Original Article

pISSN 2234-7518 • eISSN 2005-372X
https://doi.org/10.4041/kjod23.064
Korean J Orthod 2024;54(1):26-47

THE KOREAN JOURNAL of ORTHODONTICS
KJO

# Role of vitamin D for orthodontic tooth movement, external apical root resorption, and bone biomarker expression and remodeling: A systematic review

Martina Ferrillo[a]
Dario Calafiore[b]
Lorenzo Lippi[c,d]
Francesco Agostini[e,f]
Mario Migliario[g]
Marco Invernizzi[c,d]
Amerigo Giudice[a]
Alessandro de Sire[h]

[a]Dentistry Unit, Department of Health Sciences, Magna Graecia University of Catanzaro, Catanzaro, Italy
[b]Physical Medicine and Rehabilitation Unit, Department of Neurosciences, ASST Carlo Poma, Mantova, Italy
[c]Physical and Rehabilitative Medicine, Department of Health Sciences, University of Eastern Piedmont "A. Avogadro", Novara, Italy
[d]Translational Medicine, Dipartimento Attività Integrate Ricerca e Innovazione (DAIRI), Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[e]Department of Anatomy, Histology, Forensic Medicine and Orthopedics, Sapienza University, Rome, Italy
[f]Department of Neurological and Rehabilitation Science, IRCCS San Raffaele, Rome, Italy
[g]Dentistry Unit, Department of Translational Medicine, University of Eastern Piedmont "A. Avogadro", Novara, Italy
[h]Physical Medicine and Rehabilitation Unit, Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Catanzaro, Italy

**Objective:** This systematic review aimed to evaluate the correlation between vitamin D levels and the rate of tooth movement, external apical root resorption, bone biomarker expression, and bone remodeling. **Methods:** Three databases (PubMed, Scopus, and Web of Science) were systematically searched from inception until 14th March 2023 to identify studies investigating the correlation between orthodontic tooth movement and vitamin D in animals and humans. The quality assessment was made in accordance with the Joanna Briggs Institute Critical Appraisal Checklist. **Results:** Overall, 519 records were identified, and 19 were selected for the qualitative synthesis. Eleven studies investigated the effect of local administration (injections in the periodontal ligament, to the gingiva distal to the teeth, or submucosae palatal area) and systemic administration (oral supplementation) of vitamin D on tooth movement, external apical root movement, pro-inflammatory cytokines, and bone remodeling factors. The remaining eight studies investigated the correlation between serum vitamin D levels and salivary vitamin D levels on bone turnover markers and tooth movement. **Conclusions:** The findings of this systematic review support that vitamin D3 local injections might increase the rate of tooth movement via the receptor activator of the nuclear factor-kB/osteoprotegerin axis. However, the non-uniform study designs and the different protocols and outcome methods make it challenging to draw reliable conclusions.

**Key words:** Vitamin D, Calcitriol, Orthodontic tooth movement, External apical root resorption

Received April 10, 2023; Revised August 4, 2023; Accepted September 18, 2023.

**Corresponding author:** Alessandro de Sire.
Professor, Physical Medicine and Rehabilitation Unit, Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Viale Europa 88100 Catanzaro, Italy.
**Tel** +390961712819 **e-mail** martina.ferrillo@unicz.it

**How to cite this article:** Ferrillo M, Calafiore D, Lippi L, Agostini F, Migliario M, Invernizzi M, Giudice A, de Sire A. Role of vitamin D for orthodontic tooth movement, external apical root resorption, and bone biomarker expression and remodeling: A systematic review. Korean J Orthod 2024;54(1):26-47. https://doi.org/10.4041/kjod23.064

## INTRODUCTION

Orthodontic tooth movement involves applying mechanical forces that induce bone remodeling and bone resorption at the pressure sites and bone formation at the tension sites.[1] A cascade of chemical mediators might lead to a signal transmission from the extracellular matrix up to gene modulation, regulating the gene activation or suppression, changing the cytoskeletal structure, and altering the nuclear protein matrix.[2,3]

