Assessing the role of local administration of vitamin D in accelerating dental movements induced by orthodontic treatment

PhD Thesis Summary

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2017
Assessing the role of local administration of vitamin D in accelerating dental movements induced by orthodontic treatment

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Key words: conventional orthodontic treatment, bone remodeling, vitamin D, bilateral canal distal, dento-maxillary abnormality.

ABREVIERI:
1,25(OH)2D - 1,25 dihidroxivitamine D
BMP - bone morphogenetic protein
FGF - fibroblast growth factor
IGF - insulin-like growth factor
IFN-γ - interferon gamma
IL - interleukină
OPG - osteoprotegerine
PG - prostaglandine
PTH - parathyroid hormon
RANK - Receptor Activator of Nuclear Factor κ B
RANKL - Receptor activator of nuclear factor kappa-B ligand
TNF-α - tumor necrosis factor
TNF-β - tumor necrosis factor
CHAPTER 4
MOTIVATION AND OBJECTIVES OF PERSONAL STUDIES

Various studies have been carried out over time to investigate multiple possibilities that can shorten the orthodontic treatment period. We have insisted on the various factors that can influence the dental movement induced by orthodontic treatment, such as: physical, chemical (drug) and surgical factors.

The association of drug therapy with conventional orthodontic therapy has been the subject of numerous studies that have evaluated the influence of various pharmacological agents on the metabolism of alveolar bone tissue.

Modulation of host response to biomechanical forces is currently a subject of interest in literature.

The results of in vitro, cell cultures or in vivo studies (in laboratory animals) indicated that these pharmacological agents may have the following effects on bone tissue:
- stimulating effect;
- inhibitory effect of tissue metabolism;
- additive effect.

Considering the multitude of chemical compounds mentioned in the literature as having the role of influencing or interfering with the turnover of bone tissue, we have turned our attention to one of them (i.e. biologically active vitamin D3) to test the hypothesis that Results in orthodontic therapy are not primarily influenced by the biomechanical aspects, but the host's
response to the action of compressive forces is just as important as the biomechanical elements chosen at the planning stage of treatment.

Active vitamin D3 (1,25 dihydroxycalecalciferol) is one of the main biomodulators of bone tissue. Studies have shown that osteoblasts exhibit biologically active vitamin D3 receptors.

His involvement in metabolic processes of bone tissue is documented in the literature of sepciality by its effects on the RANKL / OPG system:

Thus, we have proposed in our study to test the clinical effectiveness of local administration of vitamin D3 in influencing the rate of dental displacement generated by orthodontic treatment.

The overall objectives of the research were:
> The association of drug therapy with conventional orthodontic treatment in order to accelerate the dental movement rate;
> Assessing the potential side effects of this association;
> Assessing patients' feedback on the association of local administration of pharmacological agents with conventional orthodontic treatment.

The specific objectives of the studies were:
> Evaluation of dental movement rate in patients under active biomechanical treatment associated with intraliginal injection of vitamin D3;
> Radiological evaluation of the adverse effects on local administration of vitamin D3 (external radicular resorption);
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CHAPTER 5

CLINICAL STUDY REGARDING THE ROLE OF INTRAGLIATING D3 VITAMINATION IN THE CONTEXT OF ORTHODONTIC THERAPY

5.1. Introduction

The theory of pressure-tension, attributed in the literature to the biological response of the body to orthodontic therapy, provides that the application of a mechanical force on the dental crown determines the occurrence of two zones in the periodontal ligament: the pressure zone and the tension zone respectively (Proffit et al. 2007). At the level of the pressure zone, the periodontal ligaments are compressed, while the tension zone is characterized by tense periodontal ligaments. It is also observed in these two areas and changes in blood flow (Proffit et al., 2007), so that it is diminished in the pressure zones and maintained or increased in the voltage zones. Changes in blood flow from the periodontal ligament are responsible for variations in the oxygen level in the two areas, with decreasing the oxygen level in the compression zones and maintaining or increasing it in the voltage zones. The chemical changes inherent to periodontal ligament blood flow variation stimulate the local release of key molecules in the induction of cell differentiation and stimulation of osteoblast and osteoclast cells (Proffit et al., 2007, Davidovitch, 1991,
Davidovitch et al., 1988). These chemical mediators (cytokines, neurotransmitters, growth factors) stimulate the cellular activity of osteoclasts and osteoblasts, and thus the bone resorption process is initiated in the compression and bone stress zones respectively (Schwarz, 1932, Sandstedt, 1904, Oppenheim, 1911). In this manner begins the process of bone remodeling itself (Schwarz, 1932, Sandstedt, 1904, Oppenheim, 1911). Remodeling of peridural tissues is essential in the dental movement process associated with orthodontic therapy.

