties; furthermore, it promotes osteoclast differentiation and bone resorption through the JNK-NFATc1 signaling axis, resulting in controlled osteopenia and rapid tooth movement. Therefore, 6-Shogaol administration should be considered as a potential molecule to provide a new non-invasive method to accelerate orthodontic tooth movement [27, 28].

12. Low level 970 nm laser and bone metabolism in OTM

Several randomized controlled clinical trials have been conducted in which the benefits or dangers of the use of low-level laser therapy (LLLT) during orthodontic treatment have been investigated. Thus, it is now known that LLLT stimulates the electron transfer chain through the metal ligand conjugated with cytochrome C oxidase in the mitochondria to produce more adenosine triphosphate (ATP), triggering more NO release to increase microcirculation, resulting in a higher and better rate of bone turnover. Therefore, activation of bone cells provides rapid alveolar bone turnover and accelerates directional tooth movement under orthodontic force loading [29, 30].

Thus, it has been proposed that the use of LLLT at a 970 nm diode could accelerate OTM in rats without obvious side effects and compared to other methods currently used to shorten the duration of OTM, LLLT offers an effective and non-invasive approach [31, 32].

13. Application of orthodontic force after ovulation: is there acceleration?

Studies have shown that remodeling of the periodontium is influenced by various factors, including estrogen levels, and the presence of estrogen receptors in the periodontal ligament has also been observed, which could indicate that estrogen influences the composition and degradation of collagen fibers in the periodontal ligaments and the remodeling of the alveolar bone, especially if mechanical forces of compression and tension of the PDL are applied [33].

Estrogen is a hormone that is distributed in local tissues and blood serum. Its levels fluctuate rhythmically during the menstrual cycle and may be present at different levels during the cycle:

- **Early follicular phase:** estrogen levels gradually increase and peak 1 to 2 days before ovulation during this phase.
- **Ovulation**: occurs approximately 36 hours after the estrogen peak.
- **Descent:** after the follicular phase, the estrogen level decreases rapidly.
- **Luteal phase:** estrogen levels remain low and finally decline again rapidly during corpus luteum atrophy.

Laboratory results indicate that estrogen may inhibit osteoclast activity directly or indirectly by modulating bone resorption since low estrogen levels stimulate osteoblast production and factors related to osteoclast differentiation and bone resorption activity. Thus, estrogen could inhibit alveolar bone resorption by increasing the expression of OPG in the periodontal ligament and alveolar bone [34].

The first studies were performed in laboratory rats, comparing the acceleration of tooth movement in osteoporotic rats and normal rats, showing that estrogen deficiency could accelerate tooth movement. Other studies in rats showed that the application of orthodontic force in different phases of the menstrual cycle produced different rates of tooth movement, being that the OTM is higher in the menstrual and luteal phases than any other phase of the menstrual cycle [35].

Therefore, in humans, hypothetically, the extent of tooth movement would be directly associated with estrogen levels, since when estrogen levels increase, there would be an increase in OPG and, in turn, the RANK-L/OPG interaction. This action would have a protective bone effect and would cause the bone mineral content and bone mass to increase, which in turn would reduce the rate of bone resorption. Conversely, estrogen deficiency would accelerate OTM; that is, the application of orthodontic force after ovulation may facilitate the acceleration of tooth movement.

Knowing that the OTM would be generally divided into three stages completely identified: the initial phase (7 days after the application of force) highlights the pressure or tension, the stagnation phase (15 to 21 days after the application of force) highlights the resorption on the pressure side of the bone and cell proliferation

becomes slow on the tension side, and finally the late phase (28 days after the application of force) highlights the pseudonormality of the parodont. There is an important reality present, and that is, if one intelligently assumes that the time interval between each orthodontic appointment is approximately 1 month, which coincidentally is like the estrogen lunar rhythm, one could envision orthodontic mechanics after ovulation during the luteal phase and the menstrual phase of women when estrogen levels are low [33].

The intelligent combination of orthodontic mechanical needs with the assessment of physiological variations in human behavioral biology breaks down a huge paradigm wall for orthodontists, as they could offer accelerated tooth movement; however, studies are still in progress to validate this logical assumption in humans so that it can be adapted in the future as a useful tool in the mechano-biology of tooth movement.