Several factors are involved in the bone remodeling process, including receptor activator of nuclear factor kappa B (RANK)-related ligand (RANKL), tumor necrosis factor (TNF), and osteoprotegerin (OPG),[4] whose ligand (OPG-L) was identified as a membrane-bound molecule.[4,5] Both RANKL and OPG-L can bind to the RANK, which is located on osteoclasts.[4,5] Osteoclasts secrete OPG, whose main function is blocking the activity of the osteoclast cells, and consequently the bone resorption.[4,5] TNF, interleukin-1 (IL-1), growth factors (transforming growth factor-beta [TGF-β], bone morphogenetic protein [BMP]), and prostaglandin E (PGE) are cytokines that might regulate the OPG/OPG-L ratio, affecting the osteoclast lifecycle, promoting both their differentiation and apoptosis.[5] When the balance favors the OPG, the number of active osteoclasts is reduced, whereas when the balance favors OPG-L, the number of active osteoclasts increases.[6] Among the mediators of the inflammatory process, interleukin-6 (IL-6), interleukin-1 (IL-1b), epidermal growth factor, TNF-α, and β2 microglobulin were shown to increase during orthodontic treatment.[7] The soluble RANKL/OPG ratio could also affect the external apical root resorption (EARR).[8] In fact, an increased OPG/RANKL ratio can inhibit cementum resorption and remodeling in cementocytes.[9]

Furthermore, it has been shown that the vitamin D receptor (VDR)-binding sites in the DNA may stimulate the physiological regulation of different genes at the level of transcription, including RANKL, OPG, cyclooxygenase-2 (COX-2) and lL-6, thus conditioning skeletal growth, muscle and bone homeostasis.[10-13]

In this context, vitamin D3 was shown to decrease the RANKL/OPG ratio, reducing the osteoclastic bone resorption via VDR in mature osteoblasts. On the other hand, increased levels of vitamin D were shown to increase the RANKL/OPG ratio, inducing osteoclastic bone resorption via VDR in less-mature osteoblasts.[14]

In 2021, Küchler et al.[10] showed that different physiological concentrations of vitamin D and single nucleotide polymorphisms in the VDR gene might regulate the gene expression of the periodontal ligament fibroblasts after simulation of an orthodontic compressive strain. They showed that RANKL was overexpressed, leading to an increased RANKL/OPG ratio during the pressure. This finding confirms that vitamin D might have an impact on the balance between bone formation and resorption, which is considered crucial for the orthodontic tooth movement.[10]

The scientific interest in vitamin D has been increasing in the last decade. In dentistry, vitamin D supplementation has been proposed to promote oral health.[15,16]

The scientific literature has been focused on accelerating the rate of tooth movement and on inducing bone turnover in combination with mechanical forces.[17,18] The demand for reducing the orthodontic treatment duration has been increased to avoid potential complications, including EARR. Moreover, the potential relationship between calcitriol and orthodontic tooth movement has been recently investigated, although the role of vitamin D on bone remodeling remains a subject of debate and its influence on molecular processes remains widely unknown.[19]

Therefore, this systematic review aimed to evaluate the current evidence on the role of vitamin D on orthodontic tooth movement, EARR, bone biomarkers expression, and bone remodeling.

## MATERIALS AND METHODS

### Search strategy and selection criteria

On March 14, 2023, 2 authors systematically and independently searched the PubMed, Scopus, and Web of Science databases. The search strategy is reported in Table 1.

After the duplication removal, the 2 reviewers independently screened all the records for title and abstract, then for full-text. A third reviewer was asked to solve any disagreement between the 2 reviewers through collegial discussion.

The relevant studies were selected based on the following PICO model:

(P) Participants: subjects undergone orthodontic treatment;

(I) Interventions: no restrictions for therapeutic intervention;

(C) Comparators: no restriction for comparators;

(O) Outcome measures: the correlation between orthodontic tooth movement and vitamin D was the primary outcome. Data on vitamin D serum levels, bone biomarker expression, genotype and frequency of VDR polymorphisms, and EARR were investigated as secondary outcomes.

