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Review article

Vitamin administration on orthodontic tooth movement animal model: A systematic review

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ABSTRACT

Background: *Duration is a very important aspect of orthodontic treatment and is still challenging for orthodontists. Numerous studies investigating the effects of biological substances, including dietary supplements, on orthodontic tooth movement (OTM) rate indicate positive results. Efforts to improve the OTM rate can be classified into four main categories: biological, biomechanical, physical, and surgical. Numerous animal studies have evaluated the impact of biological substances on the rate of OTM, yielding positive outcomes compared to those not given biological substances.* ***Purpose:*** *This systematic review investigated the impact of dietary supplement delivery both locally and systemically on the rate of OTM.* ***Methods:*** *Nine databases were searched until January 31, 2023, for animal studies evaluating the effect of supplement administration on OTM. The Systematic Review Center for Laboratory Animal Experimentation's (SYRCLE) risk of bias tools were employed. This review's reporting adhered to the PRISMA guidelines.* ***Results:*** *Sixteen studies were identified for inclusion. Local injections of vitamin D exhibited variable effects. Vitamin C and zinc, as well as vitamin A, showed insignificant effects based on the OTM rate. Vitamin E showed conflicting results. Combined prostaglandin E2 (PGE2) and calcium can increase the OTM. Effects of systemic administrations of omega-3 fatty acids can decrease the OTM in vivo.* ***Conclusion:*** *The pace of tooth movement in animals may vary depending on the local or systemic administration of vitamins, as applied to OTM animal models.*

Keywords: *animal model; medicine; orthodontic tooth movement; supplement; vitamin*
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INTRODUCTION

Variations in the duration of orthodontic treatment are affected by a patient's characteristics, the treatment plan, the types of malocclusions, the presence or absence of extractions, utilization of removable or fixed appliances, techniques employed with fixed appliances, method of ligation, and one-phase or two-phase treatment, which is a critical aspect of orthodontic treatment and is still challenging for orthodontists. The relatively long duration of orthodontic treatment can cause various oral health problems, including increasing the risk of caries, gingival recession, and root resorption.[1–3]

Treatment time concerns the mobility of teeth during orthodontic treatment. Tooth movement happens when a mechanical stimulus triggers modification of the periodontal ligament and alveolar bone.[2,4] Forces operating on the tooth that alter the microenvironment around the periodontal ligament can be used to influence this tooth movement.[5] Inflammatory mediators, arachidonic acid metabolites, growth factors, neurotransmitters, and macrophage colony-stimulating factor (M-CSF) are all secreted in response to the applied force that could lead to bone remodeling.[6] Osteoclast differentiation and bone resorption are favored by a reduction in osteoblasts' production of osteoprotegerin (OPG) and an increase in M-CSF and receptor activator of nuclear factor-kappa beta ligand (RANKL). The release of the cytokines' interleukin-1 beta and tumor necrosis factor-alpha (TNF-α) increases inflammation and matrix metalloprotease

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levels while inducing osteoclast formation, function, and survival.[7,8]

Biochemical agents, nutrition, mechanical or physical stimulation of the alveolar bone, and surgical treatments to accelerate tooth movement are all possibilities for changing the pace at which teeth move.[9–11] Nutrition comes from the nutraceutical, a term coined by Stephen De Felice, which means food or a part of food that provides medical or health benefits. Nutrients containing minerals, vitamin D, and vitamin C greatly affect bone health in maintaining bone homeostasis.[12] Nutrition and orthodontics have a relationship in two directions. Optimal nutrition and a quality dietary intake can affect the speed of orthodontic treatment.[12]

The impact of administering various biological agents to accelerate tooth movement during to reduce the duration of orthodontics treatments. Vitamin D3 administered locally speeds up OTM. Three months following the initial vitamin D3 therapy, a cone-beam computed tomography scan revealed no root resorption.[13] A vitamin E-enriched diet increases the rate of OTM in rats, indicating that vitamin E may help accelerate OTM.[14] An omega-3 fatty acid systemic injection decreased orthodontic tooth mobility and showed anti-inflammatory and antioxidant properties.[15] Insufficient calcium throughout the body elevated OTM.[16,17] Additionally, this study sought to use a systematic review to examine the effects of local or systemic vitamin administration on the rate of OTM in animal models and in vivo.

METHODS

Participant-Exposure-Outcome-Study type question

The reporting guideline was developed through the preferred reporting items for systemic review and meta-analysis protocol (PRISMA-P) guidelines under the registration number 537644.[18,19] This study was performed to answer the question: "Does the application of local or systemic vitamin delivery have an impact on the OTM rate in an animal model compared to baseline?" The participants are the animals and animal models, the exposure is the application of local or systemic administration of vitamins, and the outcome is the OTM rate.

Inclusion criteria

There are several inclusion criteria in this study, as follows: Male Wistar rats, male mice, male Sprague Dawley rats, local or systemic administration of common supplement agents (omega-3, vitamin A, vitamin C, vitamin D, vitamin E, zinc, and calcium), orthodontic applications (closed coil spring, rubber separator, modification fixed orthodontic appliance, and a lateral expansion spring and orthodontic elastic), placebo intervention, no intervention, or the delivery of various doses of the chemical under investigation. Studies were included if published in English between January 1st, 1995, and January 31st, 2023.

