Original Research Article

Effects of hypothyroidism associated with dental trauma on induced tooth movement of female rat molars

ABSTRACT

Aims: The aim of this study was to evaluate the influence of hypothyroidism associated with dentoalveolar trauma on the induced tooth movement of female rats molars

Study design: Experimental research.

Methodology: Forty-eight female Wistar rats were randomly divided into eight experimental groups (n=6 per group): Group 1 – control: animals that were not subjected to any experimental procedure; Group 2: animals that were subjected only to hypothyroidism (HPT); Group 3: animals that were subjected only to dentoalveolar trauma (DT); Group 4: animals that were subjected to HPT+ DT; Group 5: animals that underwent induced tooth movement (ITM); Group 6: animals that underwent DT+ITM; Group 7: animals that underwent HPT+ITM; and Group 8: animals that underwent HPT+DT+ITM. At the end of the experimental period, the animals were weighed and euthanized. The right hemimaxillae were removed, fixed in 10% formalin, decalcified, embedded in Paraplast, cut to 5 µm thickness, and stained with hematoxylin and eosin. the histological slides, and histomorphometric analysis of external root resorption were performed.

Results: The animals that consumed propylthiouracil (0.05% diluted in water) showed lower concentrations of T3 and T4 but higher thyroid-stimulating hormone. The tooth movement rate was significantly higher in the animals of the HPT+DT+ITM group than the other groups ($p<0.05$). The HPT+ITM group showed greater tooth movement than the ITM and DT+ITM groups ($p<0.05$). Among the animals in the groups without the tooth movement device, the HPT group had the smallest areas of root resorption when compared to the CTL, DT, and HPT+DT groups ($p<0.05$). In the analysis of the

groups with tooth movement devices, the HPT+ITM group had a smaller root resorption area than the other groups with tooth movement devices ($p<0.05$). Animals in the HPT+DT+ITM group exhibited the highest root resorption area out of all experimental groups ($p<0.001$). The animals in the DT, HPT+DT, ITM, HPT+ITM, and DT+ITM groups showed occasional periodontal ligament disorganization, and the animals in the HPT+DT+ITM group had moderate disorganization. In the evaluation of hyaline areas, the groups that underwent DT and/or ITM (DT, HPT+DT, ITM, DT+ITM, HPT+ITM, and HPT+DT+ITM) showed a moderate presence of hyaline areas. Regarding vascular changes in the periodontal ligament, the presence of giant cells, hyperemia, and inflammatory infiltrate were observed in the ITM, DT+ITM, HPT+ITM, and HPT+DT+ITM groups.

Conclusion: We conclude that hypothyroidism associated with dental trauma causes increase in the rate of tooth movement and greater occurrence external root resorption during orthodontic movement in female rats molars.

Keywords: Orthodontic movement, hypothyroidism, dental trauma, rats.

1. INTRODUCTION

The balance of bone cell metabolism begets bone tissue homeostasis. Bone tissue undergoes remodeling by the action of osteoblasts, cells responsible for bone formation, and osteoclasts, which perform bone resorption. Bone remodeling is controlled by local, systemic, and hormonal factors, including thyroid hormones. These hormones are produced by the thyroid gland, disorders of which can alter the production of thyroxine (T4), triiodothyronine (T3), and calcitonin, leading the individual to hypothyroidism or hyperthyroidism. When thyroid-stimulating hormone (TSH) is elevated and T4 and T3 are diminished, this causes a pathological situation called hypothyroidism [1,2].

Hypothyroidism is considered primary when it is caused by an autoimmune response (e.g., Hashimoto's thyroiditis), severe deficiency or mildly to severely excessive iodine, thyroidectomy (surgical removal of the thyroid), genetic (congenital hypothyroidism), certain drugs (therapeutic using lithium, amiodarone, sodium valproate and others), transient thyroiditis (postpartum and viral infections), absence of enzymes essential for hormone synthesis, or diseases that have infiltrated the thyroid, such

as tumor metastasis. It is considered secondary or central when it occurs due to hypothalamic insufficiency or dysfunction, pituitary dysfunction (macroadenoma and/or apoplexy), resistance to TSH-releasing hormone, or certain other drugs (somatostatins and dopamines). In addition, it can be classified as extrathyroidal when there is consumptive hypothyroidism or genetic mutations [3, 4].

