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Effect of Altered Calcium Metabolism on Orthodontic Tooth Movement: a Systematic Review

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Abstract

Aim: The aim of this study was to analyze and synthesize data from animal research on the impact of hormones and their synthetic derivatives on orthodontic tooth movement by altering calcium metabolism.
Methods: Eight databases were scanned electronically, followed by a manual search, until 27 February 2022. Animal experiments were chosen with control groups exploring the impact on orthodontic tooth movement with calcitonin, calcium, parathyroid hormone, teriparatide, and vitamin D. The reporting quality of primary studies was assessed using the CAMARADES tool. Data was collected from related studies and SYRCLE's risk of bias tool was utilized to determine risk of bias.
Results: Of the 2388 documents obtained in the search, 11 studies were included. The amount of orthodontic tooth movement reduced with the administration of calcitonin and calcium. However, with parathyroid hormone, teriparatide, and vitamin D, acceleration of tooth movement was noted. The results were statistically significant omitting three studies that assessed orthodontic tooth movement with calcium, vitamin D, and parathyroid hormone. Root resorption increased with calcium, vitamin D, PGE2, and a dose-dependent decrease was seen in higher doses of calcitonin. Bone mineral density improved with increased parathyroid hormone levels.
Conclusion: Vitamin D, their synthetic derivatives, and parathyroid hormone were found to increase orthodontic tooth movement. Calcitonin showed a dose dependent reduction in orthodontic tooth movement.

Keywords: Orthodontics, Tooth movement, Calcium metabolism

1. Background

Orthodontic tooth movement (OTM) is a desirable sequela to sustained force application that occurs through the process of bone remodeling, which is dependent on systemic and external conditions such as nutritional factors, metabolic diseases, age and drugs or hormones (1). Changes in rate of orthodontic tooth movement can be achieved by three approaches: use of biochemical agents, mechanical or physical stimulation of the alveolar bone, and surgical interventions to accelerate tooth movement. A systematic review done by Arqub et al. to study the results of local administration of biological substances on the rate of OTM surmised that the impact was inconsistent (2).

No systematic review has been conducted until now on the topical application of hormones and their derivatives in calcium metabolism. Calcium metabolism or homeostasis is integrated with bone remodeling at the cellular level. At a molecular level, mediators like Osteoprotegerin(OPG) and Receptor activator of nuclear factor kappa B ligand(RANKL) are crucial for either stimulating or inhibiting effects of various systemic hormones, growth factors, and cytokines on osteoclastogenesis. Parathyroid hormone (PTH) and vitamin D stimulate a positive osteoclast differential by stimulating RANKL and inhibiting the negative signal, OPG, in osteoblasts. A critical balance is required in production of RANKL and

inhibition of OPG to initiate or accelerate tooth movement (3).

The current need to expedite the rate of orthodontic tooth movement is also in accordance with the biology of the individual patient. As more adult patients are undergoing orthodontic treatment, it is imperative to understand the disorders affecting calcium homeostasis and altering bone physiology like osteoporosis, which is commonly observed in females, Paget's disease, hyperparathyroidism or hypoparathyroidism and rarely, bone metastasis. Vitamin D and its active metabolite [1,25-(OH)2 D3] concentrations have been recently studied in clinical trials (4).

Thus, the objective of this systematic review was to assess altered calcium metabolism on the rate of OTM by collating data from studies conducted on PTH, vitamin D, and calcitonin along with their synthetic analogues on animals.

2. Methods

This systematic review was done in accordance to preferred systematic review and meta-analysis (PRISMA) reporting items (5,6,7). The review was registered with PROSPERO: International Prospective Registry of Systematic Reviews (CRD42020147198).

Eligibility criteria

The criteria for eligibility were specified according to the PICO framework (participants, intervention, comparison, outcome, and study design) (Table 1). The amount of tooth movement was assessed in papers studying only hormones and their synthetic derivatives that effect calcium homeostasis.

Search Strategies

Eight databases were searched: PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Science Direct, SciELO, LILACS, German National Library of Medicine, and Open Gray until 27 February 2022 (Supplementary Table 1) for any article relevant to the systematic review.

Screening and Selection of Papers

Two reviewers (PK and MM) independently assessed all articles and removed duplicates using the Rayyan QCRI application (8). The third reviewer (PC) was consulted in case of any disagreements between the two reviewers. Studies done in foreign languages and duplicate literature were excluded, and titles and abstracts of articles were searched against established eligibility criteria.