Exclusion criteria

There were several exclusion criteria determined for this study: Human subjects, any OTM in animal topics, unhealthy rats, pregnant rats, other animals (e.g., rabbits, dogs, cats), other substances (e.g., platelet-rich plasma, parathyroid hormone [PTH], calcitonin, caffeine), other interventions (e.g., corticotomies, micro-osteoperforations, piezocision, low-level laser treatment, and vibration therapy), and the management of the local or systemic medications produced through chemical synthesis by mixing particular chemical components that are not regarded as biologics. These medications may include non-steroidal anti-inflammatory medicines (NSAIDs), bisphosphonates, immunosuppressants, cancer-fighting agents, and anticonvulsants. Studies were also excluded if no control group was present, the therapy was shorter than a day, other data was not being evaluated (e.g., bone density, bone volume), or if it was a case report, book review, article review, systematic study of the literature, thesis, or dissertation.

Information sources and search strategy

A health sciences librarian searched the whole contents of nine databases January 31st, 2023: ClinicalTrials.gov, Global Index Medicus, Cochrane Library, Springer, ProQuest, ScienceDirect, Scopus, EBSCO, and PubMed. The health sciences librarian's strategies were based on the MEDLINE search. The search was restricted to sources in the English language and with a start date between January 1st, 1995, and January 31st, 2023. The following keyword terms were used for identification: "orthodontic tooth movement" and "vitamin" or "vitamin D" or "Vitamin A" or "Vitamin B" or "Vitamin C" or "Vitamin E" or "Calcium" or "Zinc" or "Omega-3." Additionally, the retrieved reviews, reference lists of the included and excluded research, and other pertinent journals that were searched may be found in the Boolean database table (Table 1).[18]

Study selection

The first reviewers (H.F.L, E.I., and L.A.) independently conducted electronic literature searches and selected the studies and duplicate screening, extracting data. Disagreements were settled by consultation or conversation with a second reviewers (D.F.S., E.W.B, W.L).[5,11]

Data collection, measurements, and risk of bias individual analysis

Data was extracted according to the procedure described previously. Custom information regarding the chosen studies was gathered using a specially designed data collection form. The authors and the year of publication are included in this information, such as sample age or weight of the sample, number of samples, follow-up, study group/dose, orthodontic appliance, method delivery, outcomes, and conclusion. The Systematic Review Center for Laboratory Animal Experimentation (SYRCLE)[20] presents

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Table 1. Table of Boolean database

Database	Search strategy	Paper
ClinicalTrials.gov	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	4
Global Index Medicus	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	30
The Cochrane Library	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	20
Springer	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	411
ProQuest	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	2,262
ScienceDirect	Title, abstract, keyword: ((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	1,633
Scopus	Title, abstract, keyword: ((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	167
EBSCO	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	72
PubMed	((“orthodontic tooth) movement) AND (“Vitamin” OR “Vitamin D” OR” Vitamin A” OR “Vitamin B” OR “Vitamin C” OR “Vitamin E” OR “Calcium” OR “Zinc” OR “Omega 3”))	1,230