14. Is age important during the application of forces in orthodontic treatment?

The pressure or tension force on the OTM triggers an inflammatory response and induces the release of various inflammatory markers (chemokines and cytokines) that subsequently recruit osteoclast precursors and induce their differentiation and activation through the RANK-RANKL pathway; However, although the stages of the biology of tooth movement are clearly known, the results will depend on a complex series of biological variables that interact alone and with each other, not only in the cell signaling pathways described above but in the entire complex stomatognathic system [36]. We may find certain disjunctions, such as: Why does root resorption appear in some patients but not in others? Why are there different times for closing extraction spaces between patients if the biological mechanism is the same? Why are the functional orthopedic results promising in some patients but not at all in others? Or why do orthodontists find a wide range of clinical responses to similar treatments?

It is presumed then that one of the most important variables to answer most of these questions is age, because as age advances, the alveolar bone becomes denser and, on the contrary, the periodontal ligament becomes more fibrotic. In this sense, and under the above-mentioned conditions, young patients would show a better and faster biological response to OTM compared to older patients [37]. However, the publications presented so far have shown that it is not possible to predict the rate of tooth movement of one patient based solely on the biological response of another patient, so practitioners should understand and apply the averages of inflammatory markers within the same patient to select an optimal force range that enhances the biological responsiveness to OTM [38].

15. Can cocoa and caffeine administration accelerate OTM?

Cocoa is a natural material based on the processing of its fruit; its benefits have aroused scientific attention around the world because it contains methylxanthine, for which the administration of cocoa contributes to active orthodontic treatment by modulating the rate of tooth movement and inducing osteoclastogenesis; likewise, methylxanthine is an active compound that contains a large amount of caffeine. The use of caffeine to improve OTM has been well documented, and it is known that daily caffeine intake can contribute to the acceleration of tooth movement. In addition,

traditional Chinese medicine containing caffeine would increase the speed of OTM in human subjects. Although more clinical studies are needed to confirm the efficacy and potency of cocoa in accelerating OTM, to date it has been proven to shorten the duration of orthodontic treatment [39].

16. Baicalin: is it the new ally for the orthodontist?

Baicalin is a powerful antioxidant that is recommended for the prevention and elimination of wrinkles and fine lines because it inhibits oxidation and rancidity, resulting in healthy, youthful skin. It also has several astringent and anti-inflammatory properties and leads to a reduction in the RANKL/OPG ratio in response to lipopolysaccharide (LPS) in human PDL cells, for which baicalin is being investigated not only in the medical field but also in the dental field for its properties of inhibiting root resorption during OTM in rats. Thus, studies carried out in rats show that the ingestion of baicalin during experimental OTM increased the expression of OPG and inhibited the expression of selective RANKL, causing the suppression of root resorption without altering the distances that the teeth traveled, making baicalin treatment an effective therapy for the prevention of root resorption induced by OTM [40].

Given the high evidence of favorable results in animals, further clinical investigations are needed to clarify the effect of baicalin during OTM in humans and its relationship to the prevention of root resorption, including the safety, pharmacological prescription, and dose volume of safe baicalin in humans.

17. Acetaminophen: would it reduce apical root resorption during OTM in rats?

It is believed that root resorption at the root apex occurs due to inflammation of the parodont (protective and insetion parodont), in this case specifically due to inflammation of the apical root tissue, the periodontal ligament, and the apical pulp; also, previous human studies showed that root resorption is much more severe in vital teeth than in pulpless teeth [41]. Therefore, it is believed that apical root resorption can be reduced by the administration of nonsteroidal anti-inflammatory drugs [41].

However, the effects of nonsteroidal anti-inflammatory drugs on root resorption are controversial because decreasing inflammation improves pain but compromises OTM mechanics by drastically decreasing the number of osteoclasts; thus, Although no significant differences in tooth movement were observed between the acetaminophen and non-acetaminophen control groups, research published to date suggests that acetaminophen may reduce severe root resorption in the apex area without disturbing orthodontic tooth movement.