Table 1. PICO Framework

PICOS	Inclusion Criteria	Exclusion Criteria
Participant	Rats subjected to orthodontic treatment	Animals other than rats whether or not subjected to orthodontic treatment
Intervention	Local or systemic administration of the following pharmacological drugs or hormones during orthodontic treatment: 1. Vitamin D 2. PTH 3. Calcium gluconate 4. Calcitonin 5. Teriparatide	Administration of any other drugs or hormones not considered in the inclusion criteria Any other intervention that affects tooth movement
Comparison	Placebo or control or sham	Studies with no control groups Studies with or without control groups not subjected to orthodontic tooth movement
Outcome	Primary outcome: Quantitative analysis of orthodontic tooth movement (rate of tooth movement, amount of tooth movement, percentage of tooth movement) 1) Root resorption 2) Changes in periodontal tissues and alveolar bone	Qualitative analysis of tooth movement Inadequate outcome data

Study design	Animal intervention studies Randomized Control Trials Split mouth studies Prospective controlled trials	Case reports Retrospective studies Comments Letters to editor Reviews

Data extraction

Two other reviewers (SV and MM) derived relevant data in originally described formats from the included studies: author, reference year, study design, hormones and synthetic derivatives, animal model characteristics (species, weight, age, and gender), OTM evaluation indicator (equipment used, force delivery, duration), group characteristics (sample size, dose, and route of drug administration), outcome measures, and results.

The primary outcome of the systematic review was to assess the effects of hormones and their synthetic derivatives (calcium, calcitonin, vitamin D, teriparatide, and PTH), which alter calcium metabolism on OTM. The secondary outcomes were to evaluate the effects of these hormone analogues on root resorption and changes in periodontal tissue and bone.

Quality and risk of bias assessment of the included studies

Reporting

CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) checklist was used to report the quality of the primary studies (9). The quality was assessed on the basis of the following criteria: publishing in a peer reviewed journal, temperature monitoring, randomization, blinded outcome evaluation, allocation concealment, avoiding anesthetics with marked intrinsic properties, suitable animal models, declaration of adherence with regulatory requirements, estimation of sample size, and statement of potential conflicts.

Risk of Bias in Individual Studies

Risk of bias was assessed by two reviewers independently using the SYRCLE's risk tool based on Hooijmans et al. (10). The studies were assessed on the basis of the following criteria: sequence generation, baseline characteristics, allocation concealment, random housing, blinding (intervention), random outcome assessment, blinding (outcome), incomplete outcome data, selective outcome reporting, and other source of bias.

Synthesis of Results

The lack of homogeneity in the research layout of included papers did not permit synthesis of quantitative results. Majority of the studies had diverse parameters to measure the impact of systemic drugs on OTM. There was no homogeneity in drug dosage, route of administration, study design, appliance and force used to check OTM. A qualitative synthesis of all included studies was performed.

3. Results

Characteristics of included studies

The records screening process is displayed in the PRISMA flowchart as shown in Fig. 1. A total of 2388 studies were identified in eight electronic databases. An additional seven studies were included after a manual search conducted by two reviewers independently. Full text articles were obtained for 81 studies, of which 70 were excluded with their reasons mentioned in supplementary Table 2. Finally, 11 studies were included for a qualitative synthesis.

The general characteristics of studies included are shown in Table 2. Wistar rat male animal models were used in eight trials (11-18), Sprague Dawley female animal models in two (19,20) and Sprague Dawley male rats in one study (21). One study reported the effect of calcitonin on OTM (21),

Table 2. General Characteristics of Included Studies

Study id	Study design; Hormones administered	Animals Age /Weight	Orthodontic procedure; site; method of delivery; interval of administration	Study groups and dose	Measurement Time	Outcomes	Statistical test Results

Goldie et al. 1984(19)	Prospective Calcium	Adult female Sprague-Dawley rats	SS-CCS; Right and left maxillary first molar and second molar; 60 g; Oral 14days	Group A: Experimental group (n= 25) were lactating, a Ca deficient diet (0.0048%Ca); one time Group B: Control group (n =10) nonpregnant and nonlactating; Ca diet (1.2%); one time	1,4,7, 10, and 14 days	OTM: Measuring the space created between the first and second molars with a standard mm feeler gauge. Whole bone analysis: single humerus was dissected from each test and control group and percent bone ash was measured. Root surface resorption analysis: SEM was used to measure the area of resorption, expressed as total area of acellular cementum seen on the photomicrographs (%).	MEAN+/- SD OTM: Days 1, 4, 7, 10, 14 Ca decreased OTM in calcium deficient diet group;(StS) Whole bone analysis: Ca deficient diet (experimental group) showed bone loss. Root resorption: Day 7 and 10- Increase in area of root surface resorption in experimental group. (StS) Day 1,4,14: No significant increase in area of root surface resorption between both groups.