The speed or rate of dental movement is influenced by two variables:
- the external stimulus represented by the orthodontic force on the one hand and the
- the dynamics of periodontal tissue metabolism, on the other hand (Faure, 2011).

Regarding the physical characteristics of the force applied to the dental crown, there is precise data on the force that drives a dental movement at an optimal rate in the literature.

In this regard, the concept of "optimal orthodontic force" was defined by Schwarz in 1932 as "the force that induces a close tissue pressure as value of the blood pressure in the capillary vessels, thus preventing their collapse and obstruction in the compressed periodontal ligament" (Faure, 2011). In Schwarz's view, the forces below the optimal level do not produce any tissue reaction, and the higher than the optimal value determines the appearance of an avascular area in the periodontal ligament. These avascular areas of the periodontal ligament resulting from the application of an
inadequate force determine processes of cellular necrosis in the compression zones, a phenomenon known in the literature as "hialinization", in which the dental movement process is blocked. It is necessary to wait for osteoclastic activity and periodontal ligament scarring to resume the initiated movement. Between the two described thresholds, the dental movement is quasi-independent of the intensity of the force. Data from the literature admits that optimal force determines a corporal dental movement rate of 1-1.5 mm/month (Faure, 2011). If the first variable influencing the dental displacement rate is represented by the external mechanical stimulus that determines an optimal body movement rate of 1-1.5 mm/month, regarding the two variable represented by the dynamics of periodontal metabolism, many researchers have Modulated the response of the host to the action of the orthodontic forces in order to stimulate turnover and metabolism of the bone tissue. Vitamin D3 is involved with parathyroid hormone and calcitonin in the regulation of serum calcium and phosphate. Moreover, it promotes bone and vitamin D receptors express not only osteoblasts but also osteoclast precursors and active osteoclasts (Klein, Raisz, 1970).

5.2. Material and method

This study was conducted in the Ambulatory of Orthodontics and Orthopedics at the University of Infantile Dentistry, affiliated with "Grigore T. Popa" University of Medicine and Pharmacy, Iasi. The study protocol was conducted in accordance with ethical principles in scientific research and was approved by the
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Research Ethics Commission of the "Grigore T. Popa" University of Medicine and Pharmacy, Iasi.

Experimental hemiarcade (experimental canine) was administered intragranularly with 0.2 ml vitamin D3 (Calcitriol, Mibe, Germany). Vitamin D3 was diluted in dimethylsulfoxide, a liposoluble solvent (DMSO, Euroclone, Milano, Italy). Three administrations were performed at weekly intervals. Intraligmental administration of vitamin D3 was performed distally by canine. After finalizing the alignment and leveling step and before the dog's own bilateral distal dental arterial dilation study, all patients were given a footprint to cast the study patterns and were instructed to perform the cone-beam CT examination. One week after the last intraligation of vitamin D3 and four weeks of orthodontic bilateral canal distal therapy, both the CT cone-beam exam for the arches studied and the fingerprinting were repeated.

We measured the distance in millimeters of distal canine displacement at control hemiarcade and at Experimental hemiarcade level. To accomplish this measurement, the electronic picker was used with an accuracy of 0.01 mm.

Differences between control hemiaracades and experimental hemiarkses were compared.

For the statistical analysis of the data, the non-parametric Wilconson-Mann Whitney test was performed.

For the comparison of media comparisons, a difference with a value of $p < 0.05$ was considered statistically significant.
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Fig. 5.1. Injection solution used for intraligmental administration of vitamin D3 (Calcitriol, Mibe, Germany) and the solvent used for intra-vitamin D3 (liposoluble solvent DMSO, Euroclone, Milan, Italy).

5.3. Results

In our study six experimental sites (benefiting from the combination of vitamin D3 and convectional orthodontic treatment) and six control sites (which benefited strictly from conventional orthodontic therapy) were included (Table 5.I).

Of these, 4 experimental sites were located at the jaw and 2 experimental sites on the mandible. The situation is the same for test sites (4 jaw and 2 mandibular).