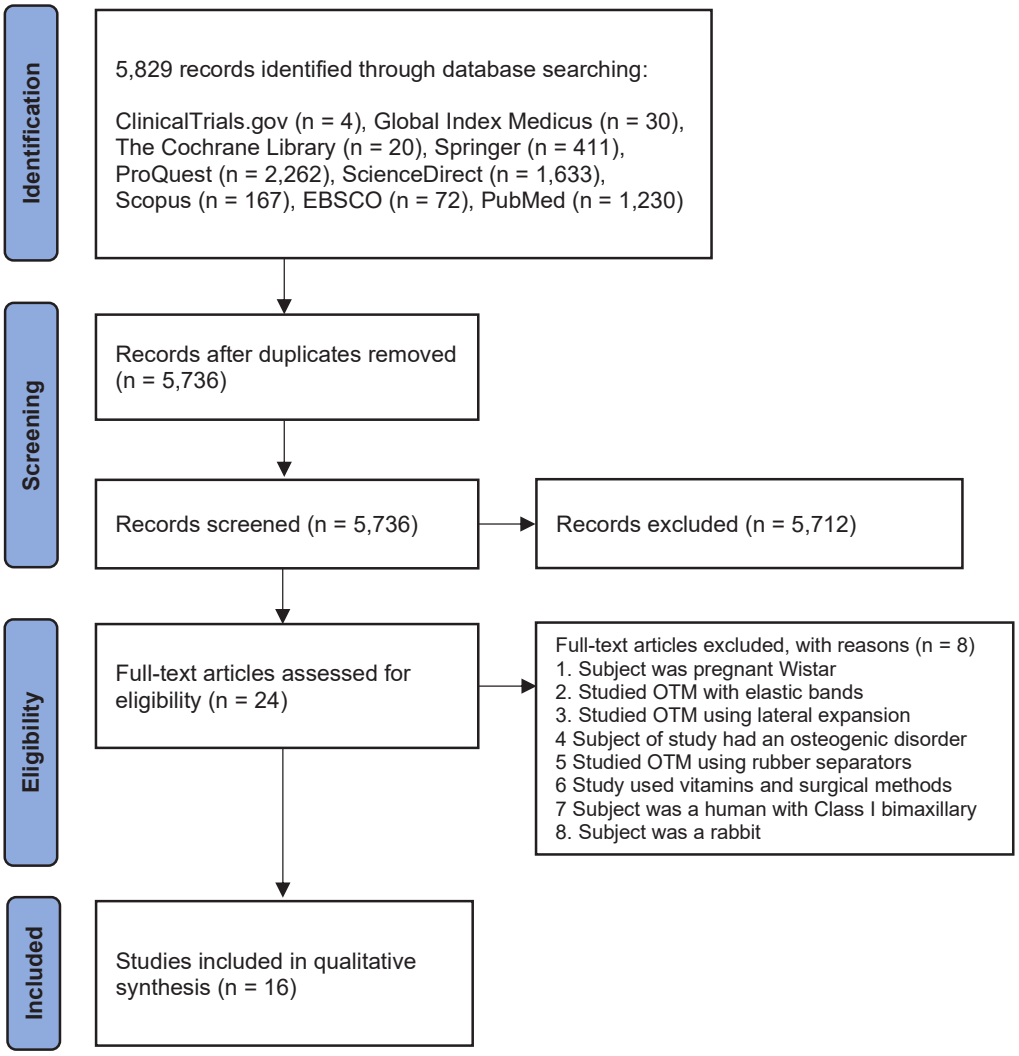

Figure 1. Preferred reporting item for systematic review (PRISMA).

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the types of biases, including selection, performance, attrition, detection, and reporting bias. The elements of the Cochrane RoB Tool relevant to animal experiments were utilized (Table 1).[21]

RESULTS

Study selection

A total of 5,829 records were identified through database searches; however, 93 were excluded as duplicates. and 5,736 records were screened. Of the remaining 24 full-text articles that were assessed for eligibility, eight articles were excluded: three articles' subjects were pregnant rats, two articles featured a sample other than a rat, one article had unhealthy rats, one article used human subjects, and one article evaluated the osteogenesis of expanding mid-palatal sutures. Finally, 16 full-text study papers from 1999–2023 were judged to be qualified for this systematic review (Figure 1).

Thirteen studies used Wistar rats,[14–17, 22–30] two used Sprague Dawley rats,[31,32] and one used male C57BL6 mice (wild type [WT] mice and GPR120-KO mice).[33] Sample age and weight varied from 40 days to 12 weeks and from 15 g to 300 g. Sample sizes were between 16 to 64 rats. Following up on OTM took anywhere from one to sixty days. Out of the 16 studies, five examined vitamin D,[22,29,32] one examined vitamin C,[14] one examined vitamin A,[25] three examined vitamin E,[14,23,28] one examined zinc,[26] two examined calcium,[16,17] and three examined omega-3.[15,27,33]

All articles included in the study were reviewed independently by the authors to assess the level of bias using SYRCLE's tool (Table 2); "yes" indicates a low risk of bias, "no" indicates a high risk of bias, and "unclear" indicates an unclear risk of bias.[20] Summaries of the study's risk of bias were made according to the Higgins et al.[21] method.

Table 3 indicates that the use of exogenous biological molecules to enhance tooth movement in orthodontic treatments has been extensively evaluated through animal studies. The administration of specific molecules, such as prostaglandin, PTH, vitamin D,[30] and vitamin E,[14,24,28] has demonstrated promising results, indicating their significant role in bone remodeling and tooth movement. Vitamin C,[24] zinc,[26] and omega-3 fatty acids have been found to reduce the number of osteoclasts and influence OTM.[33]

Tabel 2. Summary of risk of bias assessment for randomized studies—SYRCLE's tool[20]

Domain		Khalaf et al. (2022)[22]	Bolat et al. (2020)[23]	Tankura et al. (2021)[24]	Nishio et al. (2017)[25]	Gratton et al. (2022)[31]	Seong et al (2022)[14]	Akhoundi et al (2016)[26]	Seifi et al. (2003)[16]
Selection bias	Random sequence generation	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
	Baseline characteristics	Low	Low	Low	Low	Low	Low	Low	Low
	Allocation concealment	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
Performance bias	Random housing	Low	High	High	High	High	High	Low	Low
	Blinding	High	High	High	High	High	High	Low	High
	Random outcome assessment	High	High	High	High	High	High	High	High
Attrition bias	Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low
Reporting bias	Selective outcome reporting	Low	Low	Low	Low	Low	Low	Low	Low
Other bias		Low	Low	Low	Low	Low	Low	Low	Low
Overall		Low	Low	Low	Low	Low	High	Low	Low

Domain		Seifi et al. (2015)[17]	Ogrenim et al. (2018)[15]	Ma et al. (2023)[33]	Morimoto et al. (1999)[27]	Kale et al. (2004)[32]	Sufarnap et al. (2020)[28]	Kawakami et al. (2004)[29]	Moradi nejad et al. (2021)[30]
Selection bias	Random sequence generation	Unclear	Unclear	High	High	Unclear	Low	High	Low
	Baseline characteristics	Low	Low	Low	Low	Low	Low	Low	Low
	Allocation concealment	Unclear	Unclear	High	High	Unclear	Unclear	High	Low
Performance bias	Random housing	Low	High	High	Low	Low	High	High	Low
	Blinding	High	High	High	Low	Low	Low	High	Low
	Random outcome assessment	High	High	High	Low	High	Low	High	Low
Attrition bias	Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low
Reporting bias	Selective outcome reporting	Low	Low	Low	Low	Low	Low	Low	Low
Other bias		Low	Low	Low	Low	Low	Low	Low	Low
Overall		Low	Low	High	Low	Low	Low	High	Low