Hypothyroidism is associated with disorders of bone metabolism: bone lesions, excessive structural losses, growth defects, and delayed skeletal maturation. Studies suggest thyroid hormones act directly on bone, although they also may act indirectly, as they stimulate the synthesis of growth factors, cytokines, and other hormones [5]. Thus, hypothyroidism influences fundamental functions of cellular metabolism and bone remodeling, making it an important cause of orthodontic tooth movement, and is of great interest for achieving success in orthodontic treatment in patients with this hormonal dysfunction.

Orthodontic movement occurs by pressure and/or tension under appropriate and controlled conditions, promoting dynamic changes in bone structure. The initial compression is offset by internal alveolar bone resorption, while ligament stretching is balanced by bone deposition. The periodontal ligament transmits the pressure or tension essential for tooth movement [6].

In addition to bone dynamics, orthodontics is concerned with dentoalveolar trauma, especially that involving the supporting periodontium, because the success of orthodontic treatment depends on the integrity of these structures [7,8]. The prevalence of dental trauma is high in the population, especially among children and adolescents [9,10]. Orthodontic treatment in these patients represents an important part of orthodontal work. It is important to define procedures to be adopted by orthodontists regarding the ideal time to start treatment in patients who have suffered dental trauma, as well as to detail the complications that may occur during orthodontic treatment or in patients with a previous history of dental trauma [8].

Traumatic dental injury is considered a public health problem because of its high incidence, high cost and duration of treatment, and its interference with the quality of life of these patients [10]. Epidemiological studies indicate that the annual incidence of dental trauma worldwide is approximately 4.5%, and around one-third of children and infants (primary teeth) and one-fifth of adolescents and adults (permanent teeth) have suffered from traumatic dental injury, though the difficulty of access to treatment may lead to underreporting of cases [7, 11]. Dental trauma has a high financial impact in some

Western countries, in the form of the direct costs (treatment) and indirect costs (loss of productivity and wages, cost of transportation, and lowered quality of life).

The definitions and clinical significance of dentoalveolar trauma are consolidated in dental education [9]. However, the correlation between orthodontic movement, dentoalveolar trauma, and systemic changes, such as hypothyroidism, has been little studied. Thus, the aim of this study was to evaluate the influence of hypothyroidism associated with dentoalveolar trauma on the induced tooth movement of female rats molars.

2. METHODOLOGY

2.1Animals

A sample of 48 rats (n=6) was calculated considering the variables hypothyroidism, dentoalveolar trauma, and induced tooth movement, with an α of 5% and test power of 80% (GPower 3.1 software, University of Dusseldorf) [12,13].

Forty-eight female Wistar rats (45 days old, weighing approximately 150 g) were acquired from the UNIOESTE Animal Farm. The animals were adapted and kept in the sectorial bioterium of the Center for Biological and Health Sciences, Western Paraná State University (UNIOESTE), Cascavel, Paraná, Brazil. They were housed in collective polyethylene cages (43×30×15) individually or in pairs under controlled temperature (22° and 25° C), relative humidity (~55%), and photoperiod (lights on 7:00 a.m.-7:00p.m.). The animals received food and water *ad libitum.* The experimental procedures were in accordance with the Ethical Principles in Animal Experimentation adopted by the Brazilian College of Animal Experimentation (COBEA) and were approved by the Committee on Ethics in the Use of Animals of UNIOESTE (Protocol. No. 14/2020).

2.2 Experimental groups

The animals were randomly divided into eight experimental groups (n=6/group): Group 1: Control group (CTL), which were not subjected to any experimental procedure; Group 2: the animals were subjected to hypothyroidism (HPT); Group 3: the animals were subjected to dentoalveolar trauma

(DT); Group 4: the animals were subjected to HPT+DT; Group 5: the animals were subjected to induced tooth movement (ITM); Group 6: the animals were subjected to HPT+ITM; Group 7: the animals were subjected to DT+ITM; Group 8: the animals were subjected to HPT+DT+ITM.

