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Systematic Review

Effects of systemic medication on root resorption associated with orthodontic tooth movement: a systematic review of animal studies

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Summary

Background: Theoretically, root resorption could be modulated by any medication taken that exhibits possible effects on the implicated molecular pathways.
Objectives: To systematically investigate and appraise the quality of the available evidence from animal studies, regarding the effect of commonly prescribed systemic medication on root resorption associated with orthodontic tooth movement.
Search methods: Search without restrictions in eight databases (PubMed, Central, Cochrane Database of Systematic Reviews, SCOPUS, Web of Science, Arab World Research Source, ClinicalTrials.gov, ProQuest Dissertations and Theses Global) and hand searching until April 2018 took place. One author developed detailed search strategies for each database that were based on the PubMed strategy and adapted accordingly.
Selection criteria: Controlled studies investigating the effect of systemic medications on root resorption associated with orthodontic tooth movement.
Data collection and analysis: Following study retrieval and selection, relevant data were extracted and the risk of bias was assessed using the SYRCLE's Risk of Bias Tool.
Results: Twenty-one studies were finally identified, most of which at unclear risk of bias. Root resorption was shown to increase in Vitamin C treated animals in comparison with the control group, whereas a comparative decrease was noted after the administration of the alendronate, ibuprofen, growth hormone, low doses of meloxicam, simvastatin, lithium chloride and strontium ranelate. No difference was noted for acetaminophen, aspirin, fluoxetine, atorvastatin, misoprostol, zoledronic acid and zinc. Finally, inconsistent effects were observed after the administration of celecoxib, prednisolone and L-thyroxine. The quality of the available evidence was considered at best as low.
Conclusions: The pharmaceutical substances investigated were shown to exhibit variable effects on root resorption. Although the overall quality of evidence provides the clinician with a cautious perspective on the strength of the relevant recommendations, good practice would suggest that it is important to identify patients consuming medications and consider the possible implications.
Registration: PROSPERO (CRD42017078208)

Introduction

Root resorption associated with orthodontic tooth movement has been considered to result from a combination of patient-related factors pertaining to individual biologic variability and genetic predisposition, as well as the effect of various parameters relevant to treatment mechanics (1). As a condition involving non-physiologic resorptive activity on the cementum and, in severe situations, the underlying dentin, it entangles various complicated autocrine and paracrine molecular pathways modulating the activation, not only of the periodontal ligament and bone marrow–derived mononuclear precursor cells committed to odontoclast differentiation, but also of macrophages and mesenchymal dental pulp cells (2–5). Recently described molecular mechanisms include the expression of pro-inflammatory molecules, like tumor necrosis factor, inducible nitric oxide synthase and interferon γ, as well as, anti-resorptive signaling from interleukin 4, interleukin 10, and arginase I (4). Moreover, fusion and activation of clastic cells has been shown to be associated with the RANKL/RANK/OPG and ATP-P2RX7-IL1 molecular pathways (6,7), whereas odontoclast adhesion to the root surface to be connected to α/β integrins, osteopontin and extracellular matrix proteins (8–10). Theoretically, the abovementioned cascades of signals and events could be modulated by any medication taken that exhibits possible effects on molecular pathways responsible for dental and periodontal tissue homeostasis or the alterations encountered during orthodontic tooth movement and clastic cell regulation (2,11,12).

Since prescription medication use has recently expanded (13–15), it is important for the clinician to be able to identify medication consumption in prospective patients and relate them to possible effects associated with orthodontic intervention (16). Although prescription medicines are perceived to be consumed usually by adults, which comprise more than a quarter of the orthodontic population (17,18), their use has been increasing also in school-aged children (19,20). Furthermore, the use of over-the-counter medications continues to increase (21).

During the last years, the interrelationships between changes in the metabolic state and homeostasis of the bone and the administration of various substances during orthodontic tooth movement have been reviewed (22–26). However, most publications have not focused explicitly on the effects of prescription medication on root resorption associated with orthodontic tooth movement.

Objective

The objective of the present review was to systematically investigate and appraise the quality of the available evidence from animal studies, regarding the effect of prescription systemic medication on root resorption associated with orthodontic tooth movement.

Materials and methods

Protocol and registration

The present review was based on a protocol developed following the guidelines outlined in the PRISMA-P statement (27) (PROSPERO: CRD42017078208). Conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (28) and the PRISMA statement (29), respectively.

Eligibility criteria

The eligibility criteria were based on the PICOS (Participants, Intervention, Comparison, Outcomes, Study design) acronym. Potentially eligible trials should involve healthy animals under active orthodontic tooth movement for at least 2 weeks. The amount and extent of root resorption (investigated histomorphometrically, by scanning electron or 3D surface microscopy or radiographically) should be assessed after the systemic administration of human medications (30) and compared with a placebo or no intervention. Non-comparative studies and reviews were excluded (Supplementary Table 1).

Information sources and search strategy

Search without restrictions (on the language, date or status of publication) in eight databases and hand searching until April 2018 took place. One author (EGK) developed detailed search strategies for each database that were based on the PubMed strategy and adapted accordingly (Supplementary Table 2).

In addition, efforts to obtain additional studies were made and the reference lists in reviews, included or excluded studies, as well as other related articles were searched.

Study selection

Two authors (MAM and EGK) electronically assessed the retrieved records for inclusion independently, not being blind to the identity of the authors, their institution or the results of the research. The full-text of the records considered by either reviewer to meet the inclusion criteria were obtained and assessed, again independently, whereas consultation with the third author (AEA) resolved disagreements that could not be settled by discussion.