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Table 3. Study characteristics: participants (sample, age/ weight, size), intervention (orthodontic treatment), observation, comparison (biological substance), dose and route of administration, outcome (rate of tooth movement)

Author & Years	Animal species	Age / Weight	N	Follow-up (day)	Study Group/ Dose	Orthodontic appliance	Conclusion
Khalaf et al. (2021)[22]	Male Wistar Rats	8-9 weeks/ 300-330 g	16	0, 7, 14, 21	2 groups Control Group (Average Vit D levels) (n=8) Experimental Group (induced vitamin D deficiency (n=8) The injection of 0.1 ml was a dilution of Saline and paricalcitol which was injected 3 times per week for each rat	NiTi closed coil spring with force 60 g was applied upper incisor to the upper first molar.	Induced vitamin D deficiency in rats not affected the rate of orthodontic tooth movement
Bolat et al. (2020)[23]	Male Wistar Albino Rats	6 - 8 weeks/ 120-180 g	51	1 - 18	6 groups consist of 5 experimental and 1 control group Group I (n=9): The orthodontic appliance was applied, along with daily intraperitoneal injections with 150 mg/kg of vitamin E. Group II (n=10): The orthodontic appliance was applied, along with daily intraperitoneal injections with 150 mg/kg of vitamin C. Group III (n=9): The orthodontic appliance was applied, along with local injections of 20 µL of vitamin E once every three days. Group IV (n=8): The orthodontic appliance was applied, along with local injections of 20 µL of vitamin C once every three days. Group V (n=9): The orthodontic appliance was applied and the rats did not receive any vitamin injections. Control group (n=6): The rats received no treatment.	NiTi closed coil spring with force 50 g was applied upper incisor to the upper first molar.	In this experimental study, the application of systemic or local vitamin C and E did not affectthe orthodontic tooth movement rate. However, osteoblastic activity was higher at the tension side in all the vitamin groups. Administration of vitamins C and E during orthodontic tooth movement might be helpful in shortening the retention period and decreasing the risk of relapse due to the demonstrated positiveeffects on bone remodeling at the tension area.
Tankura et al. (2021)[24]	Male Wistar rat	6 weeks / 150-200 g	30	7, 14	3 groups: Control group: receiving distilled water (DW). C 500 group: 44.05 mg/kg rat body weight of vitamin C supplement equal to 500 mg in a 60-kg man. C 1,000 group: getting vitamin C supplement as 88.10 mg/kg rat body weight comparable with 1,000 mg in a man with 60 kg weight.	NiTi closed coil spring with force 60 g was applied upper incisor to the upper first molar.	Vitamin C supplement at a 1,000 mg/day dose could increase distance of OTM in Wistar rats. OTM enhancement was observed in both rats obtaining two different vitamin C concentrations with significant improvement in C1,000 group at day 14.
Nishio et al. (2017)[25]	Male Wistar rate	40 days (100±50 g)	16	7	Experimental group: 1. extraction (n=4) received isotretinoin by gavage (7.5 mg/kg). 2. extraction (control; n=4) no received isotretinoin. Control group: 3. non extraction (n=4) received sunflower oil by gavage. 4. non extraction (control; n=4) no received sunflower oil.	a NiTi closed coil spring with force 50 g was applied upper incisor to the upper second molar.	The isotretinoin did not affect the OTM.
Gratton et al. (2022)[31]	Male Sprague Dawley rats	250 g	32	0, 10, 17, 24, 47	4 groups: Systemic administration experimental gavage (EG) = received a daily solution of vitamin D (50 ng/mL) in a volume varying from the rat body weight (100 ng/kg) control gavage (CG) = received daily by phosphate buffered saline (PBS) solution (0.1 M, pH 7.2) in an equivalent dose to the volume of Vit D in EG group Local administration experimental injection (EI) = a solution of Vit D (1 3 1010 M) control injection (CI) = received the PBS solution	NiTi closed coil spring with force 50 g was applied upper incisor to the upper first molar.	The systemic administration of Vit D caused a decreased in the OTM rate by generating more higher bone mineral density.