2.3 Sedation of animals

The surgical and experimental procedures were performed under general anesthesia by intraperitoneal application of ketamine hydrochloride-based anesthetic (DOPALEN, Sespo Indústria e Comércio, Paulínia, São Paulo (SP), Brazil) at a dose of 75 mg/kg and muscle relaxant-based xylazine hydrochloride (ANASEDAN, Sespo Indústria e Comércio, Paulínia, São Paulo (SP), Brazil) at a dosage of 15 mg/kg.

2.4 Induction of hypothyroidism

At 60 days of age, the animals in the HPT, HPT+DT, HPT+ITM, and HPT+DT+ITM groups were subjected to induction of hypothyroidism through exposure for 30 days to propylthiouracil (PTU) (Sigma-Aldrich, St. Louis, MO, USA) at a concentration of 0.05% diluted in their water [14].

2.5 Application of extrusive luxation

At 90 days of age, dentoalveolar trauma was performed as proposed by Costa *et al*. (2018) [15], and Lucietto et al (2024) [16]. After anesthesia, asepsis of the region was performed with 1% povidone iodine (Riodeine®; Indústria Farmacêutica Rioquímica Ltda., São José do Rio Preto, SP, Brazil). The animals in the DT, HPT+DT, DT+ITM, and HPT+DT+ITM groups were subjected to extrusive dislocation–type dentoalveolar trauma on the maxillary right first molar, which was performed by the same operator. The animals were positioned in the dorsal decubitus position on the operating table, and the oral cavity was held open by a device. To perform the extrusive dislocation, a 0.25-mm ligature wire (Morelli®; Sorocaba, São Paulo, Brazil) was inserted in the buccal-palatal direction between the maxillary first and second molars. The two ends of the wire were placed on the mesial surface of the maxillary first molar and twisted with the aid of a 17.0-cm Mathieu needle holder (Quinelato; Rio Claro, São Paulo, Brazil) for fixation of the wire around the tooth. A loop-shaped bend was made at the distal

end of the inserted wire to fit the tensiometer (Morelli®; Sorocaba, São Paulo, Brazil). The tensiometer was positioned on the handle at an angle of 60°, and a traction force of 1500 cN was applied for 15 seconds. After trauma induction, the ligature wire was removed (Figure 1).