Data collection and data items

Data collection was performed by the same two authors in predetermined and pre-piloted data forms for the following: bibliographic; study design; verification of study eligibility; subject characteristics; mechanisms effecting orthodontic tooth movement; pharmaceutical intervention details; outcomes considered and methods of assessment and, finally, results. Any disagreements were again resolved by discussion or consultation with the third author.

Risk of bias in individual studies

The risk of bias in individual studies was assessed by MAM and EGK independently and in duplicate. The SYRCLE's risk of bias tool was used to assess the risk of bias (31). The risk of bias within a study was assessed in summary according to Higgins et al. (28). Any disagreements were resolved by discussion or consultation with the third author (AEA).

Summary measures and synthesis of results

If deemed possible, the random effects method for meta-analysis was to be used to combine data on root resorption (32,33). However, quantitative data synthesis was not carried out as planned, because of the lack of an adequate amount of data regarding each of the investigated substances, as well as, differences in the employed methods and the studied interventions (28).

Risk of bias across studies and additional analyses

If a sufficient number of studies were identified, analyses were planned for 'small-study effects' and publication bias (28). If deemed possible, exploratory subgroup analyses were planned according to intervention characteristics. In addition, the quality of evidence was assessed based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (34).

Results

Study selection

The flow of records through the reviewing process is shown in Figure 1. We initially identified 2835 references, excluded 1345 as duplicates and 1450 more on the basis of their title and abstract. From the 40 records that remained and were assessed for eligibility, 19 studies were excluded, because they involved substances administered locally, pathological conditions or less than five subjects per experimental group. Finally, 21 full-text study reports performed on animal subjects were identified (35–55).

Study characteristics

The general characteristics of the studies are presented in Table 1. Orthodontic tooth movement was usually induced by placing coil springs between incisors and molars in rats. In addition, springs that exerted expansion forces on the incisors or the molars were employed. The force exerted by the appliances varied from 10 to 80 g and force application from 2 weeks to 24 days.

The retrieved papers included the study of active substances from the following therapeutic categories (30): analgesics (38,40–42,44); antibiotics (36); antidepressants (50,51); antihyperlipidemic agents (39,49); bisphosphonates (37,44); hormones (36,41,43,54); minerals and electrolytes (35,45,46,55); prostaglandin analogues (53); and vitamins (48). Medication administration continued for 60 days at maximum. Oral administration was employed in the majority of studies. However, other studies used intraperitoneal (37,39,40,45,51,52) and subcutaneous administration (43,44,54), gastric lavage (53) or mini-osmotic pumps (36).

Most of the included studies assessed root resorption histomorphometrically, with the exception of those of Wang et al. (55) and Hu et al. (43) that assessed root resorption after micro-CT scanning. Baysal et al. (36), Gonzales et al. (41) and Ino-Kondo et al. (45) used scanning electron microscopy that was complemented in the latter two papers by three-dimensional laser scanning.

Risk of bias within studies

Table 2 presents the summary findings of the risk of bias assessment for the included studies. Most studies were considered as being of unclear risk of bias and only two of low (42,47). In general, most studies included were considered to present unclear risk of bias regarding the domains of random sequence generation, allocation concealment and blinding of the outcome assessors because of insufficient information to form a definite judgement on the risk of bias. Nevertheless, the majority of them used groups similar at baseline, in respect to gender, age and weight of the subjects and consequently were found to be of low risk of bias in the respective domain. There was no information regarding whether animals were randomly housed, as well as whether caregivers and investigators were blinded on the intervention each animal received, resulting in an unclear risk