All patients were diagnosed with dento-maxillary anomaly with clogging requiring the extraction of the first premolars, except for a single patient who was diagnosed with Anglo-Class I malocclusion and isolated dental anomalies represented by the bilateral congenital absence of the maxillary lateral incisor (bilateral anatomy of the Incisive lateral jaw) (Table 5.VI). The treatment plan for all patients included bilateral canal distraction.
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The age of patients enrolled in the study ranged from 13 to 34 years. The gender distribution was equal. The first stage of fixed orthodontic therapy, represented by the alignment and leveling step, varied between 2 and 5 months (Table 5.I). The dental displacement rates of experimental teeth and control teeth taken into study are shown in Table 5.I. And illustrated in figures 5.62-5.77.

Within 4 weeks of application of the distal force to the studied canines, for the expression and control sites respectively, the mean travel rates were as follows:
- the average canine displacement at experimental hemiarcades is 1,253 mm; (Table 5.I.)
- the average canine displacement at control hemiarcades is 0.735 mm; (Table 5.I)

On average, the control hemiarcade movement was 0.735 mm, while on the hemiarcada test (where vitamin D was administered by local administration), the mean displacement was 1.253 mm, which represents a difference of 0.518 mm between the global displacement of the experimental teeth and the overall displacement of the control teeth.

Expressed in percentage terms, this difference is 70.5% (Table 5.II). In other words, the overall movement in the test hemiarcades was 70.5% higher than the overall displacement of teeth on control hemiarcades. The mean relative displacement, calculated as the mean difference between the dental movement in the hemiarcada test and the dental movement in the control hemiarcade, is 0.518 mm.

The effectiveness of vitamin D treatment appears to be important in older patients, as long as the
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movement through mechanical actions is reduced or even non-existent during the first 4 weeks of treatment.

Table 5.I. Described statistical data. The age of the study patients, their sex, the diagnosis, the period of the first fixed orthodontic treatment (alignment and leveling), as well as the dental shift rates for each site assessed, are shown four months after the application of the distal force to the canines.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Arch</th>
<th>Diagnostic</th>
<th>Alignme</th>
<th>Control</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nt and</td>
<td>Hemiarch</td>
<td>Hemiarch</td>
</tr>
<tr>
<td>1.</td>
<td>18</td>
<td>M</td>
<td>Max.</td>
<td>ADM cu înghesuire</td>
<td>4 months</td>
<td>0.85 mm</td>
<td>1.55 mm</td>
</tr>
<tr>
<td>2.</td>
<td>34</td>
<td>F</td>
<td>Max.</td>
<td>Anodonţie IL</td>
<td>5 months</td>
<td>0 mm</td>
<td>0.44 mm</td>
</tr>
<tr>
<td>3.</td>
<td>15</td>
<td>M</td>
<td>Max.</td>
<td>ADM with intercourse</td>
<td>3 months</td>
<td>1.16 mm</td>
<td>1.34 mm</td>
</tr>
<tr>
<td>4.</td>
<td>15</td>
<td>M</td>
<td>Max.</td>
<td>ADM with intercourse</td>
<td>2 months</td>
<td>0.89 mm</td>
<td>1.18 mm</td>
</tr>
<tr>
<td>5.</td>
<td>13</td>
<td>F</td>
<td>Max.</td>
<td>ADM with intercourse</td>
<td>2 months</td>
<td>0.34 mm</td>
<td>1.03 mm</td>
</tr>
<tr>
<td>6.</td>
<td>13</td>
<td>F</td>
<td>Mand.</td>
<td>ADM with intercourse</td>
<td>3 months</td>
<td>1.17 mm</td>
<td>1.98 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.735 mm</td>
<td>1.253 mm</td>
</tr>
<tr>
<td>Me di u m val ue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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Table 5.II. Illustration of canine displacement rates on experimental hemiarkets and test hemiarcades, respectively. The displacement difference between the two hemiarcades is also illustrated. A difference of 0.518 mm was observed between the two batches, which represents, in percentages, a dental movement with 70.5% higher experimental teeth vs. control teeth.