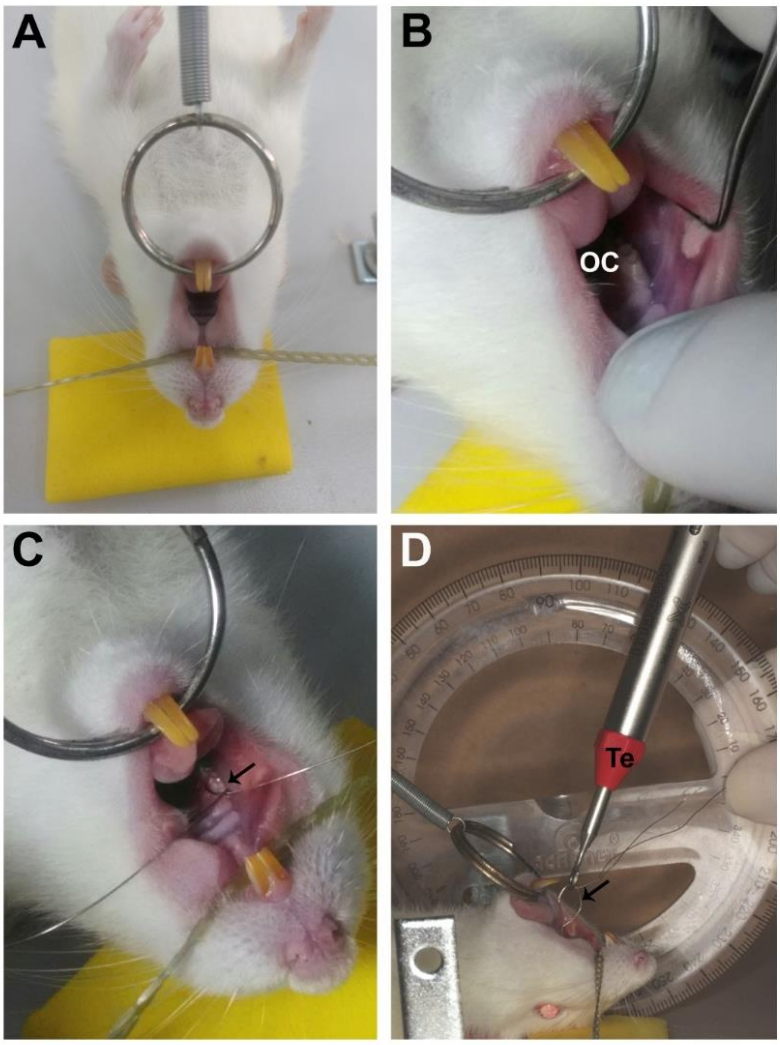

Figure 1. Photographs of the application of extrusive luxation. A. Positioning the animal in the supine position on the operating table. B. Opening of the animal's oral cavity (OC). C. Ligature wire inserted between the upper right first and second molars (arrow). D. Tensiometer (Te) positioned on the ligature loop (arrow) and traction at an 60° angle.

2.6 Installation of the device for induced tooth movement

At 97 days, the induced tooth movement device was installed in the animals of the ITM, DT+ITM, HPT+ITM, and HPT+DT+ITM groups. The device used in this study was similar to that proposed by Hller & Nanda (1979) [17], Pasa et al. (2024) [18]. The modified device consisted of a closed-section

nickel-titanium spring (Morelli®; Sorocaba, São Paulo, Brazil). The magnitude of the spring force (50 cN) was assessed using a Zeusan tensiometer (Zeusan Exporting Ltda. Campinas, SP, Brazil). Two segments of ligature wire with a thickness of 0.25 mm (Morelli, Sorocaba, SP, Brazil) connected to each end of the spring were used to install the device, one segment surrounding the upper right first molar and the other connecting the upper central incisor of the animal. To stabilize the ligature wire on the buccal surface of the incisor, a slot was made in the cervical region of the tooth, and the wire was affixed with light-curing composite resin (Filtek ™ Z350XT, 3M Company, St. Paul, MN, USA). The tooth movement period was 7 days (Figure F2).

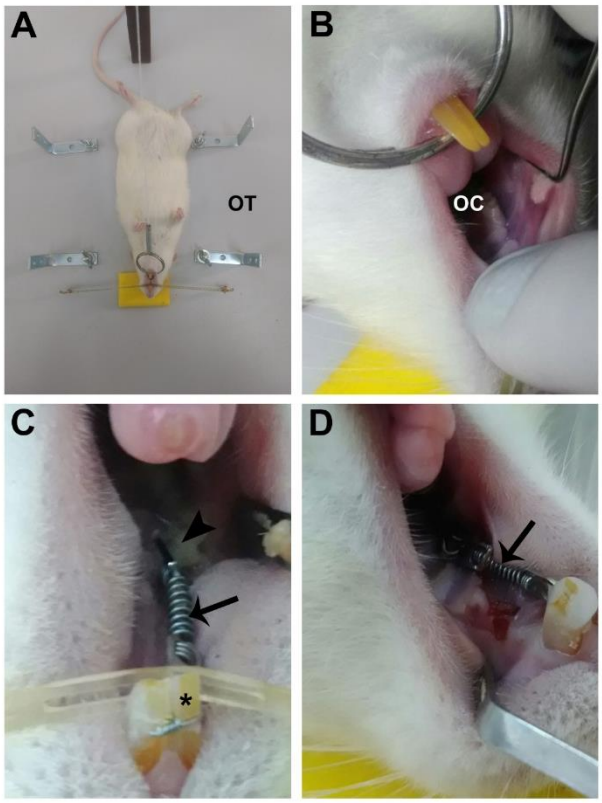

Figure 2. Photographs of the sequence of the ITM device installation. A. Positioning the animal in dorsal decubitus on the operating table (OT); B. Open oral cavity (OC); C and D. Nickel-titanium spring (arrow) with the ends connected to two segments of ligature wire, one surrounding the upper right first molar (arrowhead) and the other segment the upper right incisor (*) of the animal.