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Seong et al. (2022)[14]	Male Wistar rat	6 weeks	32	4, 14	4 groups: Group 1 (n = 8): OTM for 4 days + regular diet Group 2 (n = 8): OTM for 14 days + regular diet Group 3 (n = 8): OTM for 4 days + vitamin E diet (a custom rodent diet supplemented with 600 IU/kg of vitamin E) Group 4 (n = 8): OTM for 14 days + vitamin E diet (a custom rodent diet supplemented with 600 IU/kg of vitamin E)	NiTi closed coil spring with force 10 g was applied upper incisor to the upper first molar.	An enriched vitamin E diet increases the rate of OTM in rats, suggesting that vitamin E may be useful to accelerate OTM.
Akhoundi et al. (2016)[26]	Male Wistar rats	200-250 gr	44	1, 40, 60	4 groups(n=11): Control group 0 ppm Zn Sulfate in distilled water Experimental group Group 1: 1.5 ppm Zn Sulfate in distilled water Group 2: 20 ppm Zn Sulfate in distilled water Group 3: 50 ppm Zn Sulfate in distilled water	NiTi closed coil springs were ligated between left maxillary first molars and incisors of all rats, force of 60 g.	Systemic Zn supplementation up to 50 ppm decreased OTM.
Seifi et al. (2003)[16]	Male Wistar rats	8 weeks/ 230-300 gr	24	0, 7	3 Groups (n=8) Group 1 (Control): (i) Distilled water 0.1 ml was injected at mesiobuccally mucosa of right first molar after insertion of orthodontic appliance (normal). (ii) Left side was not under any force or injection (control). Group 2 (PGE2): 0.1 ml of 1mg/ml PGE2 dissolved in 1% lidocaine Group 3 (PGE2+Ca): 1 ml of 1 mg/ml PGE2 dissolved in 1% lidocaine+10% Ca (200 mg/kg)	Closed coil spring 5 mm long right maxillary first molar to Is by ligature wire; 60 g.	decrease in root resorption and an increase in OTM in the PGE2 + Ca group.
Seifi et al. (2015)[17]	Male Wistar rats	6-8 weeks old/ 230-300 g	64	0, 21	8 Groups (n=8) Experimental Group (A): A.1- 20 µg/kg thyroxine + orthodontic force A.2- 0.1 ml of 1mg/ml PGE2 s in 1% lidocaine + orthodontic appliance A.3-10% Ca 200 mg/kg; A.4-0.1 ml of 1 mg/ml PGE2 + 10% Ca 200 mg/kg A.5- Orthodontic appliance + 20 µg/kg thyroxine +0.1 ml of 1 mg/ml PGE2+ 10% Ca 200 mg/kg; A.6- 20 µg/kg thyroxine + 10% Ca 200 mg/kg; A.7- 20 µg/kg thyroxine + 0.1 ml of 1mg/ml PGE2 + 10% Ca 200 mg/kg; Control Group (B): 0.1 ml of distilled water (studied only for root resorption) divided into two groups: normal and control.	Archwire NiTi closed coil spring 5 mm, right first molar and anteriorly to the upper right incisor.	Combination of thyroxine and prostaglandin E2 would decrease the root resorption and increase the rate of orthodontic tooth movement in rats.
Ogrenim et al. (2018)[15]	Adult male Wistar albino rats	12-week-old	56	3, 7, 14	Rats were randomly divided into seven groups ($n = 8$ each): control group (without any treatment) tooth movement groups (three groups of animals with only tooth movement) omega groups (three groups of animals with tooth movement and omega-3 administration)	NiTi closed coil spring with force 40 g was applied upper incisor to the upper first molar.	Omega-3 fatty acids could decelerate OTM by decreasing the number of osteoclasts.

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Ma et al. (2023)[33]	Male C57BL6 mice (WT mice and GPR120-KO mice)	8-12 weeks old	16	12	4 groups (n=4) PBS (Phosphate Buffered Saline) TNF α (3µg/day) DHA (100µg/day) + TNF α (3µg/day) DHA (100µg/day)	NiTi closed coil spring with force 10 g was applied upper incisor to the upper first molar.	DHA suppresses bone resorption induced by TNF-a in vivo via GPR120, and the same tendency was also demonstrated in OTM.
Morimoto et al. (1999)[27]	Male Wistar strain rats	4-week-old	60	0, 3, 7, 14	Divided into 2 groups (n=30) Experimental Group: was fed a purified diet containing 10% refined fish oil (rich in n-3 Fatty acid) Control group: were given a diet containing 10% corn oil (rich in n-6 fatty acid)	A lateral expansion spring was placed between the right and left maxillary first molars. The spring using force of 20 g.	The amount of tooth movement in the fish oil group was 80% of that seen than in controls. The number of osteoclasts and the degree of bone resorption on the pressure side during tooth movement was significantly lower in the fish oil group, nearly 60% and 80%, respectively, of the levels observed in controls. A fish oil enriched diet reduces osteoclastic activity and the subsequent alveolar bone resorption that is key to experimental tooth movement.
Kale et al. (2004)[32]	Male Sprague-Dawley Rats	6-week-old	37	9	Divided into 5 groups: Baseline control group (n=5): no treatment for 9 days Appliance control group (n=8): received no injection. Used to observed the amount of OTM caused mechanical force alone Dimethyl sulfoxide (DMSO) group (n=8): received orthodontic appliances and 20 µL injections of DMSO on days 0, 3, and 6. DMSO is the vehicle of 1,25-DHCC. The DMSO injection group was created to evaluate whether there are any histologic effects of DMSO. 1,25-DHCC group (n=8): They received orthodontic appliances. Injections of 1,25 DHCC (20 L of 10 mol/L) were given on days 0, 3, and 6. PGE 2 group (n= 8): They received orthodontic appliances and a single injection of 0.1 mL of 0.1 g PGE 2 on the day of appliance placement.	A modification of a fixed appliance, described by Boisson and Gianelly, 35 was used to move maxillary incisors laterally. The appliance consisted of 2 incisor bands constructed with band material (0.12-4.56 mm) (Dentaurum, Ispringen, Germany) with eyelet-like attachments on their palatal sides.	Both PGE 2 and 1,25-DHCC increased the amount of tooth movement in a 9-day experimental period with no detectable adverse effects. This increase can be considered clinically significant. Although the amount of tooth movement was very similar, osteoclastic activity in the PGE 2 group was significantly greater than in the 1,25-DHCC group. On the other hand, in the 1,25-DHCC group, the number of osteoblasts on the external surface of the alveolus was significantly greater. This finding indicates that 1,25-DHCC promotes bone formation more potently than does PGE2, favoring the coupling of formation and resorption in alveolar bone remodeling during orthodontic tooth movement.