<table>
<thead>
<tr>
<th>.</th>
<th>Age</th>
<th>Sex</th>
<th>Arch</th>
<th>Alignment and leveling</th>
<th>Control Hemiarch</th>
<th>Test Hemiarch</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>18 ani</td>
<td>M</td>
<td>Max.</td>
<td>4 months 5 luni months</td>
<td>0.85 mm</td>
<td>1.55 mm</td>
<td>0.70 mm</td>
</tr>
<tr>
<td>2.</td>
<td>34 ani</td>
<td>F</td>
<td>Max.</td>
<td>5 luni months</td>
<td>0 mm</td>
<td>0.44 mm</td>
<td>0.44 mm</td>
</tr>
<tr>
<td>3.</td>
<td>15 ani</td>
<td>M</td>
<td>Max.</td>
<td>3 months</td>
<td>1.16 mm</td>
<td>1.34 mm</td>
<td>0.18 mm</td>
</tr>
<tr>
<td>4.</td>
<td>15 ani</td>
<td>M</td>
<td>Mand.</td>
<td>2 months</td>
<td>0.89 mm</td>
<td>1.18 mm</td>
<td>0.29 mm</td>
</tr>
<tr>
<td>5.</td>
<td>13 ani</td>
<td>F</td>
<td>Max.</td>
<td>2 months</td>
<td>0.34 mm</td>
<td>1.03 mm</td>
<td>0.69 mm</td>
</tr>
<tr>
<td>6.</td>
<td>13 ani</td>
<td>F</td>
<td>Mand.</td>
<td>3 months</td>
<td>1.17 mm</td>
<td>1.98 mm</td>
<td>0.81 mm</td>
</tr>
<tr>
<td>Medium value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.735 mm</td>
<td>1.253 mm</td>
<td>0.518 mm</td>
</tr>
</tbody>
</table>
5.4. Discussion

Our study evaluated the efficacy of intraligmentation of biologically active D3 vitamin D (1,25 dihydroxycalciferol) in influencing the dental shift rate from active biomechanical orthodontic treatment.

The role of calcitrophic hormone in vitamin D3 is well known in the literature, and it is also involved in promoting osteoid tissue deposition and inhibiting the release of parathyroid hormone (Bartzela et al., 2009), whose role in osteoclastogenesis is good known.

Parathomon causes osteogenesis by two mechanisms: couples with specific membrane receptors present on the surface of osteoclasts and induces the release of chemical compounds that initiate the osteoclastogenesis process on the one hand and inhibits osteoprotegerin secretion and stimulates RANKL expression in osteoblasts on the other.

In our study, the dental displacement rate of the experimental canines was higher than the tooth displacement rate of the control teeth, with a statistically significant difference between the two batches. This suggests or confirms the role of vitamin D3 bone biomodulator, being involved, in the present case, in increasing the rate of dental movement and thus the turnover of bone tissue.

Other similar studies performed on laboratory animals reported the involvement of vitamin D3 in the dental movement acceleration process, the dental shift rate depending directly on the dose of calcitriol
administered locally (Bartzel et al., 2009). Vitamin D3 acts on osteoblasts and osteoclasts to accelerate dental movement through several mechanisms (Al-Hasani et al., 2011). It is involved in the formation of osteoclasts from its precursors and stimulates the activity of osteoclasts existing in the periodontal ligament. In vitro studies have shown that after vitamin D3 administration, the bone resorption zone is 2 to 4 times higher than the control group (Al-Hasani et al., 2011). The same effect of vitamin D3 to stimulate osteoclast activity was also observed in the incubation of osteoclasts. Colins and Sinclair mentioned that intraligmentation of vitamin D3 provides an optimal balance between resorption and bone resorption processes, modulating the turnover of bone tissue. Studies on modulation of host response to orthodontic forces are at the beginning and promising results.

The increase in the dental displacement rate at the level of the experimental hemiarcades is correlated, in our study, with intraliginal administration of vitamin D3 at the experimental sites. The combination of vitamin D3 and conventional orthodontic therapy modulates the response of the host to the action of the orthodontic forces in order to regulate the bone remodeling process, so we have obtained a higher dental displacement rate in our study compared to the control teeth. Thus, our study confirms the hypothesis that the metabolism of the peritoneal alveolar tissue of the teeth to be displaced orthodontically depends on a number of systemic and local factors, one of which tested in this study is
biologically active vitamin D3 or 1, 25 dihydroxycolecalciferol.