18. Cyclosporin-A: what is its effect on OTM in rats?

Cyclosporine A (CsA) is a drug widely used as an immunosuppressant to prevent transplant rejection and reduce the activity of the human patient's immune system; however, a pattern of osteopenia was observed in animals, and other studies suggest that the use of CsA could influence the healing of post-extraction tooth sockets. On the other hand, gingival overgrowth was a significant local side effect that appeared

during treatment with CsA at doses >10 mg/kg and >30 mg/kg body weight. Thus, direct evidence of the effect of CsA on the OTM is still lacking to improve the rate of tooth movement and avoid osteopenia in the alveolar process, which can lead to increased selective osteoclastic activity [42].

19. Vibration as an alveolar biological modulator during OTM and craniofacial bone

Non-surgical methods to accelerate OTM, including low-level laser therapy, are currently gaining interest because they have produced positive results in accelerating tooth movement and are preferred over surgical methods such as corticotomies and piezocision by patients, parents, and orthodontic professionals. However, the high cost of equipment coupled with the limited applicability of the in-office approach limits the applicability, so vibration has gained popularity as it is easy to use and convenient for patients to use a device from the comfort of home [43, 44].

Much of the research in medicine related to vibration has focused on whole body vibration as a means of increasing bone mass in osteoporosis, and low intensity vibration (LIV) is mentioned as having the most significant effects on bone density, demonstrating bone mineral density gain in the femoral and vertebral bones of women with osteoporosis but requiring strict daily compliance. This LIV has been defined as an oscillating mechanical signal of high frequency (>25–50 Hz) and low acceleration (<1 g). It is generally explained that vibration as a dynamic load has an anabolic effect, while static loads have a catabolic effect [45, 46].

The effects of vibration on OTM have been studied in both animal and clinical models; however, conflicting results have been found regarding the accelerating effects of vibration on tooth movement rate. Perhaps biological evidence that can be observed clinically may be more important in evaluating the effects of vibration on tooth movement velocity [47, 48].

20. Effects of angiotensin II type I losartan on the OTM

Losartan, or losartan, is an angiotensin II receptor antagonist drug used primarily to treat high blood pressure. The renin-angiotensin system (RAS) is a novel component of the osteoclast differentiation system, leading to increased bone resorption. Blocking the RAS pathway could inhibit this resorption process, decrease the risk of bone disease in the elderly, and modulate OTM. Thus, orthodontists should consider the pharmacologic prescriptions that will interact during orthodontic treatment planning and execution, as it is prudent to assume that chronic use of RAS blockers by orthodontic patients could suppress tooth movement and thus prolong treatment times [49].

21. Omega-3 fatty acids in the OTM: biochemical, histological, immunohistochemical, and gene expression analysis in rats

Omega-3, a polyunsaturated fatty acid composed of -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), shows anti-inflammatory effects by decreasing the level of pro-inflammatory cytokines and

inflammatory mediators. In a study with rats, omega-3 fatty acids were shown to inhibit osteoclast activity and bone resorption while stimulating osteoblast activity and new bone formation. Therefore, it would be reasonable to expect that systemic administration of omega-3 fatty acids reduces proinflammatory cytokines, which could slow down orthodontic tooth movement by decreasing the number of osteoclasts [50].

22. Regular nicotine intake what happens to our smoking patients?

The harmful effects of nicotine and tobacco smoke have been frequently studied and discussed in relation to cancer, cardiovascular diseases such as atherosclerosis, and respiratory diseases such as obstructive pulmonary disease (COPD), which can affect children and adults; in addition, limited attention has been given to the possible effects on the oral system, with OTM. According to the World Health Organization, tobacco use is "the single most preventable cause of death and disease" worldwide. "Europe has the highest prevalence of adult tobacco use (28%) and one of the highest prevalences of tobacco use among adults and adolescents (12%), with adult prevalence rates in the United States ranging from 13–22% [51].

Nicotine consumption at a dose corresponding to that of an average European smoker during OTM, along with osteoclast activity and osteoclastogenesis, would explain the observed increase in orthodontic-induced inflammatory dental root resorption (OIIRR) and periodontal bone loss due to synergistic release of proinflammatory cytokines and RANK-L-mediated differentiation of osteoclasts within areas of periodontal ligament compression, in addition to the acceleration of orthodontic tooth movement at 14 and 28 days.

Thus, although the achieved acceleration of OTM would be desirable for purposes of reducing overall treatment time, the associated risks and side effects observed are serious and indicate the need to adequately inform orthodontic patients about the risks and the need for nicotine abstinence during orthodontic treatment [51].