2.7 Euthanasia and collection of biological material

At the end of the experimental period (approximately 104 days), all animals were sacrificed in a CO_2 chamber with subsequent decapitation. Blood samples from the cervical region were collected, and plasma was obtained by centrifugation at 1,200g for 15 min and stored in a freezer at -80°C for analysis

of the concentrations of T3, T4, and TSH. The right hemimaxillae were removed and fixed in 10% buffered formalin for 24 hours, washed under running water for 48 hours, decalcified in Allkimia® decalcifying acid solution (Campinas, SP, Brazil) for 19 hours, and stored in 70° alcohol.

2.8 Hormonal analysis

Plasma concentrations of T3, T4, and TSH in females were obtained using a commercial enzyme-linked immunosorbent assay kit (USCN Life Science Inc. Houston, TX, USA). Each sample was measured in duplicate. No cross-reactivity or significant interference was observed.

2.9 Quantitative analysis of tooth movement

Immediately after euthanasia, the amount of tooth movement was calculated as the difference between the distances from the mesial surface of the maxillary 1st molar to the distal surface of the maxillary 3rd molar on the moved right side and the nonmoved left side, methodology proposed by [18,19]. The measurements were obtained using a digital caliper (Mitutoyo, São Paulo, Brazil).

2.10 Laboratory processing

After decalcification, the specimens were dehydrated in an increasing series of alcohol, cleared in xylene, and embedded in Paraplast Plus (Sigma-Aldrich, St. Louis, MO, USA). For the histological analyses, serial sections were performed in the transverse and longitudinal planes of the mesiobuccal and distobuccal roots of the maxillary right first molar, from mesial to distal, with 5 µm thickness, using a manual rotating microtome (Olympus 4060, Tokyo, Japan) equipped with a steel razor. The sections obtained were deparaffinized with xylene, hydrated with distilled water, and stained with hematoxylin and eosin.

A light microscope (Olympus BX60, Tokyo, Japan) was used for histological analysis. Photomicrographs were taken with an Olympus DP71 digital camera with DP Controller 3.2.1.276 software.

2.11 Histopathological analysis

The specific areas of the descriptive analysis were 1) periodontal ligament of the mesiobuccal and distobuccal roots on the mesial and distal surfaces, cervical, middle and apical thirds; 2) periodontium of the furcation region; 3) mesial bone crest; 4) interradicular septum; and 5) interdental septum between the upper right first and second molars. The histopathological changes investigated were the organization of the periodontal ligament, external root resorption, areas of hyalinization, inflammatory infiltrate, presence of multinucleated giant cells, and presence of vascular changes. Each alteration was evaluated as follows: absence, occasional presence, moderate presence, or intense presence [15].

2.12 Histomorphometric analysis of external root resorption

For the quantitative analysis of external root resorption, the mesial surface of the distal root in its cervical and middle thirds was considered because this is the region most affected by compression of the periodontal ligament both in trauma from extrusive dislocation and in induced tooth movement. The photomicrographs at 400× magnification were analyzed using Image-Pro Plus 6.0 software (Media Cybernetics, Rockville, MD, USA), where the total area of each resorption was quantified in square micrometers (μm^2). Each measurement was performed three times and the mean of each set taken. When the root presented more than one area of external root resorption, the areas were added together to obtain the total area of resorption per animal [18].

2.13 Statistical analysis

Student's t test and one-way ANOVA with Tukey's posttest were used for data analysis. Differences were considered statistically significant when $p<0.05$. Statistical analyses were performed using SigmaPlot software, version 11.0 (Systat Software Inc., San Jose, CA, USA).

3. RESULTS

3.1 Thyroid hormone concentrations

The animals that consumed PTU (0.05% diluted in their water) showed lower plasma concentrations of T3 and T4 and higher concentration of TSH than the control group (P<0.05) (Table 1).

Table 1 - Plasma concentrations of T3, T4, and TSH in the control and PTU-treated groups.

GROUP	T3 (ng/mL)	T4 (µg/dL)	TSH (µlU/L)
Control group (drinking water)	126.90±1.91	229.86±1.29	1105.36±12.25
Treated group (0.05% PTU diluted in water)	69.18±0.99*	172.37±1.23*	1485.50±18.16*

Data are expressed as mean ± standard error. N=20 animals/group. Student's t test. (*) indicates significant differences from the control group (P<0.05).