CHAPTER 6
RADIOLOGICAL EVALUATION OF THE SECONDARY POTENTIAL EFFECTS LOCAL POST-ADMINISTRATION OF VITAMIN D3 IN THE CONTEXT OF BIOMECATRIC ORTHODONTIC TREATMENT

6.1. Introduction
Orthodontic treatment consists in the prolonged application of a force in the dental crown to move the tooth in the desired direction to restore intra- and intercostal balance (Proffit et al., 2007). The mechanical pressures exerted at the level of the dental crowns are taken up by the periodontal ligament and transmitted to the alveolar bone which will undergo a bone remodeling process (Davidovitch, 1991, Davidovitch et al., 1988, Schwarz, 1932, Sandstedt, 1904, Oppenheim, 1911).

The bone remodeling process, inherent to any orthodontic dental movement, can be influenced by a series of electrical and chemical exogenous factors that have a stimulating effect on cells involved in the bone remodeling process (Yamasaki et al., 1982, Yamasaki et al., 1984, Stark, Sinclair, 1987):
- osteoclasts (responsible for mineral phase dissolution of the bone matrix and secretion of lysosomal enzymes in the dissolution of the organic phase of bone tissue); and
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osteoblasts (recruited at the resulting resorption gap, called the Howship loop, whose role is to synthesize at the Howship loop the non-mineralized matrix consisting of type I collagen and non-collagen proteins and to produce enzymes such as alkaline phosphatases which increase the concentration of calcium ions and phosphate to form hydroxyapatite crystals, thereby ensuring calcification of the bone matrix).

Adjusting the bone remodeling process involves:
- systemic factors and a
- local factors.

SYSTEMIC FACTORS involved in the bone remodeling process are represented by:
- Parathyroid hormone: is involved in regulating phosphocalcic metabolism. It favors osteolysis that allows the release of calcium in the blood (hypercalcemic effect) by two mechanisms:
  ● fixes the membrane receptors of osteoclast precursors and induces the release of soluble factors that generate osteoclastogenesis;
  ● inhibits osteoprotegerin secretion (OPG) concomitantly with activation of RANKL expression favoring the activation of osteoclast precursor cells.
- active vitamin D3 (calcitriol): regulates phosphocalcic metabolism and skeletal mineralization, stimulating the digestive uptake of calcium and phosphate. It interferes with the bone remodeling process;
  ● stimulates differentiation and maturation of osteoblasts;
  ● Stimulates osteoblast activity (stimulating the expression of genes for alkaline phosphatases,
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osteocalcin, type I collagen required for bone matrix synthesis);

- stimulates the expression of RANKL in osteoblasts, which activates the differentiation and proliferation of osteoclasts (involved in organic matrix resorption and bone calcium mobilization) (Collins, Sinclair, 1988, Kale et al., 2004, Raisz et al., 1972, Takano-Yamamoto et al., 1992, Al-Hasani et al., 2011).
  - calcitonin: has antiresorptive effect (decreases calcium release from the bone marrow, explaining its hypocalcemic effect):
    - act on osteoclasts, diminishing their mobility and accelerating the apoptosis process (Diravidamani et al., 2012).
- Sex hormones:
  - estrogens: potent inhibitors of bone resorption: inhibits the synthesis by osteoblasts of cytokines involved in osteoclast activation (IL1, IL6).
  - androgen: Anabolic role on bone tissue (stimulates bone formation);
  - progesterone: stimulates the differentiation and proliferation of osteoblasts.
- Thyroid hormones: Controls bone growth and maturation. They are involved in osteosynthesis and bone resorption processes.
- growth hormones: have a stimulating effect on bone formation, stimulating the release of IGF-1 that increases osteoblast differentiation and diminishes collagen destruction.
LOCAL FACTORS involved in the bone remodeling process are represented by:
- growth factors (Davidovitch et al., 1988):
  TGF-beta (transforming growth factor beta): (stored in the bone matrix). They have chemotactic action on osteoblast precursors and induce differentiation of osteoblasts from undifferentiated mesenchymal cells.
  IGF (Insulin-like Growth Factor): Stimulates the differentiation and proliferation of osteoblasts.
  FGF (fibroblast growth factor): (synthesized by osteoblasts and stored in the extracellular matrix). It stimulates the proliferation of osteoblasts as well as the production of osteocalcin and alkaline phosphatase.
- cytokines:
  PROSTAGLANDINE (PG): are locally synthesized by osteoblasts by expression of prostaglandin-synthetase expression, called COX-1, COX-2. Depending on the dose, the effect of prostaglandins is stimulation or inhibition of bone formation (Yamasaki et al., 1982, Yamasaki et al., 1984, Leiker et al., 1995, Seifi et al., 2003, Klein, Raisz, 1970)
  TNF-alpha (tumor necrosis factor alpha): is synthesized by monocytes and osteoblast cells, respectively. Increases production of osteoclasts, stimulating bone resorption.
  INTERLEUKINE (IL1, IL6, IL11): IL1 (potent bone resorption stimulator): favors the recruitment of osteoclasts, stimulates their activity and delays their apoptosis. It is synthesized by monocytes, osteoblasts, stromal cells. IL6 activates bone resorption by two mechanisms: stimulates osteoblast expression of factors
that trigger differentiation and proliferation of osteoclasts and acts directly on osteoclast precursors.
Hematopoietic cells to stimulate their differentiation into osteoclasts). IL11 is produced by the medullary cells. Stimulates the differentiation of osteoblast cells from undifferentiated mesenchymal cells from the medulla tree level.
IFN-gamma (interferon gamma): inhibits bone resorption preventing the formation and maturation of osteoclasts.
- RANK-L / RANK system, OPG. RANKL is a protein synthesized by osteoblast cells that have affinity for the RANK receptor present in osteoclasts, inducing differentiation, maturation and inhibition of their apoptosis. Osteoprotegerin (OPG) has an antagonistic effect compared to RANKL. It is also synthesized by osteoblast cells and has the property of binding to RANKL, preventing its activity (inhibiting differentiation, osteoclast maturation).