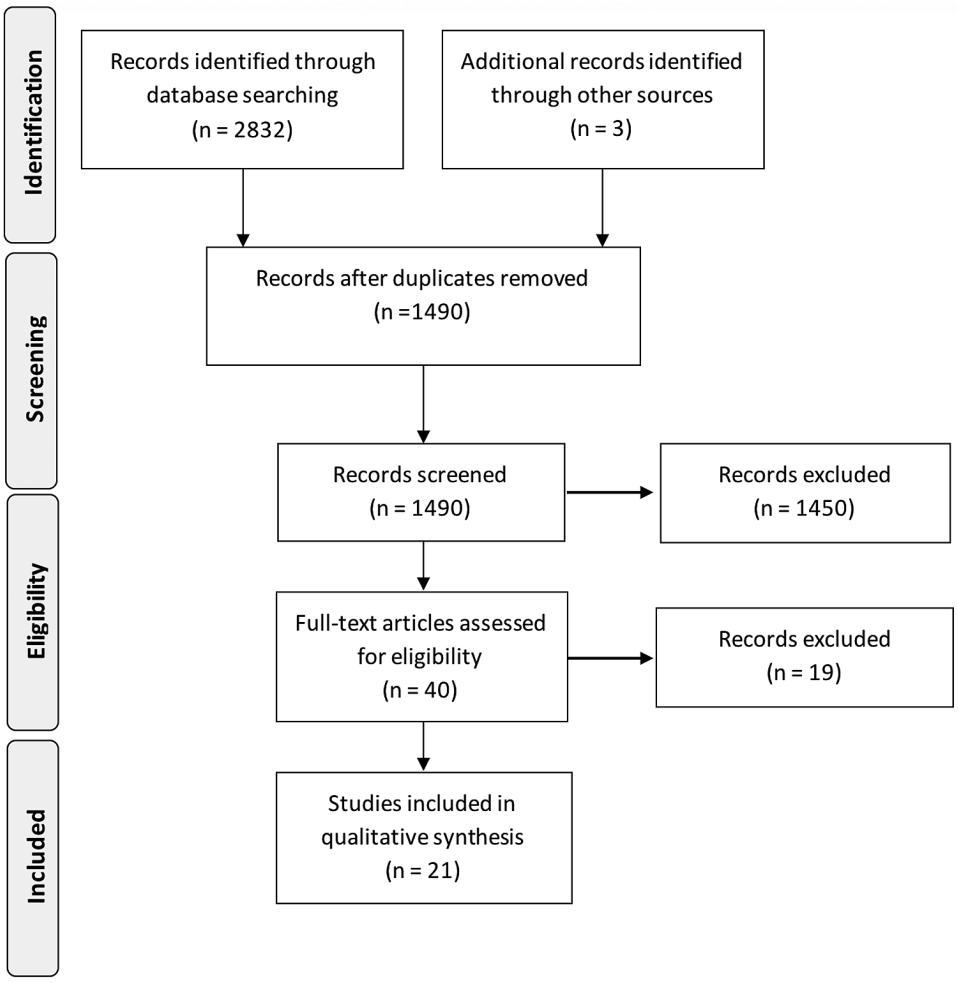

Figure 1. Flow of records through the reviewing process.

Table 1. Characteristics of the studies included in the systematic review.

Therapeutic category [active substance and study]	Subjects and tooth movement model [species; gender; age; weight]	Group characteristics [no; substance; dosage; route; administration]	Methodology [area of assessment]	Resorption measurements [definition]	Results*
Analgesics Acetaminophen Gonzales et al. (41)	Wistar rats; male; 10 w; 230–250 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG_1:** 5; acetaminophen [20 mg/kg]; PO; daily in water **EG_2:** 5; acetaminophen [100 mg/kg]; PO; daily in water **CG:** 5 **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial cerv/mid third M, DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]* Depth of lacunae [µm] Volume of lacunae [10^6 µm^3] *[area × average depth]* Roughness of lacunae [µm] *[average (resolution 0.01 µm)]*	[20 mg/kg] M: n; DB: n; DP: n [100 mg/kg] M: n; DB: n; DP: n [20 mg/kg] M: n; DB: n; DP: n [100 mg/kg] M: n; DB: n; DP: n [20 mg/kg] M: n; DB: n; DP: n [100 mg/kg] M: n; DB: n; DP: n [20 mg/kg] M: n; DB: n; DP: n [100 mg/kg] M: n; DB: n; DP: n
Analgesics Aspirin Gonzales et al. (41)	Wistar rats; male; 10 w; 230–250 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG_1:** 5; aspirin [60 mg/kg]; PO; daily in water **EG_2:** 5; aspirin [300 mg/kg]; PO; daily in water **CG:** 5 **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial cerv/mid third M, DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]* Depth of lacunae [µm] Volume of lacunae [10^6 µm^3] *[area × average depth]* Roughness of lacunae [µm] *[average (resolution 0.01 µm)]*	[60 mg/kg] M: n; DB: n; DP: n [300 mg/kg] M: n; DB: n; DP: n [60 mg/kg] M: n; DB: n; DP: n [300 mg/kg] M: n; DB: n; DP: n [60 mg/kg] M: n; DB: n; DP: n [300 mg/kg] M: n; DB: n; DP: n [60 mg/kg] M: n; DB: n; DP: n [300 mg/kg] M: n; DB: n; DP: n
Analgesics Celecoxib Brunson (38)	Wistar rats; female; 7 w; 105–115 g NiTi CCS: Mx Is to left FM [80 g] **Force application:** 2 w	**EG_1:** 5; celecoxib [40 mg/kg]; PO; daily in water **EG_2:** 7; celecoxib [80 mg/kg]; PO; daily in water **CG:** 14 **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin or Mallory M and D roots	Root resorption area [mm^2]	[40 mg/kg] T: ↓ [80 mg/kg] T: ↓
Analgesics Celecoxib Gameiro et al. (40)	Wistar rats; male; 3.5 m; 350 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG:** 7; celecoxib [10 mg/kg at 1 ml/kg ns]; IP; 1 daily **PG:** 7; 1 ml/kg ns; IP; 1 daily **Sample size calculation:** No **Medication administration:** 2 w[§]	**Histomorphometry** Hematoxylin; grid Disto-apical aspect M root	Root resorption ratio [%] *[lacunae grids / total grids]*	[10 mg/kg] M: n
Analgesics Celecoxib Gonzales et al. (41)	Wistar rats; male; 10 w; 230–250 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG_1:** 5; celecoxib [3.2 mg/kg]; PO; daily in water **EG_2:** 5; celecoxib [16 mg/kg]; PO; daily in water **CG:** 5 **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial cerv/mid third M, DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]* Depth of lacunae [µm] Volume of lacunae [10^6 µm^3] *[area × average depth]* Roughness of lacunae [µm] *[average (resolution 0.01 µm)]*	[3.2 mg/kg] M: n; DB: n; DP: n [16 mg/kg] M: n; **DB:** ↓; **DP:** ↓ [3.2 mg/kg] M: n; DB: n; DP: n [16 mg/kg] M: n; **DB:** ↓; **DP:** ↓ [3.2 mg/kg] M: n; DB: n; DP: n [16 mg/kg] **M:** ↓; **DB:** ↓; **DP:** ↓ [3.2 mg/kg] M: n; DB: n; DP: n [16 mg/kg] **M:** ↓; DB: n; DP: n