3.2 Analysis of tooth movement

The tooth movement rate was significantly higher in the animals of the HPT+DT+ITM group than the other groups (p<0.05). The HPT+ITM group showed greater tooth movement than the ITM and DT+ITM groups (p<0.05). There was no significant difference in the movement rate between the ITM and DT+ITM groups (Table 2).

Table 2 - Tooth movement rate in the different experimental groups subjected to induced tooth movement (ITM).

PARAMETER	ITM	HPT+ITM	DT+ITM	HPT+DT+ITM
Tooth movement rate (mm)	0.22 ±0.02[a]	0.33±0.03[b]	0.24±0.02[a]	0.48±0.03[c]

Values are expressed as mean ± standard error. N= 6 animals/group. Analysis of variance (one-way ANOVA) with Tukey's posttest. Values followed by different letters [a, b,] and [c] indicate significant differences between groups (*P*<0.05).

3.3 Morphometric analysis of external root resorption

Among the animals in the groups without the tooth movement device, the HPT group had the smallest areas of root resorption when compared to the CTL, DT, and HPT+DT groups ($p<0.05$) (Table 3). In the analysis of the groups with tooth movement devices, the HPT+ITM group had a smaller root resorption area than the other groups with tooth movement devices ($p<0.05$). There were no significant differences in root resorption areas in the comparison between the ITM and DT+ITM groups; however, both had greater root resorption areas when compared to the HPT+ITM group ($p<0.05$). The animals in the HPT, DT+ITM and HPT+DT+ITM groups showed larger root resorption areas than all the groups without the tooth movement device ($p<0.05$), and the HPT+DT+ITM group showed the largest amounts of root resorption areas when compared to all experimental groups ($p<0.001$) (Table 3).

Table3 - Area of external root resorption in the different experimental groups.

PARAMETER	CTL	HPT	DT	HPT+DT	ITM	HPT+ITM	DT+ITM	HPT+ DT+ITM
Area of external root resorption (μm^2)	1650,74 ±165,01[a]	883,81 ±161,36[b]	1838,89 ±276,10[a]	1604,16 ±89,11[a]	4333,67 ±1251,58[c]	2037,55 ±300,32[a]	5344,11 ±748,00[c]	8413,51 ±1489,19[d]

Values are expressed as the mean ± standard error. N= 6 animals/group. Analysis of variance (one-way ANOVA) with Tukey's posttest. Similarly, values followed by different letters [a, b, c, and d] indicate significant differences between groups (*P*<0.05).

3.4 Histopathological analysis of periodontal tissue

In the CTL group, the periodontal ligament was normal. It was rich in fibroblasts and collagen fibers, which were obliquely arranged in the cervical third, horizontally in the middle third, and disorderedly in the root apex and furcation regions. The root surfaces, including cementum, were continuous in most sections. The interradicular and interdental septa between the maxillary right first and second molars were intact (Figure 3A).

Animals in the DT, HPT+DT, ITM, HPT+ITM, and DT+ITM groups exhibited occasional periodontal ligament disorganization, and the HPT+DT+ITM group exhibited moderate disorganization (Figure 3B). In the evaluation of hyaline areas, the groups that underwent DT and/or ITM (DT, HPT+DT, ITM, DT+ITM, HPT+ITM, and HPT+DT+ITM) showed a moderate abundance of hyaline areas. Hyalinization was predominant on the distal surface of the cervical and apical regions of the distal root of the maxillary right first molar (Figure 3B and E).

Regarding vascular changes in the periodontal ligament, the presence of giant cells, hyperemia, and blood leakage were observed in the ITM, DT+ITM, HPT+ITM, and HPT+DT+ITM groups (Figures 3D and E). The presence of moderate inflammatory infiltrate in the cervical region of the distal root and furcation was observed in the animals of the groups that suffered DT and/or ITM (DT, HPT+DT, ITM, DT+ITM, HPT+ITM and HPT+DT+ITM) (Figures 3C and F).