6.2. Material and method
The radiological evaluation of the dental shift rate was performed as follows:
- a conventional axial plane passing through the enamel-cement junction of the two premolars was determined on the coronary section (Figures 1a and 1b);
- On this conventional plane was drawn a horizontal line passing through the middle of the pulp chamber of the right two premolars (Figure 2a);
- using this horizontal line as a reference, we determined the sagittal position of the control teeth and the experimental teeth respectively before and one month...
after the initiation of canine distal treatment (Figure 2b and 2c) respectively;
- I compared the results obtained between the control teeth and the experimental teeth respectively. I calculated:
- the average tooth movement rate of the control teeth;
- the average displacement rate of the experimental teeth;
- the difference between the average displacement of the control teeth and the average displacement of the experimental teeth.

Media comparison was performed using the non-parametric Wilcoxon-Mann Whitney test. A difference with a value of \( p < 0.05 \) was considered statistically significant.

Qualitative assessment of root cement was performed on cone-beam CT images taken 3 months after the first intraligation of vitamin D3.

Fig. 6.1. The axial plane passing through the cement enamel junction of two maxillary premolars.
6.3. Results

Four weeks after application of the dog's distal force, the following results were obtained:
- the average displacement rate for test hemi-cartridges is 1.00 mm;
- the average displacement rate for the control hemiarcs is 1.70 mm;
- the mean relative displacement calculated as the mean difference between the dental movement in the hemisphere test and the dental movement in the control hemiarca is 0.70 mm.

Four months after intralingmentation of vitamin D3, no external root resorption was observed in both experimental teeth and control teeth. On average, the displacement on the control hemiarca was 1.00 mm, while on the hemiarca test where active vitamin D3 was applied, the mean displacement was 1.70 mm, which is a difference of 0.70 mm, which means that the displacement Dental was more important with 70% in experimental hemiarca.

On average, treatment with vitamin D3 induces a dental shift in absolute value 0.70 mm higher than conventional orthodontic treatment (mean dental movement on control hemiarca is 1.00 mm compared to 1.70 mm hemiarca on hemiarca test), which means Percentages a 70% greater displacement rate at the experimental hemiarces compared to the test hemiarces.

The nonparametric Wilcoxon-Mann-Whitney test suggests that:
1. There are no statistically significant differences according to gender (p > 0.05);
2. There are no statistically significant differences depending on the oblique dental arch (maxillary or mandibular) (p > 0.05);
3. Dental displacement does not vary linearly with the duration of alignment and leveling. In contrast, Wilcoxon Tissue suggests that there is a statistically significant difference between the test group and the control group (p value of 0.0313).

6.4. Discussions

Inflammatory root resorption following orthodontic treatment was first cited in 1914. It is a localized, pathological or physiological condition characterized by the loss of a cellular layer that protects the root surface from the action of cementocytic cells (Estrela et al., 2009).

Radical resorption may be minor, moderate or severe (Brin et al., 2003). Minor root resorption may be reversible at the end of dental movement by deposition of secondary cement. However, when root resorption becomes severe the root repair capacity is exceeded (Estrela et al., 2009, Pancherz, 2003).