Table 1. Continued

Therapeutic category [active substance and study]	Subjects and tooth movement model [species; gender; age; weight]	Group characteristics [no; substance; dosage; route; administration]	Methodology [area of assessment]	Resorption measurements [definition]	Results*
Analgesics Celecoxib Hashemi et al. (42)	Wistar rats; male; 4 m; 220 ± 30 g NiTi CCS: Mx I to right FM [60 g] **Force application:** 2 w	**EG_1:** 8; celecoxib [25 mg/kg]; PO; specific times daily **EG_2:** 8; celecoxib [50 mg/kg]; PO; specific times daily **EG_3:** 8; celecoxib [100 mg/kg]; PO; specific times daily **CG:** 8 **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin Mesial and distal surface M root	Number of lacunae	[25 mg/kg] M: n [50 mg/kg] M: n [100 mg/kg] M: n
Analgesics Ibuprofen Brunson (38)	Wistar rats; female; 7 w; 105–115 g NiTi CCS: Mx Is to left FM [80 g] **Force application:** 2 w	**EG_1:** 10; ibuprofen [25 mg/kg]; PO; daily in water **EG_2:** 9; ibuprofen [50 mg/kg]; PO; daily in water **CG:** 14 **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin or Mallory M, DB, DP roots	Root resorption area [mm^2]	[25 mg/kg] Total: ↓ [50 mg/kg] Total: ↓
Analgesics Meloxicam Gonzales et al. (41)	Wistar rats; male; 10 w; 230–250 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG_1:** 5; meloxicam [13 mg/kg]; PO; daily in water **EG_2:** 5; meloxicam [67 mg/kg]; PO; daily in water **CG:** 5 **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial cerv/mid third M, DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]* Depth of lacunae [µm] Volume of lacunae [10^6 $µm^3$] *[area × average depth]* Roughness of lacunae [µm] *[average (resolution 0.01 µm)]*	[13 mg/kg] M: n; DB: n; DP: n [67 mg/kg] M: n; DB: n; DP: n [13 mg/kg] M: n; DB: n; DP: n [67 mg/kg] M: n; DB: n; DP: n [13 mg/kg] M: n; DB: n; DP: n [67 mg/kg] M: n; DB: n; DP: n [13 mg/kg] M: n; DB: n; DP: n [67 mg/kg] M: n; DB: n; DP: n
Analgesics Meloxicam Kirschneck et al. (47)	Fischer-344 rats; male;6 w; 264 ± 11 g NiTi CCS: Mx Is to left Ms [0.25 N] **Force application:** 10 d +2 w	**EG:** 7; meloxicam [3 mg/kg in PBS]; PO; 1 daily **PG:** 7; PBS; PO; 1 daily for 24 d **Sample size calculation:** Corresponding to other studies **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin DB root SecM	Root resorption ratio [%] *[lacunae area / root area]*	[3 mg/kg] **DB SecM:** ↓
Antibiotics Doxycycline Baysal et al. (36)	Wistar rats; male; 50–60 d; 132.5 ± 12.6 g Elgiloy CCS: Mx Is to FM [50 g] **Force application:** 2 w	**EG:** 7; Doxycycline [1.2 mg/kg/day]; mini-osmotic pumps **PG:** 7; serum; mini-osmotic pump **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin MB root	Root resorption ratio [%] *[lacunae area / root area]*	[1.2 mg/kg] **MB:** ↓
Antidepressants Fluoxetine Mirhashemi et al. (50)	Wistar rats; male; 200-250 g NiTi CCS: Mx left I to FM [60 g] **Force application:** 3 w	**EG:** 15; fluoxetine [10 mg/kg at 1 ml ns]; 1 daily for 21 d **PG:** 15; 1 ml ns; 1 daily for 21 d **Sample size calculation:** No **Medication administration:** 3 w	**Histomorphometry** Hematoxylin-eosin M root	Depth of lacunae [µm] Width of lacunae [µm]	[10 mg/kg] M: n [10 mg/kg] M: n

Table 1. Continued

Therapeutic category [active substance and study]	Subjects and tooth movement model [species; gender; age; weight]	Group characteristics [no; substance; dosage; route; administration]	Methodology [area of assessment]	Resorption measurements [definition]	Results*
Antidepressants Fluoxetine Rafiei et al. (51)	rats; male; 8-10 w NiTi CCS: Mx left I to FM [50 g] **Force application:** 3 w	**EG:** 15; fluoxetine [10 mg/kg]; IP; 5 d/w **PG:** 15; ns; IP; 5 d/w **Sample size calculation:** Yes **Medication administration:** 7 w	**Histomorphometry** Trichrome Masson MB root	Root resorption ratio [%] *[lacunae area / root area]* Number of lacunae	[10 mg/kg] MB: n [10 mg/kg] MB: n
Antihyperlipidemic agents Atorvastatin MirHashemi et al. (49)	Sprague-Dawley rats; male; adult; 220 ± 20 g NiTi CCS: Mx Is to left FM [60 g] **Force application:** 3 w	**EG:** 12; atorvastatin [5 mg/kg in CMC vehicle]; PO; 1 daily **PG:**12; CMC vehicle; PO; 1 daily **Sample size calculation:** No **Medication administration:** 3 w	**Histomorphometry** Hematoxylin-eosin MB root	Depth of lacunae [μm] Width of lacunae [μm]	[5 mg/kg] MB: n [5 mg/kg] MB: n
Antihyperlipidemic agents Simvastatin Esfahani et al. (39)	rats; male; 8–10 w; 200–250 g NiTi CCS: Mx I to FM [0.5 N ≈ 50 g] **Force application:** 17 d	**EG:** 16; simvastatin [2.5 mg/kg in 1 ml ns]; IP; 1 daily **PG:** 16; 1 ml ns; IP; 1 daily **Sample size calculation:** No **Medication administration:** 17 d	**Histomorphometry** Hematoxylin-eosin MB root	Root resorption ratio [%] *[lacunae area / root area]* Number of lacunae	[2.5 mg/kg] **MB:** ↓ [2.5 mg/kg] **MB:** ↓
Bisphosphonates Alendronate Igarashi et al. (44)	Wistar rats; male; 9–10 w; 217 g [average] Expansion spring left and right FM [16.8 ± 2.4 g] **Force application:** 3 w	**EG:** 6; Alendronate [0.5 mg P/kg]; SC; every other day **PG:** 6; 0.9% NaCl; SC; every other day **Sample size calculation:** No **Medication administration:** 3 w	**Histomorphometry** Hematoxylin-eosin MB root pressure side	Number of lacunae Surface per lacuna [μm^2]	[0.5 mg P/kg] **MB:** ↓ [0.5 mg P/kg] **MB:** ↓
Bisphosphonates Zoledronic acid Brunet et al. (37)	Wistar rats; male; 9 w; 300–350 g NiTi CCS: Mx right I to right FM [30 cN] **Force application:** 2 w	**EG:** 30; Zoledronic acid [0.1 mg/kg]; IP; once 1 w before movement **CG:** 30; no drug **Sample size calculation:** No **Medication administration:** 1 w before movement	**Histomorphometry** Hematoxylin-eosin MB root	Root resorption [+/–]	[0.1 mg /kg] MB: n
Hormones rHGH Hu et al. (43)	Wistar rats; male; 7 w; 215 ± 16 g NiTi CCS: Mx Is to right FM [50 g] **Force application:** 2 w	**EG:** 20; rHGH [2 mg/kg/d]; SC; twice daily **CG:** 20; equivalent voluems of saline; SC; twice daily **Sample size calculation:** No **Medication administration:** 2 w	**Micro-CT** DB root	Root resorption ratio [%] *[lacunae area / root area]*	[2 mg/kg/d] DB: ↓
Hormones L-Thyroxine Baysal et al. (36)	Wistar rats; male; 50–60 d; 132.53 ± 12.65 g Elgiloy CCS: Mx Is to FM [50 g] **Force application:** 2 w	**EG:** 7; L-thyroxine [0.02 mg/kg/day]; mini-osmotic pumps **PG:** 7; serum; mini-osmotic pump **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin MB root	Root resorption ratio [%] *[lacunae area / root area]*	[0.02 mg/kg] **MB:** ↓