Table 2. Continued

Takana-Yamamoto et al. 1992 (12, A)	Split mouth prospective 1,25(OH)2D3	20 male Wistar rats; 7 weeks ; 180- 200g	CCS; right maxillary First molar to Is; 5-30 g; submucosal palatal area of the root bifurcation of the maxillary right first molar; micro syringe; once every seven days for 21 days.	Group A: Experimental A1- 20 μ l of 10-10 mol/lt 1,25(OH)2D3 + 5 g force (n=5) A2- 20 μ l of 10 -10 mol/lt 1,25(OH)2D3; + 20 g force (n=5) Group B: Control B1- 20 μ l L PBS containing 0.001% ethanol + 5 g force (n=5) B2- 5; 20 μ LPBS containing 0.001% ethanol+20 g force (n=5)	0,7,14 and 21 days	OTM: The distance between the mesial pit of maxillary right first molar and left first molar was measured with digital calipers (Digimatic caliper, Mitutoyo Co, Tokyo; accurate to 0.01 mm). Stained sections with H&E and viewed under microscope	Day 21 No. of osteoclasts -1,25(OH)2D3 group > control Areas of undermining resorption: 1,25(OH)2D3 group > control Howship's lacunae associated with osteoclastic activity, could be seen on the labial (compression) side. Bone resorption area of alveolar bone was seen on the palatal sides in 1,25(OH)2D3 group. Osteoblastic cells were seen on palatal (tension) side in both groups
Takana-Yamamoto et al. 1992 (12, B)	Split mouth prospective 1,25(OH)2D3	10 male Wistar rats; 7 weeks; 180-200g; 30 males Wistar rats; 28 weeks 400-420 g	CCS; right maxillary first molar to Is; 20 g Subcutaneous (infusion and injection); site not specified; 21 days	Group A: Experimental group A.1- 20 μ l of 10-10 mol/lt 1,25(OH)2D3 + inactivated appliance (7 wks; n=5) A.2- 20 μ l of 10-10 mol/lt 1,25(OH)2D3 + activated appliance (28 wks; n=6) A.3- 20 μ l of 10-10 mol/lt 1,25(OH)2D3 + activated appliance (28 wks; n=6) A.4- 20 μ l of 10-10 mol/lt 1,25(OH)2D3 + inactivated appliance (28 wks; n=6) Group B- Control group B1- 20 μ l PBS + activated appliance (7wks; n=5) B2- 20 μ l PBS in 0.01% ethanol + inactivated appliance (28 wks; n=6) B3-20 μ l PBS in 0.01% ethanol + activated appliance (28 wks; n=6)	0, 7, 14 and 21 days	OTM: The distance between the mesial pit of maxillary right first molar and left first molar was measured with digital calipers (digimatic caliper, Mitutoyo Co, Tokyo) accurate to 0.01 mm.	Day 20: Young rats (with Vit D) promoted 1.2 times more OTM than control; Mature rats (with Vit D) promoted 2.5 times than control; 10^{-10}>10^{-8} Vitamin D increases OTM
Soma et al. 1999 (13)	Prospective PTH (1-34) PTH (1-84)	40 male Wistar rats; age not specified; 350-400 g	CCS; right maxillary first molar to Is; 30 g of force; subcutaneous (infusion and injection); site not specified; once daily for 12 days	Group A: Experimental A.1-PTH (1-84) SC (infusion) 10 µgm/100g BW per day; (n=8) A.2- PTH (1-34) SC (infusion) 0.4 µgm /100 g BW per day; (n=8) A.3-PTH (1-34) SC (infusion) 4 µg/100 g BW per day); (n=8) A.4- PTH (1-84) SC (infusion) 4 µg /100 g BW per day; (n=8) Group B- vehicle infusion; (n=8)	0, 1, 3, 10 days	Measuring interproximal distance between first and second molars on casts under a microscope with calipers having an accuracy of 0.05 mm Dual energy X-ray absorptiometry was used to measure bone mineral density.	MEAN+/- SEM On Day 12; OTM- 1. PTH 1-84 infusion was more than Control (StS), 2. PTH-1-34) (infusion 0.4,4 μ g) was more than Vehicle (StS); 3. PTH 1-34 Injection 4 μ g = vehicle infusion 4. PTH 1-34 injection NSD; PTH accelerated OTM Increased bone mineral density in PTH group.