23. Atorvastatin: would it prevent recurrence by controlling osteoclast inhibition?

Currently, the stimulation of remodeling of the protective and attachment parodontium in the final stages of orthodontic treatment is one of the main causes of relapse and osteoclast cellular adaptations in the areas of compression, so pharmacological inhibition could be expected to offer clinically relevant effects on the regulation of OTM.

The drug atorvastatin is a member of the statin family that is used to lower blood cholesterol levels and prevent cardiovascular disease, as well as help stabilize plaques and prevent embolism, studies have suggested that statins may influence bone turnover by enhancing osteogenesis and suppressing bone resorption. These effects involve modulation of RANK, RANK-L, and OPG, which ultimately promote suppression of osteoclastogenesis. The effects of statins on orthodontic relapse have been little explored until it was observed that simvastatin had the ability to minimize tooth displacement due to decreased RANK-L and increased expression of OPG, thus accelerating tooth stability and aiding in the retention phase. As well, simvastatin

produces increased bone volume in rats affected by periodontal disease, apparently with decreased RANK-L expression [52].

Although it is known that statins could be well tolerated by children and adults, there are several preclinical in vitro and in vivo studies that suggest undesirable long-term effects. Due to the increase in chondrocyte proliferation and longitudinal bone growth and the significant increase in the anteroposterior length of skulls, ulnae, femurs, and tibias in rats with achondroplasia, this could contraindicate this drug as a pharmacological strategy for orthodontics in children. However, these drugs would not have any serious repercussions for adults or young adults [53].

Then, it is possible to mention that although the administration of atorvastatin (5 mg/kg by gavage) would decrease the rate of tooth movement in rats, this would also affect endochondral ossification of long bones, which could limit its clinical use in the pediatric population; likewise, it is evident to suggest that even when animal studies suggest that a treatment will be safe and effective, more than 80% of potential therapies fail when tested in humans; therefore, these findings seem to be far from being useful in clinical practice in humans.

24. Conclusions

The first studies on tooth movement were carried out on animals as early as 1899 and later progressed to clinical trials and clinical cases in which various types of orthodontic mechanics for tooth movement were discovered, which led to the creation of various orthodontic philosophies, Thus, it was demonstrated by means of specific techniques "that the relationship of osteoblasts with osteoclasts during inflammatory interaction explains dental movement from the pressure/tension perspective", subsequently, osteocytes gained importance in the study of dental movement since they would become the architects of the new bone structure; However, things are not so simple, or rather, the subject of moving teeth is no longer a mechanics done and presented as a recipe, but rather an intelligent path in which you should not worry about a specific mechanics or technique followed to the letter from start to finish, but rather, orthodontists could enhance the ability of the teeth to be moved, orthodontists could enhance these orthodontic mechanics and techniques through the use of various mechanical, physical, biological, pharmacological, nutritional and other resources in search of the ideal acceleration of dental movement within the biological limits of the human body, with the knowledge and respect of the collateral or harmful effects that could occur. Likewise, this topic is in constant evolution and further research is expected with technological applications and autologous biological resources that will allow the insightful use of orthodontic treatment according to the accurate diagnosis previously made.

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Conflict of interest

"The authors declare no conflict of interest."

Acronyms and abbreviations

OTM	orthodontic tooth movement
PTH	parathormone
PDL	periodontal ligament
SGP	stress-generated potential
cyclic AMP (cAMP)	cyclic adenosine monophosphate
RANK	receptor activator of nuclear factor kappa-B
RANK-L	receptor activator of nuclear factor κB receptor ligand
OPG	osteoprotegerin
TNF	tumor necrosis factor
M-CSF	macrophage colony-stimulating factor
eNOS	endothelial nitric oxide synthase
NO	nitrous oxide
MEPE	matrix extracellular phosphoglucoprotein
CTGF	connective tissue growth factor
OPN	osteopontin
RAP	regional acceleration phenomenon
EARR	external apical root resorption
AD	Alzheimer's disease
LLLT	low level laser therapy
ATP	adenosine triphosphate
CsA	cyclosporine A
LIV	low intensity vibration
RAS	renin-angiotensin system
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
COPD	pulmonary obstructive pulmonary disease
OIIRR	orthodontic-induced inflammatory intraocclusal resorption of teeth

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