Table 1. Continued

Therapeutic category [active substance and study]	Subjects and tooth movement model [species; gender; age; weight]	Group characteristics [no; substance; dosage; route; administration]	Methodology [area of assessment]	Resorption measurements [definition]	Results*
Hormones L-Thyroxine Seifi et al. (52)	Wistar rats; male; 6–8 w; 230–300 g NiTi CCS: Mx right I to FM [60 g] **Force application:** 3 w	**EG:** 8; L-thyroxine [0.02 mg /kg]; IP; 1 d/w **PG:** 8; 0.1 ml distilled water SM right FM **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin M root	Root resorption area [mm^2]	[0.02 mg/kg] M: n
Hormones Prednisolone Gonzales et al. (41)	Wistar rats; male; 10 w; 230–250 g NiTi CCS: Mx Is to left FM [50 g] **Force application:** 2 w	**EG_1:** 5; prednisolone [0.13 mg/kg]; PO; 1 daily **EG_2:** 5; prednisolone [0.67 mg/kg]; PO; 1 daily **CG:** 5 **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial cerv/mid third M, DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]* Depth of lacunae [µm] Volume of lacunae [10^6 $µm^3$] *[area × average depth]* Roughness of lacunae [µm] *[average (resolution 0.01 µm)]*	[0.13 mg/kg] M: n; DB: n; **DP:** ↓ [0.67 mg/kg] **M:** ↓; **DB:** ↓; **DP:** ↓ [0.13 mg/kg] M: n; **DB:** ↓; **DP:** ↓ [0.67 mg/kg] M: n; **DB:** ↓; **DP:** ↓ [0.13 mg/kg] M: n; **DB:** ↓; **DP:** ↓ [0.67 mg/kg] **M:** ↓; **DB:** ↓; **DP:** ↓ [0.13 mg/kg] M: n; **DB:** ↓; DP: n [0.67 mg/kg] M: n; **DB:** ↓; **DP:** ↓
Hormones Prednisolone Verna et al. (54)	Wistar rats; male; 6 m; 350–500 g NiTi CCS: Mx Is to left FM [25 g] **Force application:** 3 w	**EG_1:** 23; prednisolone [8 mg/kg]; SC; 1 daily **EG_2:** 22; prednisolone [8 mg/kg]; SC; 1 daily **CG:** 19 **Sample size calculation:** No **Medication administration:** EG_1 3 w; EG_2 7 w	**Histomorphometry** Goldner trichrome; grid M root	Root resorption ratio [%] *[intersections hitting resorption / intersections hitting the root]*	[8 mg/kg; 3 w] **M cor:** ↑ [8 mg/kg; 3 w] M apic: n [8 mg/kg; 7 w] M cor: n [8 mg/kg; 7 w] M apic: n
Minerals and electrolytes Calcium gluconate Seifi et al. (52)	Wistar rats; male; 6–8 w; 230–300 g NiTi CCS: Mx right I to FM [60 g] **Force application:** 3 w	**EG:** 8; Ca [200 mg/kg]; IP; 1 d/w **PG:** 8; 0.1 ml distilled water SM right FM **Sample size calculation:** No **Medication administration:** 2 w	**Histomorphometry** Hematoxylin-eosin M root	Root resorption area [mm^2]	[200 mg/kg] M: n
Minerals and electrolytes Lithium chloride Wang et al. (55)	Sprague-Dawley rats; male; 8 w; 200 ± 10 g NiTi CCS: Mx I to FM [50 g] **Force application:** 2 w	**EG:** 5; LiCl [200 mg/kg in gavage]; PO; every 2 d **CG:** 5; standard chow **Sample size calculation:** No **Medication administration:** 2 w	**SEM** Mesial surfaces DB, DP roots	Root resorption ratio [%] *[lacunae area / root area]*	[200 mg/kg] **DB, BP:** ↓
Minerals and electrolytes Lithium chloride Ino-Kondo et al. (45)	Sprague-Dawley rats; female; 10 w; 194–234 g NiTi CCS: Mx Is to left FM [10 cN] **Force application:** 2 w	**EG_1:** 8; LiCl [0.32 mM/kg]; IP; daily **EG_2:** 8; LiCl [0.64 mM/kg]; IP; daily **EG_3:** 8; LiCl [1.28 mM/kg]; IP; daily **CG:** 8; ns; IP; daily **Sample size calculation:** No **Medication administration:** 2 w	**SEM; LSM** Mesial surfaces M, DB, DP roots	Resorption area [10^4 $µm^2$] Resorption depth [µm] Resorption volume [10^7 $µm^3$]	[0.32 mM/kg] Total: **n** [0.64 mM/kg] Total: ↓ [1.28 mM/kg] Total: ↓ [0.32 mM/kg] Total: **n** [0.64 mM/kg] Total: **n** [1.28 mM/kg] Total: ↓ [0.32 mM/kg] Total: **n** [0.64 mM/kg] Total: ↓ [1.28 mM/kg] Total: ↓