We excluded case reports, case series, abstracts, studies not written in English, and studies including participants with pathological disorders affecting calcium homeostasis.

This systematic review followed the statement of Preferred Reporting Items for Systematic Reviews and Meta-

**Table 1.** Search strategy

| |
|---|
| PubMed:<br>((“vitamin d”[MeSH Terms] OR “vitamin d”[All Fields] OR “cholecalciferol”[MeSH Terms] OR “cholecalciferol”[All Fields] OR “ergocalciferols”[MeSH Terms] OR “ergocalciferols”[All Fields] OR “calcifediol”[MeSH Terms] OR “calcifediol”[All Fields] OR “25 oh d3”[All Fields])) AND (“Orthodontics”[Mesh Terms] OR “Orthodontics”[All Fields]) OR ((“tooth”[MeSH Terms] AND “movement”[MeSH Terms]) OR (“tooth”[All Fields] AND “movement”[All Fields])) OR (“malocclusion”[MeSH Terms] OR “malocclusion""[All Fields]) OR (“dental occlusion”[MeSH Terms] OR (“dental”[All Fields] AND “occlusion”[All Fields]) OR “dental occlusion”[All Fields]) OR (“oral health”[MeSH Terms] OR “oral health”[All Fields]) OR (“oral status” [All Fields])) |
| Scopus:<br>TITLE-ABS-KEY (((vitamin d) OR (cholecalciferol) OR (25 oh d3)) AND ((Orthodontics) OR (tooth movement) OR (malocclusion))) |
| Web of Science:<br>ALL = ((“vitamin d” OR “cholecalciferol” OR “25 oh d3”) AND (“Orthodontics” OR “tooth movement” OR “malocclusion”)) |

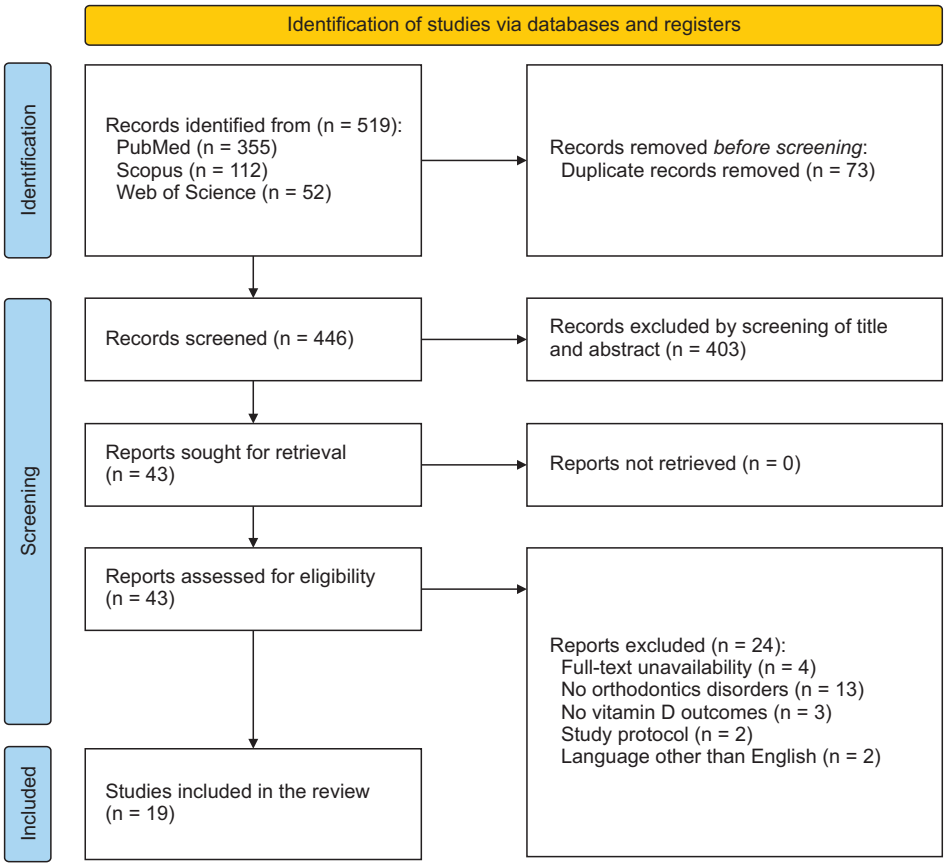


**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram.

Analyses (PRISMA)[20] and was registered on PROSPERO (CRD42022332980).