Soma et al. 2000 (14)	Prospective PTH (1-34)	56 male Wistar rats; 20 weeks old; 350-380 g	NiTi-CCS; right maxillary first molar to Is 30 g of force, subperiosteum in the mesiopalatal region of right maxillary first molar Systemic injection (subcutaneous) injection in the dorso cervical region 12 days	Group A: – experimental A.1- Orthodontic force + PTH 0.1 µg (local injection) dissolved in MC gel; (n=8) A.2 - Orthodontic force + PTH 1 g dissolved in MC gel; (n=8) A.3 - Orthodontic force + PTH 1 µg + 0.9% saline (local injection); (n=8) A.4- Orthodontic force + PTH 1 µg dissolved in MC gel (systemic injection); (n=8) A.5 - No orthodontic force, PTH 1 µg dissolved in MC gel (local injection); (n=8) Group B- Control B1- Only orthodontic force; (n=8) B2- Orthodontic force + local injection dissolved in MC gel (2 % w/v PTH in MC solution); (n=8)	0, 3, 6, 9, 12 days	OTM: By measuring the inter proximal distance between the first and second molar on the plaster cast under a microscope (40x) with a caliper having an accuracy of 0.05 mm Histological examination: 8 μ mm section thickness in mesiodistal direction of mesial side of distobuccal root of first molar was examined under microscope	MEAN+/- SD Day 12; B1 = B2 (MC gel); local PTH/MC (1 g) showed increase in OTM than in control (MC gel) (StS); PTH 1 μ g dissolved in saline, 1 μ g local PTH/MC gel and systemic PTH 1 μ g MC gel, 0.1 μ g PTH=MC control, local injection of PTH showed increased tooth movement Narrowing of PDL space in compressed side
Seifi et al. 2003 (15)	Prospective split mouth Calcium PGE2	24 male Wistar rats; 8 weeks; 230-300 g	CCS 5 mm long right maxillary frist molar to Is by ligature wire; 60 g, for 21 days Submucosal PGE2 injection at mesiobuccal mucosa and intraperitoneal Ca	Group A: A.1; [n=8] (i)-Distilled water 0.1 ml was injected at mesiobuccal mucosa of right first molar after insertion of orthodontic appliance (normal) ii), left side was not under any force or injection (control) A.2:- 0.1 ml of 1mg/ml PGE2 dissolved in 1% lidocaine; (n=8) A.3: 0.1 ml of 1 mg/ml PGE2 dissolved in 1% lidocaine+10% Ca (200 mg/kg) ; (n=8)	0 and 7 days	OTM: Measured using a gauge with an accuracy of 0.01 mm Root resorption: recorded dimensions and areas of resorbed surface cavities on mesial surface of roots measured on sections of 5 µm thickness that were taken in a mesiodistal direction.	MEAN+/- SD Day 21; PGE2 + Ca < PGE2 (NSS); Ca decreases OTM Root resorption was increased in PGE2 group. (StS)

Table 2. Continued

Kale et al 2004 (21)	Prospective 1,25 DHCC DMSO PGE2	37 Male Sprague-Dawley rats; 6-week-old; 160+/- Gms	Modification of Boisson and Gianelly's appliance that consisted of two incisor bands with eyelet-like attachments on palatal side. 8 mm long helical loop made from 0.012 round stainless-steel wire that was inserted through the eyelet-like attachments; 20 g of force, Micro syringe Injected gingival to maxillary incisor 9 days	Group A: Experimental A.1- Orthodontic force + 20 μ l of 10-10 mol/lt 1,25 DHCC dissolved in 10-10 mol/lt DMSO on day 0; (n=8) A.2- Orthodontic force + 1-25 DHCC 20 µl of 10-10 mol/L on days 0, 3, 6; (n=8) A.3- 0.1 ml of 0.1 g of PGE2 on 0 day; (n=8) Group B - Control B.1- No treatment (only to observe histology of periodontium); (n=5) B.2- Mechanical force plus no injection; (n=8) PGE2 was first dissolved in 1 mg/ml ethanol and diluted with 2% lidocaine to concentration of injection	0 and 9 days	Lateral movement of incisors was measured intraorally with digital caliper accurate to 0.01mm at gingival margins of incisors bands of appliance Histological examination: Premaxilla were decalcified De Castro solution and then were dehydrated and embedded in paraffin. 30 sections of 5 µmm thickness were obtained under light microscopy.	MEAN+/- SD Day 9; OTM- DHCC showed increased OTM than control (StS); Vitamin D increased OTM Number of osteoblasts per 1 mm2: - DHCC>PGE2>Control>DMSO>Control group without mechanical force Number of Howship's lacunae per 1 mm2: PGE2 group>DHCC>DMSO> Control Number of capillaries: PGE2 group>DHCC>DMSO> Control

Salazar et al. 2011 (17)	Prospective	48 Wistar rats, 8 weeks; NS	NiTi CCS 7 mm Left maxillary first molar to Is 1 mm of activation provided 40cN force	Group A: Experimental group A.1- Ovariectomized rats; (n=16) Group A.2-30 μ g/kg/day Teriparatide + Ovariectomy; (n=16) Group B- Control; (n=16) Subcutaneous injection Not specified 14 days	OTM: 0, 5, 7 days; Bone mineral density: 3 months after surgery; Histological examination: 0, 5, 7 days	OTM: Measuring the distance between first and second molar from each cervical dental crown region using a ruler coupled to an optical microscope (magnification of 10x) Bone density was measured by densitometer aided by Encore software to measure bone density 3 months post-surgery. Histological examination: 5 μ mm sections of maxilla in longitudinal direction was obtained. The thickness of PDL was measured in the region of root fork of first molar's PDL using same rules with optical microscope. Number of osteoclasts was determined in the pressure area of first molar distal root using optical microscope.	MEAN+/- SD OTM; Day 7; Teriparatide> Ovx> Control; Teriparatide increases OTM Bone mineral density- Teriparatide> Control>Ovx Thickness of PDL- at 7 days Control>Teriparatide>ovx (Pressure side) At 7 days Control=Ovx>Teriparatide (Tension side) Number of osteoclasts- Control>Ovx>Teriparatide (Pressure side)
Li et al 2013 (11)	Prospective PTH (1-34)	60, Male Wistar rats, 8 weeks 200±10 g	CCS; Right maxillary 1st molar to Is 40 g of force was used; daily injection; site not specified; 12 days	Group A - Experimental group PTH (1-34) of 4 μ g /100 g BW dissolved in phosphate buffered saline at a concentration of 1 μ g/mL; (n=30) Group B- control (n=30)	0, 3, 6, 9, 12 days	OTM-Distance of separation between first and second molar using a vernier caliper with an accuracy of 0.02 mm. Histological examination: Osteoclast, RANKL, osteoprotegrin was measured using: 1) Osteoclast number measured using light microscopic images on compression side of distal root of maxillary first molar at mesiocoronal area (100x) and bifurcation area (400x). 2) RANKL Immunoreactivity measured using automatic image analysis system.	MEAN+/- SD Day 9 and 12; OTM in PTH group > Control group; PTH increased OTM TRAP positive osteoclasts at day 6, 9, 12 PTH> vehicle Histologic section- on compression side osteoclasts accumulated and formed lacunae Day 6- Number of osteoclasts same in both groups Day 9- Number of osteoclasts increased active resorption of bone PTH> control Day 12- No. of osteoclasts increased and active resorption of bone PTH> control 1) RANKL in PDL increased in PTH group (StS) 2) Osteoprotegrin in PDL increased in PTH group (NSS)