Table 1. Continued

Therapeutic category [active substance and study]	Subjects and tooth movement model [species; gender; age; weight]	Group characteristics [no; substance; dosage; route; administration]	Methodology [area of assessment]	Resorption measurements [definition]	Results*
Minerals and electrolytes Strontium ranelate Kirschneck et al. (46)	Wistar rats; male; 40 d; 196 g average NiTi CCS: Mx Is to left FM [0.25 N ≈ 25 g] **Force application:** 4 w	**EG:** 24; Sr ranelate [900 mg/kg][§§]; PO; 1 daily **CG:** 24; 1.5 ml ns in gavage; PO **Sample size calculation:** No **Medication administration:** 7 w	**Histomorphometry** TRAP-hematoxylin MB root	Root resorption ratio [%] *[lacunae area / root area]*	[900 mg/kg] **MB:** ↓
Minerals and electrolytes Zinc Akhoundi et al. (35)	Wistar rats; male; 200–250 g NiTi CCS: Mx Is to left FM [60 g] **Force application:** 20 d	**EG_1:** 11; $ZnSO_4$ in water [1.5 ppm]; PO **EG_2:** 11; $ZnSO_4$ in water [20 ppm]; PO **EG_3:** 11; $ZnSO_4$ in water [50 ppm]; PO **CG:** 11; drinking water **Sample size calculation:** No **Medication administration:** 60 d	**Histomorphometry** TRAP-hematoxylin M root	Number of lacunae Depth of lacunae [μm] Width of lacunae [μm]	[1.5 ppm; 20 ppm; 50 ppm] M: n [1.5 ppm; 20 ppm; 50 ppm] M: n [1.5 ppm; 20 ppm; 50 ppm] M: n
Prostaglandin analogues Misoprostol Sekhavat et al. (53)	Sprague-Dawley rats; male; age not mentioned; 250 ± 20 g NiTi CCS: Mx right I to FM [60 g] **Force application:** 2 w	**EG_1:** 8; misoprostol [0.0025 mg/kg]; by gastric lavage; daily **EG_2:** 8; misoprostol [0.005 mg/kg]; by gastric lavage; daily **EG_3:** 8; misoprostol [0.01 mg/kg]; by gastric lavage; daily **EG_4:** 8; misoprostol [0.025 mg/kg]; by gastric lavage; daily **EG_5:** 8; misoprostol [0.05 mg/kg]; by gastric lavage; daily **EG_6:** 8; misoprostol [0.1 mg/kg]; by gastric lavage; daily **PG:** 8; 0.5 ml water by gastric lavage	**Histomorphometry** Hematoxylin and eosin Mesial and distal surfaces M root	Depth of lacunae [μm]	[0.0025 mg/kg]: M: n [0.005 mg/kg]: M: n [0.01 mg/kg]: M: n [0.025 mg/kg]: M: n [0.05 mg/kg]: M: n [0.1 mg/kg]: M: n
Vitamins Vitamin C Miresmaeili et al. (48)	36 Wistar rats; male; 36 w; 225 ± 32 g SS spring exerting lateral force: Mx Is [30 g] **Force application:** 7 d +17 d	**EG:** 18; Vit. C [1 wt% in drinking water]; PO **CG:** 18 **Sample size calculation:** Yes **Medication administration:** 17 d	**Histomorphometry** Hematoxylin-eosin Distal aspect I root	Number of lacunae	[1 wt%] I: ↑

*all results shown represent comparisons with control or placebo groups; [§] the first injection was made 2 h before appliance placement; [§§]in 1.5 ml normal saline in gavage

↑: increase in resorption amount relative to control or placebo groups; ↓: decrease in resorption amount relative to control or placebo groups; apic: apical; CCS: closed coil spring; cerv/mid: cervical/middle; CG: control group receiving no kind of pharmacological intervention, neither the vehicle plus the active substance nor the vehicle only; d: days; cor: coronal; DB: disto-buccal molar root; DP: disto-palatal molar root; EG: Experimental group that received pharmacological intervention, different than placebo; FM: first molars; I: incisor(s); IP: Intraperitoneal; IM: Intramuscular; LSM: 3D Laser Scanning Microscope; M: mesial molar root; mag: magnification; MB: Mesio-buccal root; Mx: Maxillary; n: no difference in resorption amount relative to control or placebo groups; ns: normal saline; PBS: Phosphate buffered saline; PG: Placebo group receiving the vehicle preparation without the active substance; PO: Per os; SecM: Second molar; rHGH: recombinant Human Growth Hormone; SM: submucosally; SC: subcutaneously; SEM: scanning electron microscope; SS: stainless steel; T: total; w: week(s); +/−: presence or absence

Table 2. Summary of risk of bias assessment according to SYRCLE (31).