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Sufarnap et al. (2020)[28]	Healthy male wistar rats	4-5 months / 15-250 gr	56	0, 1, 3, 7	Wistar rats (n=56) were divided into two groups: Group 1: served as the control groups. Group 2: was given vitamin E for 14 days before application of orthodontic force. Each group was divided into four subgroups (n=7), corresponding to the number of days orthodontic force lasted, i.e. 0, 1, 3, 7 days.	A rubber separator was inserted between the maxillae's incisors to produce non-invasive experiments.	The outcome of this study demonstrated that group 2 resulted a better tooth movement compared to group 1 and significantly found on day 3, based on the distance measurement. The osteoclast cell numbers were the same within both control groups, whilst the number of osteoblast cells in group 2 was significantly higher than those in group 1.
Kawakami et al. (2004)[29]	Male wistar rats	7 weeks old	16	7, 14	Group 1: a piece of orthodontic elastic band (0.5-mm thickness) was inserted bilaterally between the first and second maxillary molars of each rat, according to Waldo and Rothblatt. (n=8) and with vehicle on the left side (non-TM PBS; n=8). Group 2: rats without the insertion of elastic bands was injected with the same dose e of 1,25(OH)2D3 on the right side (non-TM 1,25(OH)2D3; n=8) and with vehicle on the left side (non-TM PBS; n=8).	Orthodontic elastics were inserted between the maxillary first and second molars on bilateral sides in male rats.	These findings suggest that local application of 1,25(OH)2D3 enhances OTM.
Moradi nejad et al. (2021)[30]	Adult male Wistar rat	12 weeks/ 252.5± 18.9 g	32	0, 14	The rats were randomized into the following 4 groups: (1) D3, (2) ALN, (3) ALN1D3, (4) no medication	The modification of the fixed appliance.	Systemic vitamin D3 can reverse this inhibitory effect of ALN on OTM may accelerate OTM.

DISCUSSION

OTM is described as a biological reaction to the disruption of the dentofacial complex's physiological balance caused by an externally applied force. The cellular, molecular, and tissue-response processes during OTM have been thoroughly examined. Individual or collective variables may impact remodeling processes and, consequently, tooth displacement, whereas changes in bone turnover and density might influence movement velocity. Numerous biological factors contribute to the inflammatory process and modify the pathways associated with bone remodeling during OTM. This systematic review assessed the efficacy of locally administered biological substances (including vitamins D, C, E, and A, as well as zinc, calcium, and omega-3 and its derivatives) in significantly accelerating OTM in animal models.[34,35]

In this present study, male rats were chosen because of the fluctuation of estrogen's sex hormones in females. Estrogen is a hormone crucial in bone metabolism, particularly in bone remodeling throughout orthodontic treatment. It is recognized for inhibiting osteoclast activity, either directly or indirectly. Estrogen directly inhibits bone remodeling by decreasing osteogenesis and chondrogenesis. Estrogen may indirectly influence osteoclasts by enhancing calcitonin production. Estrogen-induced calcitonin secretion inhibits osteoclast activity in bone resorption.[36,37]

According to the evaluation presented in Table 1, 13 studies were assessed to have a low risk for bias, while three were classified as high risk. Random sequence generation was identified as having unclear risk, with four instances categorized as high risk [14,27,29,33] and two as low risk.[28,30]

Vitamin D is essential because it helps the body absorb calcium, magnesium, iron, phosphate, and zinc in the intestines. Vitamin D helps the body use calcium and phosphorus, chemicals the jaws and teeth need to grow. Vitamin D treatment improves bone growth for stabilization after OTM. This group had more the periodontal ligament vessels, lacunae, osteoclasts, and osteoblasts than the control group and other treatment groups. Studies have shown that alveolar bone resorption, the amount or activity of osteoclasts, and osteoblast counts all increased. Vitamin D may speed up the movement of teeth by increasing bone turnover. This can happen by boosting bone resorption by turning osteoclasts into osteoblasts and making them more active and increasing bone formation by turning osteoclasts into osteoblasts.[34] Because vitamin D has been shown to speed up OTM, it was thought that treating OTM with vitamin D would have a harmful effect.[31] Another substance that has been tested to move teeth more effectively in orthodontics is 1,25-dihydroxycholecalciferol (1,25-DHCC). It is the active form of vitamin D, one of the three calcific hormones.[32] The study results suggest that local injections of prostaglandin E2 (PGE2) and 1,25-DHCC can increase the amount of tooth movement. Due to its well-balanced influence on bone formation and bone resorption, 1,25-