### Data extraction and synthesis

All data were extracted and synthesized into tables, providing a qualitative synthesis of the study characteristics and main findings. The data synthesis was performed by two authors independently based on full-text documents.

The relevant data extracted were: I) title, authors, and publication year; II) nationality; III) sample characteristics; IV) interventions' characteristics; V) comparator characteristics; VI) outcomes; VII) study results.

### Quality assessment

Two independent reviewers assessed the quality of the studies included according to the Joanna Briggs Institute Critical Appraisal Checklist.[21] Any disagreement was resolved by a third reviewer.


https://doi.org/10.4041/kjod23.064

## RESULTS

Through the literature search, 519 studies were recognized. After removing the duplicates, 446 records were considered suitable for title and abstract screening. Out of these, 43 articles were assessed, and 24 were excluded for the following reasons: full-text unavailability (n = 4), no orthodontics disorders (n = 13), no vitamin D outcomes (n = 3), study protocol (n = 2), and language other than English (n = 2).

Consequently, we included 19 studies[22-40] as reported by the 2020 PRISMA flow diagram (Figure 1).

Out of the 19 included studies, 9 (47.4%) were conducted on animal models,[24,25,27-30,32,38,40] and 10 (52.6%) on humans (2 [10.5%] retrospective studies,[37,39] 5 [26.3%] prospective studies,[22,23,26,31,33] 1 [5.3%] cross-sectional study,[34] and 2 [10.5%] randomized controlled trials[35,36]).

Eleven studies (57.9%) were performed in Asia[22,25,28-30,32,34-37,40]: 2 from Iraq,[22,36] 2 from Saudi Arabia,[29,30] 3 from Iran,[34,37,40] 2 from Japan,[28,32] 1 from China,[25] and 1 from India.[35] Four studies (21.1%) were performed in the Americas: 2 from the USA,[23,33] 1 from Canada,[38] and 1 from Brazil.[26] Four studies (21.1%) were performed in Europe[23,27,31,39]: 1 from France,[23] 1 from Germany,[39] 1 from Turkey,[27] and 1 from Poland.[31]

In the animal studies, 244 subjects (5 cats, 170 Wistar rats, and 69 Dawley rats) were analyzed; the study cohorts ranged from 5[24] to 60[32] subjects, with an overall age ranging from 6 weeks[27] to 28 weeks old.[32]

In the studies involving human, there were 890 participants; the study cohorts ranged from 14.9 years old[26] to 36.5 years old.[31] Regarding the follow-up evaluations, the longest study follow-up was 6 months.[26]

Table 2 details all the main characteristics and findings of the papers included in the systematic review.

### Animal models

Collins and Sinclair[24] evaluated the effects of dimethylsulfoxide (DMSO) injections containing 50 pg/mL of $1.25(OH)_2D_3$ into the periodontal ligament of the left canines and 0.1 mL of DMSO alone in the right canines in cat model. After 21 days of canine retraction, they found a significant improvement of 60% ($P < 0.05$) in the teeth movement in the study group (receiving weekly intraligamentous injections of vitamin D) compared to the control group.

Cui et al.[25] investigated the effect of $1.25(OH)_2D_3$ on the expression of high mobility group box 1 (HMGB1) in periodontal ligament cells of rats during orthodontic tooth movement (nickel-titanium coil spring delivering a force level of 0.5 N). The $1.25(OH)_2D_3$ was administered via gavage every other day (100 ng/kg body weight). The expression of HMGB1 was evaluated at 7 and 28 days and compared to the basal expression of HMGB1 protein in a control group. The authors reported a significant reduction in IL-6 and TNF-α expression in the vitamin D group ($P < 0.01$), suggesting that administration of vitamin D3 might provide a down-regulating expression of HMGB1.