	Signalling questions										
Study	1	2	3	4	5	6	7	8	9	10	Summary
Akhoundi et al. (35)	Unclear	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Baysal et al. (36)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Brunet et al. (37)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Brunson et al. (38)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Esfahani et al. (39)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Gameiro et al. (40)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Gonzales et al. (41)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Hashemi et al. (42)	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Hu et al. (43)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Igarashi et al. (44)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear	Unclear
Ino-Kondo et al. (45)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Kirschneck et al. (46)	Unclear	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
Kirschneck et al. (47)	Low	Low	Unclear	High	Unclear	Low	Unclear	Low	Low	Unclear	Low
Miresmaeili et al. (48)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
MirHashemi et al. (49)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Mirhashemi et al. (50)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Rafiei et al. (51)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Seifi et al. (52)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Sekhavat et al. (53)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Verna et al. (54)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Wang et al. (55)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear

1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation adequately concealed?; 4: Were the animals randomly housed during the experiment?; 5: Were the caregivers and investigators blinded to the intervention that each animal received?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study apparently free of other problems that could result in high risk of bias?

of bias for the majority of the studies. With regards to the random selection of animals for outcome assessment and the existence of incomplete data, the risk of bias was rated as low for almost half of them as the data from all the subjects were analysed, whereas it was unclear for the remaining studies as there was insufficient information to draw a definite conclusion except for one (44). Moreover, the review authors did not assume that bias was introduced by selective outcome reporting. Finally, it was not possible to determine if the studies were free of any additional problems that could increase the risk of bias.

Results of individual studies

The results retrieved from the included studies are presented in Table 1. Root resorption associated with orthodontic tooth movement was shown to increase in Vitamin C treated animals (48). On the contrary, a decrease in root resorption was noted after the administration of low doses of meloxicam (47), ibuprofen (38), alendronate (44), doxycycline (36), human recombinant growth hormone (43), simvastatin (39), lithium chloride (45,55) and strontium ranelate (46). No difference in terms of root resorption was noted for acetaminophen (41), aspirin (41), fluoxetine (50,51), atorvastatin (49), misoprostol (53), zoledronic acid (37) and zinc (35). Finally, inconsistent effects were observed after the administration of celecoxib (38, 40, 42), prednisolone (41,54) and L-thyroxine (36,52).

Risk of bias across studies and additional analyses

Due to the limited retrieved information, analyses for 'small-study effects', publication bias or subgroup analyses were not possible. Overall, regarding the effects of the investigated substances on root resorption associated with orthodontic tooth movement the quality of available evidence was considered at best as low (Supplementary Table 3).

Discussion

Summary of evidence

Overall, the retrieved studies revealed that the investigated prescription pharmaceutical substances may exhibit variable effects on root resorption associated with orthodontic tooth movement. Despite the finding that the quality of evidence was deemed at best as low, compelling the clinician to approach the relevant recommendations with caution, good practice would suggest that it is important to identify patients consuming medications and consider the possible implications. Especially when patients are taking medication that may be associated with an increase in root resorption, frequent radiographic follow-up might be warranted. However, as unequivocal evidence is generally still lacking, the above good practice might be appropriate in other occasions as well. In general, orthodontists should have a knowledge of the potential adverse effects of the drugs their patients take (19).

Only few studies per investigated substance were retrieved. The consequent lack of extensive data is rather surprising, bearing in mind the expanding use of prescription and over-the-counter medication, in all age cohorts (13–15,20,21) and the fact that root resorption is considered to be a not uncommon consequence of orthodontic tooth movement (56). As any pharmaceutical may theoretically exhibit possible effects on the signaling pathways related to orthodontic tooth movement and the homeostasis of the cementum and root dentine (2,11,12), it is reasonable to assume that the

clinician should be capable of identifying the use of prescription and over-the-counter medication in prospective patients and related them to possible risks and complications (16). Thus, evidence-based information relevant to root resorption associated with orthodontic tooth movement would be beneficial in maintaining high standards of clinical care.

Root resorption associated with orthodontic tooth movement was shown to increase after the administration of Vitamin C (48). Vitamin C stimulates osteoclast formation, although it has been shown to subsequently limit the osteoclast lifespan, resulting in the overall bone preservative effect observed in vivo (57,58).

Decrease in root resorption was noted after the administration of ibuprofen (38), meloxicam (47), simvastatin (39), alendronate (44), recombinant human growth hormone (43), lithium chloride (45,55) and strontium ranelate (46). Non-steroidal anti-inflammatory drugs represent the most frequently used type of medication for analgesia worldwide (59,60). The administration of ibuprofen, meloxicam and bisphosphonates has been proven to result in a decrease of osteoclastic activity (61–63). Statins have been shown to upregulate bone formation and decrease resorption, especially in usual doses (64). The lipophilic statins like simvastatin are believed to exert a greater influence on bone turnover than other substances of the same category (65–73). Growth hormone has a regulatory effect on the bone cells through the RANKL/OPG axis, as well as by IGF-1 (43). Lithium chloride has been shown to present suppressive effects on the cell lines, like the osteoclasts, that are associated with root resorption during orthodontic tooth movement (74,75). Furthermore, experimental models have presented evidence that strontium ranelate also influences bone metabolism by attaching to the calcium-sensitive receptors in osteoblasts and osteoclasts (76,77) and subsequently decreasing the differentiation, proliferation and the activity of osteoclasts (78–81).