Table 2. Continued

Seifi et al. 2015 (16)	Prospective split mouth Calcium Thyroxine PGE2	64, male Wistar rats, 6-8 weeks 230-300 g	CCS, 5 mm, right first molar to Is by ligature wire; 60 g; micro syringe; intraperitoneal thyroxine submucosal; PGE2; intraperitoneal calcium; 12 days	Group A- Experimental A.1- 20 µg/kg thyroxine + orthodontic force; (n=8) A.2- .1 ml of 1mg/ml PGE2 s in 1% lidocaine + orthodontic appliance; (n=8) A.3-10% Ca 200 mg/kg; (n=8) A.4-0.1 ml of 1 mg/ml PGE2 + 10% Ca 200 mg/kg; (n=8) A.5- Orthodontic appliance + 20 µg/kg thyroxine +0.1 ml of 1 mg/ml PGE2+ 10% Ca 200 mg/kg; (n=8) A.6- 20 µg/kg thyroxine + 10% Ca 200 mg/kg; (n=8) A.7- 20 µg/kg thyroxine + 0.1 ml of 1mg/ml PGE2 + 10% Ca 200 mg/kg; (n=8) Group B- Control; (n=8) 0.1 ml of distilled water (studied only for root resorption) divided into two groups: i) normal ii) control	0 and 21 days	OTM Measuring the distance between distal of 1st molar and mesial of 2nd molar using a feeler gauge with an accuracy of 0.01 mm Histological analysis- A grid sheet was used for evaluation and grid relative to pixels in irregular areas of root resorption were established for calculation of area of root resorption	MEAN+/- SD OTM- Day 21; Ca group < Control (StS); PGE2+Ca< PGE2 (StS); Thyroxine+ Ca < Thyroxine (StS); Root resorption- PGE2>Thyroxine+PGE2> PGE2+Ca>Control >Thyroxine + Calcium
Ling Guan	Prospective	80, male	NiTi CCS; left maxillary	Group A- Experimental group	0 and 14	OTM was measured from	MEAN+/- SD

et al. 2017 (18)	calcitonin	Wistar rats; 7-weeks old 200-250 g	first molar and Is 50 gms; buccal sub-periosteum adjacent to furcation of maxillary right first molar with a micro syringe; 14 days	A.1- 0.2 IU per kg/day calcitonin; (n=16) A2- 1 IU per kg/day calcitonin; (n=16) A3- 5 IU per kg/day calcitonin; (n=16) Group B- Control group B1- Control; (n=16) B2- Negative control; (n=16)	days	the closest distance from 1st and 2nd molar from plaster model under a stereoscopic microscope Histologic analysis- Changes in periodontal tissues were examined in sections stained with H&E and no. of osteoclasts around pressure side of root under optical microscope. Root resorption – Mesial side of distal buccal root was observed under scanning electron microscope at distance and orientation	Day 14; negative control (-) > positive control (+) > CT (0.2 IU)> CT(1IU) > CT(5IU); CT decreases OTM OTM and TRAP positive cells on root resorption ratio- periodontal destruction and resorption of maxillary root decreased with increased doses of Calcitonin. TRAP expression- .5IU per kg/day CT> 1 IU per kg/day CT>0.2 IU per kg/day CT Greatest root resorption positive control 0.2 IU>1IU>5IU
Lee et al. 2018 (20)	Prospective PTH	30 Sprague Dawley female rats; 8 weeks old 250 g	NiTi CCS; right maxillary first molar to Is ligated by a ligature wire; force of 50 cN; injected on buccal and palatal gingival side of left first molar; micro syringe subcutaneous PTH (1-34); 3 weeks	Group A: Experimental A1- Ovx+ 0.1 mole/L Tris HCL and 2% rat serum albumin A2- Ovx + 30 µg/kg PTH (1-34) Group B- Sham operated	3 weeks	OTM- Week 1,2 and 3- the distance between mesial surface of 1st molar and distal surface of 3rd molar with a digitronic caliper having an accuracy of 0.1mm Relapse-Distance was measured by subtracting R3 from T3 After a duration of 3 weeks. Micro CT- intra radicular bone area of 1st molar from the CEJ to apex of root measured using a Micro CT scanner in an axial direction for parameters- 1.(tv) 2. (bv) 3. (bv/tv) 4. (bmd) 5. (tbTh) 6. (tbSp.) 7. (tb.N)	Median OTM After 3 weeks; Ovx > C> PTH; PTH did not increase OTM(NSS) Relapse- Ovx> PTH> Control (in mm) Microstructural parameters- 1. tv- PTH>Ovx>Control 2. bv- PTH=Ovx<control 3. bv/tv- control>PTH>ovx 4. bmd- control>PTH>ovx 5. tbSp- Control>ovx=PTH 6. tbTh- control=Ovx>PTH 7. tb. N- PTH>control>Ovx