Orthodontic treatment presents a number of risk factors for root resorption such as:
- duration of treatment;
- the direction of dental movement;
- apical displacement distance;
- type and magnitude of applied force (Weltman et al., 2010).
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For this purpose, we evaluated this potential adverse effect of vitamin D in the biologically active test by performing the CBCT exam. I chose the CBCT to assess the root aspect of the teeth included in the study precisely to assess the three-dimensional potential changes that might occur following local administration of vitamin D3 in the context of conventional orthodontic therapy to augment the experimental teeth displacement rate.

According to a study in laboratory animals (pigs) in which the accuracy and reliability of CBCT was assessed, dental and radicular measurements were not significantly different from real dimensions (less than 0.3 mm) compared to periapical radiographs Comparatively underestimated the actual dimensions, an average of 2.5 mm (Sherard et al., 2009).

In another study, radicular resorption was reported in orthodontic patients with Herbst using the conical beam CT scan technique. The C.B.C.T. Of 980 human dental roots, of which 57.96% had root resorbtions, but these were minimal, clinically insignificant (Schwartz et al., 2015).

It has been shown that cone-beam CT is a very accurate method used in the diagnosis of root resorption compared to panoramic radiography where root resorption is underestimated, resulting in CBCT being an important paraclinical examination that should not be absent before / during / And after orthodontic treatment (Dudic et al., 2009).
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Fig. 6.2. Light radicular resorption. (Dudic et al., 2009).

Fig. 6.3. Medium radicular resorption. (Dudic et al., 2009).

Fig. 6.4. Severe radicular resorption. (Dudic et al., 2009).
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The total duration of treatment is directly proportional to apical external root resorption (Segal et al., 2004). In a clinical case where total active treatment time was approximately 10 years from the start of fixed treatment in 1991 to the end of the second treatment in 2001, an increase in the severity of external root resorption seen on radiographs in the first therapy Fixed and second fixed therapy, the interval between the two being 6 years (Topkara et al., 2012).

In our study, the results or evaluations performed on CBCT at one week, one month and three months respectively after the topical administration of the pharmacological product indicated the absence of any radiation at the root level and therefore the absence of the potential adverse effect on the root teeth of the experimental teeth.

Intraligamental administration of vitamin D3 did not result in external root resorption three months after application to experimental teeth. Although the number of sites evaluated is low (six), there is a statistically significant difference between the two groups assessed by the Wilcoxon-Mann-Whitney non-parametric test, which may suggest a clinical safety of local administration of vitamin D3 with The condition of physiological dose compliance.
CHAPTER 7
EVALUATION OF ANXIETHIC DEGREE AND PATIENT PERCEPTION IN RELATION TO LOCAL ADMINISTRATION OF VITAMIN D3 IN THE CONTEXT OF ACTIVE BIOMECANIC TREATMENT

7.1. Introduction

Anxiety disorders are among the most widespread mental illnesses. According to epidemiological studies, one third of the population is affected by this life-long disorder, being more common in females, with an increased prevalence somewhere in the middle of their life. These disorders are associated with major feelings of depreciation, excessive maintenance of general health, a major economic burden on society (Bandelow, 2015). Although there is psychological and pharmacological treatment for these types of disorder, many people with these conditions do not require specialized treatment, and few people receiving treatment are not correctly diagnosed or treated appropriately (Bandelow, 2015).

The overall objective of this study is to assess the degree of comfort / discomfort of patients undergoing orthodontic treatment in the context of the possibility of shortening the treatment period by using adjuvant methods.

In this study, the specific objective was to evaluate in 4 steps the degree of anxiety and perception of the patients included in the local D3 vitamin delivery group before starting the active biomechanical treatment before, at an intermediate stage and at the end of intraliginal drug therapy to To speed up the dental movement rate.
7.2. Material and method

All patients benefited from the following protocol:
> Completing a first anxiety assessment questionnaire.
> Start of orthodontic treatment
> Filling in the questionnaire waiting room. Checking the boxes is done by hatching or x, then setting the individual score without the patient knowing the result.
> Local administration of intraligmentary vitamin D3 after topical anesthesia of periodontitis.
> Completing the third questionnaire, setting your personal score.
> Local administration of vitamin D3 in the second week
> Local administration of vitamin D3 in the third week
> Completing a final questionnaire, setting the individual amount after the last vitamin D3 administration

7.3. Results

A score greater than or equal to 19 obtained by completing the questionnaire indicates the treatment of anxiety.
Statistically, increasing anxiety is significant between first and second visits (p 0.05). There is also a gradual decrease between the second and third and third and fourth sittings respectively (Figure 7.1).
Fig. 7.1. Graphic representation of the scores obtained during the 4 evaluation moments.