No difference in terms of root resorption was noted for acetaminophen (41), aspirin (41), fluoxetine (50,51), atorvastatin (49), zinc (35), zoledronic acid (37) and misoprostol (53). Acetaminophen and aspirin have been shown not to alter the rate of orthodontic tooth movement, although aspirin might diminish the number of osteoclasts (41,61). Fluoxetine, a selective serotonin re-uptake inhibitor targets the serotonergic system, whose several components, such as 5-HT receptors and 5-HTT transporters, are expressed in both osteoclasts and osteoblasts (82,83). Peripherally, fluoxetine has anti-resorptive properties, directly impairing osteoclast differentiation and function; however, it triggers centrally a rise in sympathetic output that increases bone resorption sufficiently to counteract its local anti-resorptive effect (84). Although, dietary calcium supplements reduce the number of osteoclasts and decrease alveolar bone resorption (85,86), no influence on root resorption was noted. Moreover, no difference between treated and control groups was also noted for the zinc compounds (35), although it has been observed that Zn may influence the metabolism of bone by stimulating the activity of osteoblasts and decreasing bone resorption by the osteoclasts (87). It may be the case that the bone effects of zinc are dependent on the duration of its administration, suggesting possible normalization with time (88), or that supplementary zinc is effective only where there is a pre-existing deficiency (76). Regarding atorvastatin, it has been suggested that it may not influence bone turnover as much as lipophilic statins like simvastatin do (65–70,77). Although misoprostol upregulates RANKL and osteoclastogenesis, no effect on root resorption was noted (89).

Finally, inconsistent effects on root resorption associated with orthodontic tooth movement were observed after the administration of celecoxib (38,40,42), prednisolone (41,54) and L-thyroxine (36,52). Celecoxib, which is a selective cyclooxygenase-2 inhibitor, has been shown not to interfere with the recruitment and activation of osteoclasts (90) nor the rate of orthodontic tooth movement (91,92). Prednisolone has been shown to affect negatively both osteoblasts and osteoclasts in animals (93), especially in the initial phases of RANKL stimulated osteoclastogenesis (94). However, in prolonged cultures, decreased apoptosis has been observed and an enhancement in the number of osteoclasts formed (94). As thyroid hormones are essential both for normal bone maturation and resorption (13), an unequivocal effect could not be discerned (36,52).

Strengths and limitations

The strengths of the present review include the use of a well-established methodology. The employed strategy for data retrieval from electronic and manual sources was exhaustive up to April 2018, and comprehensive, without pre-set limitations regarding language, date and status of publication. Moreover, the processes of screening, verification of eligibility, abstraction of information, assessment of risk of bias and the quality of evidence were performed in duplicate so as to diminish as possible biases. Disagreements were resolved by discussion or consultation with the third co-author until a final consensus was achieved.

There are also some limitations to the present review, arising mainly from the nature and the characteristics of the included studies per se and the data retrieved during the review process, which resulted in an assessment of the level of available evidence being, at best, low. The scarcity of relevant evidence-based information precluded meta-analytic procedures. Moreover, most studies were considered to be of unclear risk of bias. This relative uncertainty becomes greater in the case of inconsistent effects.

Furthermore, the currently available information is not only indirectly related to humans because the data originate from animal studies, but also involves the administration of substances for periods of time, dosages with questionable equivalence between species and routes of administration unlike many clinical situations in humans (30,95,96). Additionally, the use of specific modes to induce orthodontic tooth movement further circumscribes the generalizability of the retrieved information to human clinical scenarios. Moreover, the retrieved studies involved the administration of medication in healthy animals, a situation that may relate to tissue homeostasis (2,11,12). Also, the applicability of the results reported in this investigation may be moderated by the methodology employed for the assessment of resorption. Although root resorption associated with orthodontic tooth movement constitutes a three-dimensional process, most studies investigated the existence and amount of resorption using conventional, light microscopy, paraffin histological analyses, which can only be performed in two dimensions (97,98). The thus to be expected error, might be corrected, but not completely nullified, by employing standardized assessment of multiple slices and relatively quantifying the lesions in relation to the corresponding root area (47). In this respect, it has been suggested that it would be helpful to use cone-beam computed tomography (99,100). Finally, the lack of power sample calculations, increases the uncertainty about the precision of the observed estimates, as well as, the clinical significance of the results, if one would like to extrapolate the retrieved animal information to everyday clinical scenarios in humans.

Recommendations for future research

The expansion of both prescription and over-the-counter medication use among all age groups makes further well-designed experimental

animal studies and, if possible, clinical studies on the effects of different substances on root resorption associated with orthodontic tooth movement quite important. Also, it would be meaningful that such studies become standardized (101) and the methodology for assessing the outcomes more appropriate to the three-dimensional nature of the phenomenon (97–100). Moreover, possible sources of risk of bias should receive the appropriate attention (31) and future investigation should simulate, as closely as it is feasible, scenarios in clinical practice in humans in terms of period, equivalence of dosage and route of administration, as well as the characteristics of the employed biomechanical systems for force application.

Conclusions

The pharmaceutical substances investigated were shown to exhibit variable effects on root resorption associated with orthodontic tooth movement. Although the overall quality of evidence provides the clinician with a cautious perspective on the strength of the relevant recommendations, good practice would suggest that it is important to identify patients consuming medications and consider the possible implications.

Supplementary material

Supplementary material is available at *European Journal of Orthodontics* online.

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Conflict of interest

None to declare.

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