BMD: bone mineral density; BV: bone volume; BV/TV: bone volume/total volume; Ca: Calcium; CCS: closed coil spring; cN: centi Newton; CT: Calcitonin; DHCC: dihydroxycholecalciferol, (OH)2D3: dihydroxycalciferol; DMSO: dimethyl sulfoxide; DW: distilled; H&E: haematoxylin and eosin; IP: intraperitoneal; Is: incisors; IU: international units; MC: methylcellulose; NiTi: nickel-titanium; NSD: no significant difference; NSS: not statistically significant; OTM: orthodontic tooth movement; OVX: ovariectomized; PTH: parathyroid hormone; PBS: phosphate buffered saline; PGE2: prostaglandin; RANKL: receptor activator of nuclear factor kappa- B ligand; SD: standard deviation; SEM: scanning electron microscope; SS: stainless steel; StS: statistically significant; SC: subcutaneous; TRAP: tartrate-resistant acid phosphatase; tv: total volume; tbN: trabecular number; tbSp: trabecular separation; wks: weeks; %: percentage

four examined PTH (11,13,14,20), one teriparatide [17] (synthetic form of PTH), three studies assessed effects of calcium in the diet (15,16,21) and two evaluated vitamin D (12,19). Eight included studies examined rats aged between 6-8 weeks, two studies (12,14) assessed mature rats at 28 and 20 weeks respectively and two studies did not specify the age of rats (13,19).

All included studies were prospective animal interventions with three split mouth design (12,15,16). Experiments lasted between nine days (minimum observation days) (21) to 21 days (maximum observation) (12,15,16,20) to assess OTM. Sample size calculation was not disclosed in any of the studies.

Orthodontic tooth movement in rat models was measured using coil springs in all studies except one, which used a Boisson and Gianelly fixed appliance (21). In most studies, coil springs were attached from incisors to first molars on the right side (11-16,20) and only two placed it on the left side (17,18).

One study used coil springs extending from the maxillary first molar to the second molars bilaterally (19). The force used was within the range of 5 g (12) to 60 g (15,16,19) to assess OTM. The administration of drugs was through a microsyringe in all studies except for one (19), which used an oral route of administration. Subcutaneous injections were given in four studies (13,14,18,20), submucosal injections in three studies (12,18,21), intraperitoneal injections in two studies (15,16), and one study did not specify the route of administration (11).

The rate of tooth movement was assessed using either a feeler gauge (15,16,19), a digital caliper (12-14,20,21), ruler coupled to an optical microscope (17), vernier caliper (12), or a stereoscopic microscope (18).

Risk of Bias

Several methods are used to determine the consistency of animal experiments currently, but none of these tools rely exclusively on internal validity. CAMARADES checklist was used to assess the quality of all included studies (Table 3). Overall, for the 11 studies included, the median quality score was low (5; interquartile range: 4), with scores between 3 and 8, although a score of 0 or 10 was not obtained from any study. Four studies obtained high-quality scores (11,18,20,21), and

these studies recorded randomization, allocation concealment with effective blinding strategies and issued a declaration of conflict of interest. One study with a poor-quality score recorded randomization (20). The randomization of animals into treatment groups was not mentioned in five trials with poor quality scores (12-14,17,19). Five studies (12,17,18,20,21) screened physiological parameters such as body temperature and five (11,16-18,20) did not find any possible conflicts of interest.