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DHCC is more efficient for controlling bone regeneration during OTM.[32] A systemic dose of vitamin D supplement (0.25 µg) accelerates canine retraction movement over 60 days in the experimental group as compared to the control group. The average speed of movement was faster in the experimental group than in the control group.[38] During OTM, vitamin D tells osteoblasts whether to multiply or die, controls their development into cells that make a bone matrix, and then controls the mineralization of the bone matrix to bone remodeling.[39] Another study showed that vitamin D deficiency may not significantly harm OTM rates, and vitamin D injections throughout the body decreased the OTM rate. This variation could be caused by many factors that were taken into account in each trial, such as the length and dosage of the drug as well as various orthodontic equipment.[22,31] After administering vitamin D3 to humans, Shetty et al.[40] demonstrated outcomes resembling reduced tooth movement. Tashkandi et al.[41] discovered that while lower or higher amounts of vitamin D in saliva hindered the OTM, normal levels allowed maximal tooth movement. The vitamin D injection group's lack of conclusive results was likely caused by an inadequate dosage of the vitamin injected into the alveolar bone rather than by the absence of an impact. Other elements that affect OTM are the RANKL/OPG ratio, serum calcium, phosphorus, and parathyroid hormone. These may change how bones work and how they are controlled by hormones in the body and things in the bone that affect bone cells.[22] Based on the studies, it was found that the different biological agents had different effects on the rate of movement. For example, PGE2 combined with vitamin D caused an increase in OTM, while vitamin D alone also increased in the rate of movement.[16,22,32] According to the biological agents studied, PGE2 plays the most significant role in speeding up OTM because it affects osteoclasts and osteoblasts.[22]

The pace of OTM was not affected by the systemic or topical administration of vitamins C and E, according to another study. However, in all vitamin groups, osteoblast activity was more significant on the tension side. Following OTM, it was discovered that the group utilizing vitamins C and E systemically had more collagen fibers than the group using equipment without vitamins, both in terms of stress and pressure. Interestingly, in all device groups, the distance on the control side shrunk dramatically because the right incisors were drawn apart by the impact of the left ligature's pull. Additionally, it has been found that rats' molars gradually migrate farther apart. This phenomenon may have an impact on how mobile teeth are.[23] Several studies have shown that ascorbic acid (vitamin C) stimulates osteoclasts in cell growth media. Osteogenesis and dental tissue organization stop when there is not enough vitamin C. Systemic vitamin C supplemented at a 1,000 mg/day dose could increase the distance of OTM in Wistar rats.[24] Local injection of vitamin C and vitamin E positively affected bone formation on the tension side of the teeth during OTM experiments, but it did not affect the OTM rate.[23]

As a well-known antioxidant, vitamin E is one of the most well-liked supplements in the US. Vitamin E could impact bone metabolism. On days 4 and 14, rats fed with a high vitamin E diet had a considerably higher OTM rate than rats fed with a standard diet. However, although the pace of OTM increased on days 4 and 14, there was no discernible variation in the number of osteoclasts at that point.[14,28] Systemic vitamin E supplements of 600 IU/kg influence OTM acceleration.[14] Administering 60 mg/kg of vitamin E through a gavage needle will stop teeth from moving because it reduces inflammation. It will also help bones grow.[28]

Isotretinoin is a pharmaceutical drug derived from vitamin A. Isotretinoin is widely used to treat severe cystic acne in young adults. The mechanism of action of isotretinoin is not fully understood; it is believed that this drug affects cellular differentiation, growth, morphogenesis, and apoptosis while controlling tumor growth and modifying cellular cohesiveness. Isotretinoin did not affect the OTM, nor did it cause an alteration in maxillary bone volume.[25]

The mineral zinc is known to help many types of cells grow and divide, including osteoblasts (MC3T3-E1 cells), vascular cells, smooth muscle cells, and CD8+T cells. Stem cell growth is directly related to a lack of zinc. One percent of all zinc is found in plasma. Zinc plays a role in multiple biological processes, including cell structure, regulation, and catalysis. Over 300 enzymes use it as a ligand.[42] Many studies have shown that zinc is essential to human and animal chemistry. Zinc is involved in cell metabolism, gene expression control, protein production, mineralization, and bone formation.[43] It has been advised that zinc supplements be taken during the early stages of an inflammatory response since it is known to be extremely important in tooth mobility. Additionally, several investigations have shown that zinc can only function in areas where it is deficient.[44] Previous research has shown that the length of time zinc is applied may affect its effect on bones. Therefore, any possible effects of this mineral become less potent over time. OTM decreased from the first amount of zinc up to 20 ppm. However, OTM increased in group 3 when they were given 50 ppm of zinc. Because of the hypothesized anti-resorptive properties of zinc, there may be a decrease in OTM, but the explanation for the rise might be more complicated.[26] No interaction with the OTM rate was observed after administering zinc compounds. Nevertheless, zinc may change bone metabolism by increasing osteoblasts' activity and reducing bone resorption. The length of administration might affect the effects of zinc on bone. Structures with changed surface properties that contain zinc help bones grow better. Surface treatment techniques coat titanium with zinc. Mechanical tests on rabbit models show that the surface-modified material caused more bone to adhere to it.[45] Zinc concentrations were also observed by O'Connor et al.[44] It has been found that rats need to be exposed to a substantial amount of zinc for acute poisoning to happen. The LD50

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for zinc given orally was 237–623 mg/kg, and the LD50 for zinc given intraperitoneally was 28–73 mg/kg. Several studies have shown that zinc affects bone metabolism by increasing osteoblastic activity and decreasing osteoclastic bone loss. Adding up to 50 ppm of zinc to the body's diet reduced OTM.[26]