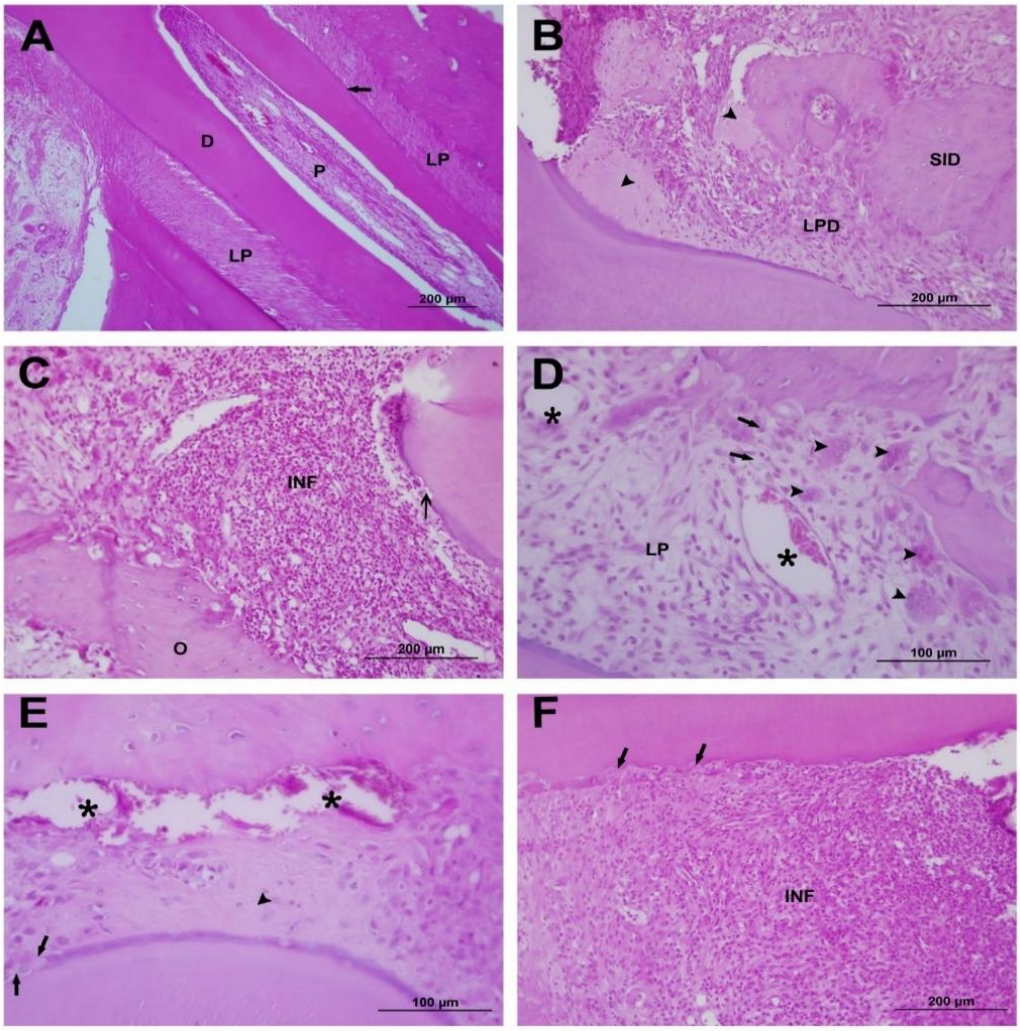

Figure 3. Photomicrograph of the dental and periodontal structure of animals from the different experimental groups. A. Periodontal tissues and dental structure with normal appearance. Periodontal ligament (LP), cementum (arrow), dentin (D), pulp tissue (P); B. Disorganized periodontal ligament (LPD), bone, interdental septum (SID), hyaline areas (arrowhead); C. Periodontal ligament with inflammatory infiltrate (INF), bone of the interdental septum (O), areas of external root resorption (arrow); D. Disorganized periodontal ligament (LP), hyperemia (*), multinucleated giant cells (arrowhead); E. Hyperemia (*), hyaline areas (arrowhead), areas of root resorption (arrows); F. Inflammatory infiltrate in the periodontal ligament (INF), areas of root resorption (arrow). Stain = Hematoxylin and Eosin