Table 3. Quality of evidence using CAMARADES

CAMARADES checklist	Goldie 1984	Takano-Yamamoto 1992	Soma 1999	Soma 2000	Seifi 2003	Kale 2004	Salazar 2011	Li 2013	Seifi 2015	Ling Guan 2017	Lee 2018
Publication in peer reviewed journal	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statement of control of temperature	N	Y	N	N	N	Y	Y	N	N	Y	Y
Randomization of treatment or control	N	N	N	N	Y	Y	N	Y	Y	Y	Y
Allocation concealment	NG	NG	NG	NG	NG	Y	NG	Y	NG	NG	Y
Blinded assessment of outcome	NG	NG	NG	Y	NG	Y	NG	Y	NG	NG	NG
Avoidance of anesthetics with marked intrinsic properties	N	Y	N	N	N	Y	Y	Y	N	Y	Y
Use of suitable animal model	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sample size calculation	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Statement of compliance with regulatory requirements	Y	NG	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statement regarding possible conflict of interest	N	NG	N	N	N	N	Y	Y	Y	Y	Y
Total (on 10)	3	4	3	4	4	8	6	8	5	7	8

*Y,Yes;N,No;NG,Not given

Table 4. Risk of bias assessment using SYRCLE Risk of Bias Tool

Author	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding (intervention)	Random outcome assessment	Blinding (outcome)	Incomplete outcome data	Selective outcome reporting	Other source of bias	Summary
Goldie 1984	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Takano-Yamamoto 1992	Unclear	Low	High	Low	Unclear	Unclear	Unclear	Low	High	High	High
Soma 1999	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Soma 2000	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Seifi 2003	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Kale 2004	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Salazar 2011	High	Low	Unclear	High	Unclear	High	Unclear	Low	Low	Low	Low

Li 2013	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Seifi 2015	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Ling Guan 2017	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Lee 2018	Unclear	Low	High	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

The description of the risk of bias using the SYRCLE's tool for included studies has been provided in Table 4. Four studies presented with an unclear risk of bias (13,15,19,20), one with high risk (12), and six with low risk of bias. In many of the studies, three variables were found with low risk of bias, which were incomplete outcome data, baseline characteristics, and selective outcome reporting. High risk of bias was noted with respect to allocation concealment, blinding outcome assessment, and selective outcome reporting in one study (12). Most studies included rats with similar age, sex, and weight at baseline and were considered as having a low risk of bias.

Result of Individual Studies
Primary Outcome of OTM

Two studies evaluating the effects of calcium on OTM (15,16) showed decrease in OTM, out of which one study reported the outcome statistically non-significant (15). One study reported an increase in tooth movement in calcium deficient rats at ($p>0.05$), suggesting that calcium decreases tooth movement (19). Although the dose, concentration, frequency, and observation period considered was varied among all the studies, calcium reduced OTM. However, when used in conjunction with agents like PGE2 and thyroxine (16), opposite results were noted. Calcitonin demonstrated dose dependent reduction in OTM with an increase in the dosage of calcitonin, which was statistically significant (18).

PTH showed conflicting results. An increase in the amount of OTM was noted at $p>0.05$ in three studies (11,13,14). However, one study reported a decrease in OTM, but no statistically significant difference existed (20). The dose, frequency, and route of administration of PTH seemed to have no effect on the role of PTH on OTM, as these parameters were altered in all the studies. Teriparatide, a derivative of PTH, depicted an increase in OTM at seven days, which was reported to be statistically significant (17).

Two studies reporting OTM under the influence of vitamin D concluded that it increases OTM at $p>0.05$ (17,26), of which one study used local as well as systemic injections of vitamin D in both young and mature rats (12). It was noted however, that the increase in OTM with weekly injections was not statistically significant.

Secondary Outcomes (Root resorption and changes in periodontal tissue and alveolar bone)

Studies reported a statistically significant accelerated OTM with PGE2; however, it was reported with a high risk of root resorption with increased areas of Howship's lacunae, even when combined with calcium (15,16). A dose dependent relation was found with calcitonin in relation to root resorption and OTM (18).

PTH was examined against several parameters where it was found that PTH stimulates an increase in multinucleated cells and initiates osteoclastic activity (11). Additionally, it also caused an increase in RANKL and OPG levels in the PDL along with PDL widening (11). On further evaluation of bone density and histology of the bone, it was reported that PTH causes increase in bone volume (BV), bone mineral density (BMD) (13,20), trabecular separation (TbSp) and trabecular thickness (TbTh) at $p>0.05$ (20).

On histological analysis of the effects of vitamin D when compared with PGE2 and the control on OTM, the number of osteoblasts per 1 mm2 were markedly elevated in the vitamin D group (21). The number of Howship's lacunae and capillaries were higher in PGE2 followed by vitamin D with controls showing the least number (21). This was substantiated by another study that found an increased number of osteoclasts and areas of undermining resorption in the group receiving local injections of vitamin D (12).