There is a slight increase in anxiety between T0 and T1, which could be explained by the uncertainty of the patients over the new workmanship to be achieved. Initially, prior to consultation, the degree of anxiety was lower compared to the T1 moment. The patient's personal contact with the treatment room could contribute to a slight increase in anxiety between T0 and T1, respectively, which would explain the results obtained after completing the questionnaire at T1.

Subsequently, at the time T2 and T3 there is a decrease in the degree of anxiety of the patients in relation to the performed maneuvers, which could lead to the conclusion that the habit of the patients with the medical staff, with the treatment room, the trust in the medical personnel has helped to increase comfort once the therapy progresses.
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Also, the significant decrease in the degree of anxiety between the third and fourth sittings leads to the conclusion that patients' feedback on the local administration of vitamin D by the ligament is positive. Although administered intragranularly, drug therapy associated with conventional orthodontic therapy in the case of bilateral distal superior canines has been shown to be effective from the perspective of patient comfort.

The results of our study indicate that patient feedback was a positive response to intraligigation, which opens up perspectives on the possibility of expanding the ligand administration of pharmacological products tested to accelerate dental movement in therapy orthodontic.

CHAPTER 8
FINAL CONCLUSIONS OF THE THESIS

1. Modulation of host response to biomechanical forces associated with vitamin D drug therapy and conventional orthodontic treatment enhances metabolism (turnover) of alveolar bone tissue.
2. Biologically active vitamin D (1,25 dihydroxycalecalciferol) contributed to a higher displacement rate of experimental teeth compared to control teeth.
3. The combination of adjuvant drug therapy with conventional orthodontic treatment allows the shortening of the fixed orthodontic therapy period.
4. Intraliginal administration of vitamin D3 at physiological doses (42 pg / mL) has no adverse effects on root cement, assessed by CBCT.
5. Patient anxiety over intraliginal administration of biostimulating medicinal products in the context of active orthodontic treatment is low or insignificant.
6. Method of accelerating dental movement by associating biostimulator pharmacological products is a simple, minimally invasive and clinically effective method of optimizing the response of the host to the action of orthodontic forces.
7. The results of our study confirm the hypothesis that the metabolism of alveolar bone tissue is influenced by a number of systemic or local factors, of which calciotrophic hormones and local growth factors have a predominant influence on stimulation of osteoblasts and osteoclasts, respectively. By the accelerated dental movement observed at the level of the experimental teeth compared to the control teeth, we certify the role of vitamin D3 bone biomodulator and its potential influence on osteoblastic and osteoclastic cell activity.
8. The combination of drug therapy / conventional orthodontic treatment emphasizes the primordial role of host tissues in responding to mechanical stimuli, represented in our case by orthodontic forces.

9. The response to orthodontic therapy may be augmented or influenced by certain pharmacological agents. Knowing their action on bone cell activity is paramount in determining the body's response to orthodontic therapy.
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10. The importance of this PhD thesis lies in emphasizing the role of the patient's land in response to biomechanical forces. The existence of good systemic health is the essential premise for the success of orthodontic treatment. The lack of systemic bone damage or bone damage, such as the lack of chronic ingestion by patients of chronic drug treatment as part of the therapeutic recommendations present in various systemic conditions, are the premises necessary to carry out the normal remodeling process Bone-free process without which the dental movement of orthodontic therapy would not be possible. Another aspect underlined in our PhD thesis is the possibility of influencing this metabolism (of the bone tissue) by various exogenous agents in order to modify the response of the host to the orthodontic therapy. Of all the accelerators of bone metabolism studied in the literature (electricians such as oscillating electromagnetic radiation, laser therapy, mechanical agents such as mechanical forces generated by rotating brushes, surgical techniques associated with conventional orthodontic treatment), local administration of vitamin D3 constituted a Simple, minimally invasive, clinically effective labor, with minimal adverse effects and reduced discomfort caused to the patient, with the prospect of efficiency not only of the period and cost of orthodontic therapy, but also of the quality of the results achieved by conventional orthodontic post-treatment.
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