4. DISCUSSION

Alveolar bone remodeling and changes in the periodontal ligament are the foundations of orthodontic movement [20]. One of the most common complications of orthodontic treatment is root resorption [21, 22,23]. In this context, the goal of orthodontics is to perform the treatment with the highest speed of tooth movement possible along with the least root damage [24]. Thyroid hormones play a crucial role in bone development and maintenance [25]. Administration of thyroid hormones in rats increases the speed of tooth movement and reduces the occurrence of root resorption [26]. In the present study, the rats with hypothyroidism showed a significant decrease in serum T3 and T4 levels and an increase in TSH, which demonstrated a successful induction of experimental hypothyroidism [27].

The tooth movement rate was significantly higher in animals from the hypothyroid, trauma, and movement groups (HPT+DT+ITM and HPT+ITM) than in the other groups. Thyroid hormones directly stimulate bone apposition by binding to osteoblast receptors or indirectly, mediated by growth hormone and insulin-like growth factor I (IGF-I) [28, 29]. The T3 hormone stimulates the production of IGF-I, which in turn has an anabolic effect on bone tissues. T3 influences the action of IGF-I and consequently bone metabolism [28]. Thus, it is understood that hypothyroidism causes the opposite effects, reducing general metabolism, decreasing bone mineralization, and favoring induced tooth movement, as found in our study [30].

Except for the HPT+DT+ITM group, all the groups with hypothyroidism had smaller root resorption areas than the groups without hypothyroidism. Thyroid hormones are related to increased bone resorption due to their association with prostaglandins that act on osteoclasts, increasing intracellular concentrations of cyclic AMP and increasing its resorption activity, while prostaglandin E2 stimulates osteoblast differentiation and expression of receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) [24]. An increase in RANKL and macrophage colony-stimulating factor and a decrease in OPG release by osteoblasts favor resorption [31]. The mechanisms of bone resorption and orthodontically induced root resorption are similar, as they both correlate with high concentrations of the RANKL and reduced concentrations of OPG in the periodontal ligament [31,32].

At low concentrations, thyroid hormones have a protective effect on the root surface and reduce resorption [24]. Along these lines, the studies conducted by [25, 26] demonstrated that the administration

of low doses of thyroid hormone in rats reduces the extent of root resorption. In line with the results of our study, the HPT group had lower root resorption values than all groups without a tooth movement device.

The animals in the ITM, DT+ITM, and HPT+DT+ITM groups presented larger root resorption areas than all the groups with and without a tooth movement device ($p<0.05$). Orthodontic tooth movement combines the physiological process of adaptation of the alveolar bone with mechanical stresses that induce reversible lesions in the periodontium. The classical pressure–strain theory proposes that chemical molecules generate the stimulus for cell differentiation, resulting in tooth movement [31]. If a force is maintained on the compression side, blood flow will be altered, and regional hypoxia will develop. The reduction in oxygen stabilizes hypoxia-inducible factor 1, a status responsible for activating endothelial growth factor and the expression of RANK-L in fibroblasts of the periodontal ligament and osteoclasts, favoring resorption in areas of compression [31, 32].

The groups that underwent DT and/or ITM had higher rates of inflammatory infiltrate and blood extravasation, especially in the regions of the distal root, the site most affected by both DT and ITM induction [16]. In turn, the formation of hyaline areas, although undesirable in the induced tooth movement, was expected because the force applied to the ITM compressed the LP blood vessels, causing hypoxia and forming hyaline areas, which can be understood as exacerbated inflammation that results in damage to the structural components of the pulp tissue with transformation of intra- and extracellular proteins into homogeneous, vitreous, pink material [33].

5. CONCLUSION

In conclusion, the hypothyroidism associated with dental trauma causes increase in the rate of tooth movement and greater occurrence external root resorption during orthodontic movement in female rats molars.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was in accordance with the Ethical Principles in Animal Experimentation adopted by the Brazilian College of Animal Experimentation (COBEA) and were approved by the Committee on Ethics in the Use of Animals (CEUA) of UNIOESTE.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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