4. Discussion

Orthodontic treatment induces force in the underlying bone and periodontal ligament by a coordinated process of resorption and deposition (22). Osteoblasts and osteoclasts are the important cells that initiate this cascade by activating RANK/RANKL pathways (23). Some drugs that affect osteoblasts-osteoclast turnover are calcitonin, PTH, and vitamin D, and their synthetic derivatives like teriparatide and calcium gluconate, thereby altering OTM (24). While surgical procedures have

been used by clinicians to accelerate tooth movement in clinical scenarios, nonsurgical approaches are favored because they are efficient and non-invasive. These techniques involve systemic or local administration of pharmacological agents or physical stimulation methods such as resonance vibration, magnetic field forces, cyclic forces, and low-intensity laser irradiation. To understand the biology of tooth movement, nonhuman animal models have been used to carry out experimental studies. Laboratory rats are considered to be ideal animal models for research as they share many similarities to humans. They are regarded as suitable models to study orthodontic tooth movement as large samples can be stored for a long time. Also, their histological preparation is straightforward compared to other animal models. Antibodies required for cellular and molecular biological techniques are only available for mice and rats (25).

As the skeletal target cells for PTH are osteoclasts, it promotes bone resorption. A persistent increase in circulating PTH causes the prevalence of osteoclastic resorption sites and the proportion of the bone surface covered by non-mineralized matrix increases with inhibition of osteoblastic activity (26,27,28). The impact of PTH and its synthetic derivatives on OTM has been evaluated in five (11, 13,14,17,20) of the included studies. Three studies evaluated only the synthetic form of PTH (1-34) (11,14,20) and one study evaluated both the human recombinant form of PTH (1-84) and the synthetic form (1-34) (13). The dose varied in all the included articles ranging from 0.1 mcg/100 g body weight (minimum dose) (14) to a maximum dose of 30 mcg/100 g body weight (15). The mode of administration was through a microsyringe in all studies. One study evaluated the synthetic derivative, teriparatide, which was also given at a dose of 30 mcg/100 g body weight (12). Out of five studies, four reported a statistically significant improvement in the rate of tooth movement (11,13,14,17). This could be attributed to positive RANKL production, which plays a crucial role in osteoclast development (29).

Additional outcomes reported in these studies regarding PTH were increased bone mineral density, bone volume, trabecular separation, and trabecular thickness (13,17,20). The metabolism and removal of calcitonin is regulated by the concentration of plasma calcium that interacts directly with osteoclast receptors to reduce the surface area of the ruffled border, thereby reducing activity of the receptor (30). Calcitonin was reported by two studies to control root resorption and dental eruption (31,32). Another study found that calcitonin had a direct stimulatory impact on bone formation and osteoblast mineralization (33). Three included studies evaluated the effect of calcium and one study assessed the effect of calcitonin on OTM (15,16,18,19). One study reported an increase in OTM, which was statistically significant in calcium deficient rats (19). Two other studies showed a substantial reduction in OTM, which was statistically significant (16,18).

As a secondary outcome, it was noticed that by minimizing the number of osteoclasts at the pressure site of the alveolar bone, various doses of calcitonin inhibited OTM (18). Root resorption was reported to be high even when used with calcium and was also noted to be dose dependent (15).

In calcium homeostasis, vitamin D plays a more active part. Two studies evaluated the effects of vitamin D on OTM (12,21). The observation period ranged from nine days (21) to 20 days (12). It was noted that both young and mature rats demonstrated a 1.2-2.5 time increase in the amount of OTM when compared to controls with local injections of vitamin D. Weekly injections of vitamin D in young rats did show increases in OTM; however, the results were not statistically significant (12). Vitamin D dosage was similar in both studies (20 µl of 10-10 mol/lt). Additional outcomes reported in these studies were the increase in the number of osteoblasts (21). However, the number of osteoclasts and areas of undermining resorption increased in the vitamin D group in another study (12).

Overall, it was found that animal studies assessing the effect of PTH, vitamin D, and calcitonin lack standardization in the amount of force to be applied, the orthodontic appliance to be used, and assessment methods. Further, conducting animal studies with robust methodology will aid in future research where specific cells could be targeted for controlled and safe accelerated orthodontic tooth movement.

The findings of this study have to be seen in light of some limitations as many of the primary studies were determined to poor quality, which in turn could affect the overall review results. It highlights the need to conduct well-designed animal studies in a manner where findings could be translated to humans in clinical trials. The split mouth design has limitations such as carry-across effects, period effects, and difficulty in finding patients with similarities between randomization units (jaws, quadrants). Moreover, split-mouth designs can be difficult to be done and assessed, especially when

sites are nested within patients and teeth are nested within sites, leading to clustering effects.

Standardization of methodology will also allow future researchers to implement quantitative synthesis as we were not able to done a meta-analysis due to diverseness in the primary studies (difference in dosage of the hormone and their synthetic derivative, frequency, type of orthodontic appliance, amount of force delivered and methods to assess orthodontic tooth movement).

Conclusion

Local application of vitamin D, its synthetic derivatives and PTH were found to increase orthodontic tooth movement, whereas calcitonin reduced tooth movement. For orthodontists, having sound knowledge of hormones involved in calcium metabolism will enable optimum clinical practice, especially while treating patients with osteoporosis or on supplements such as vitamin D, their synthetic derivatives, and calcium. In the future, topical application of these hormones and their synthetic derivatives could be used to stimulate bone cells directly or indirectly to increase or decrease orthodontic tooth movement.

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