An insufficiency of zinc and protein deficit results in inadequate bone growth concurrent with malocclusion of teeth. In the preliminary study, it is known that the amount of calcium content in 100 g of anchovy fish is 800 mg. Anchovies contain minerals, proteins, and vitamins, and it is expected to stimulate new bone formation by enhancing the proliferation of growth factors that contribute to the increased activity of osteoblasts and the inhibited activity of osteoclasts. Vitamin D helps the body use calcium and phosphorus, which are essential for building bones and teeth. Without enough vitamin D, rickets, maxillary dysplasia, trouble with facial stitches closing, an open bite, transverse hypo dimension, and a malformed mouth can develop.[46] The rate at which teeth move is also based on the patient's unique biology. Because more adult patients are getting orthodontic care, it is important to know about conditions that affect calcium homeostasis and bone physiology. These include Paget's disease, hyperparathyroidism or hypoparathyroidism, osteoporosis, which mostly affects women, and, very rarely, bone metastasis.[47] The aforementioned suggests that the calcium injection-induced hypoparathyroidism in the current investigation should have prevented bone remodeling and tooth displacement.[48]

Systemic calcium shortage (cit Goldie and King) increased OTM. According to the study's findings, OTM occurred with a larger decreased root resorption in the calcium group than in the control group, compared to PGE2; calcium and PGE2 both lowered OTM.[16,17] Secondary hyperparathyroidism is brought on by low calcium levels, which also enhance the release of vitamin D active metabolites and parathyroid hormone (PTH).[47,48] PTH acts directly on osteoblasts and osteoclasts in the bone to trigger a rapid calcium release, but it also promotes long-term changes.[44]

Omega-3, a mixed fatty acid, reduces inflammation by lowering the amounts of cytokines and molecules that cause inflammation. Eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) make up omega-3. Some essential fatty acids, such as EPA and DHA, can change how bones grow and shape. The omega-3 supplement slowed the movement of teeth in the dental group.[15,27,33]

The effect of dietary lipids of omega-3 fatty acids, systemic administration of omega-3 fatty acids, and DHA on OTM in rats showed decreased OTM rates.[15,27,33] Numerous medical professionals advise using omega-3 fatty acid dietary supplements because of their advantageous effects on the human body.[15] The long-chain n-3 polyunsaturated fatty acid DHA, which has 22 carbon atoms and six double bonds, is one of the polyunsaturated fatty acids.[33]

Omega-3 fatty acids reduce the production of PGE2, a similar effect to NSAIDs. NSAIDs inhibit prostaglandins (PGs) synthesis by inhibiting cyclooxygenase, an enzyme that produces PGs from arachidonic acid.[27,49,50] Changes in arachidonic acid levels affect bone resorption, a critical factor in tooth movement.[15] DHA has been shown to have various advantageous health benefits, including anti-inflammatory properties. According to research, DHA inhibits the growth of osteoclasts through binding to the GPR120 omega-3 fatty acid receptor. TNF-α is produced by orthodontic force and promotes osteocyte differentiation in the OTM. DHA inhibits the formation of osteoclasts, and bone resorption is stimulated by TNF in GPR120-KO mice but not WT mice in vivo, suggesting that GPR120 is a regulator of DHA's ability to inhibit TNF-induced bone loss of osteoblasts.[33] Soy isoflavone genistein can be given to increase the amount of osteoblasts around tension points and lower OTM.[50] Active ingredients in *Stichopus herrmanni* include proteins (86% of which are collagens), glycosaminoglycans (such as hyaluronic acid and chondroitin sulfate), cell growth factor, EPA, and DHA—all of which are important in tissue healing.[51] EPA can raise TRAP-6 levels, which is an osteoclast activity that breaks down periodontal tissue and alveolar bone in areas where teeth are moving in orthodontics.[52] Anchovy also contains protein, which can change the balance of calcium in the body in positive and negative ways. The effects of protein on bone growth and fractures depend on the amount of calcium in food. Giving people with broken bones protein in their food may help the body produce growth factors, such as insulin-like growth factor 1, which tells osteoblasts to make bones.[53] Natural ingredients, such as anchovies, fish oil, and soybean oil, have been recommended for medical uses, such as speeding up tooth movement by eating chocolate with caffeine. Caffeine affects bone apposition and resorption, which is what makes OTM possible.[54] Tooth movement during orthodontic treatment involves bone breaking down on the stress side and bone growth on the pressure side.[55]

Most studies had a high or unclear risk of bias because of how they were conducted. Inconsistent or contradictory findings added to the uncertainty about the level of evidence. This problem lowers the overall quality of evidence in the animal context. Doses and methods of administration were not always similar to those used in animals.

The effects of several supplement agents on the pace of tooth movement are summarized in this systematic study. The experimental group's canine retraction movement is accelerated over 60 days compared to the control group by a systemic vitamin D supplement (0.25 μg).[2] A 600 IU/kg systemic vitamin E supplement has been shown to speed up OTM, whereas a 1,000 mg/day vitamin C supplement may lengthen OTM in Wistar rats.[3] This study describes the shortcomings of the clinical trials undertaken thus far to assess the efficacy of these medicines in animals and offers some recommendations for thorough investigation.

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As the most efficient method of speeding up OTM to shorten treatment times, vitamin administration treatment is extremely difficult for orthodontists. Additional research on biological agent improvement of the present OTM methods may prove beneficial. Future research should also standardize study design regarding medication dosages, the type and duration of tooth movement, and control of the factors associated with the risk of bias. Furthermore, additional studies of periodontal and dental changes over more extended periods will be crucial to clarify the biological mechanisms pertinent to these studies.

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