Kale et al.[27] compared the effects of injecting PGE2 and $1.25(OH)_2D_3$ into the gingiva distal to the maxillary incisors of rats. PGE2 and $1.25(OH)_2D_3$ significantly ($P < 0.001$) increased the rate of tooth movement in comparison with the control group.

Kawakami and Takano-Yamamoto[28] showed that tooth movement in rats without injection of $1.25(OH)_2D_3$ in the submucosal palatal area decreased the mineral appositional rate on the compression area at 7 days ($P < 0.05$), whereas repeated injections of $1.25(OH)_2D_3$ in the orthodontically treated animals stimulated alveolar bone formation at 14 days with a significant increase in mineral appositional rate on the tension site ($P < 0.05$).

In 2022, Gratton et al.[38] evaluated the rate of tooth movement in rats after $1.25(OH)_2D_3$ supplementation as an oral solution (50 ng/mL) or submucosal injection of $1.25(OH)_2D_3$ solution, and compared the results to a control group (receiving phosphate-buffered saline solution systemically or focally administered). The authors reported a lower tooth movement rate and relapse in animals receiving systemic vitamin D supplementation compared to the control ($P < 0.05$).

In the same year, Moradinejad et al.[40] assessed the effects of orthodontic appliances combined with vitamin D3 intraperitoneal injection, alendronate solution administration, or vitamin D3 intraperitoneal injection combined with alendronate solution administration. The authors reported significant differences in orthodontic tooth movement between groups, with significant advantages for groups treated with vitamin D3 administration ($P < 0.001$). In contrast, tooth movement was smaller in rats treated with alendronate alone ($P < 0.001$).

However, Khalaf and Almudhi[29] showed that hypovitaminosis D did not affect the rate of orthodontic tooth movement in rats after orthodontic therapy with fixed appliances at 7, 14, and 21 days. On the other hand, the same authors[30] analyzed the effects of vitamin D deficiency on the serum blood levels of RANKL/OPG in rats and showed significantly lower levels of serum RANKL and RANKL/OPG ratio ($P < 0.001$).

Furthermore, Takano-Yamamoto et al.[32] showed that the rate of tooth movement was significantly increased (about 245%) after $10^{-10}$ mol/L injections of $1.25(OH)_2D_3$ into the submucosal palatal area of the right first molar simultaneous with the application of mechanical force (delivered forces ranging from 5 to 20 g).

### Human models

In studies involving human, Al-hasani et al.[22] treated

**Table 2.** Main characteristics of the studies included in the present systematic review

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Al-Attar and Abid (2022)[36] | International Journal of Dentistry | Randomized controlled trial | Iraq | Total: n = 33; M/F = N/A<br>Group 1: n = 17; M/F = N/A<br>Group 2: n = 16; M/F = N/A | Total: 20.13 ± 1.81; (18–30)<br>Group 1: 20.5 ± 1.61<br>Group 2: 19.70 ± 1.95 | Group 1: vitamin D3 level was measured before orthodontic intervention; if the level was below the normal value (30 ng/mL), then the participants were referred to an endocrine specialist to optimize the level of vitamin D3 to normal before bonding the appliance. Patients were treated with a fixed orthodontic appliance. | Group 2: orthodontic treatment was performed without measuring the level of vitamin D3 until completion of the alignment phase. Patients were treated with fixed orthodontic appliance. | - Vitamin D3 level<br>- Mandibular incisor crowding<br>- EARR<br>- Pain perception | T0 (baseline), T1 (4 wk), T2 (8 wk), T3 (12 wk), T4 (16 wk), and T5 (20 wk) | The results showed that there were statistically significant improvements in time elapsed for the complete alignment of the mandibular incisor crowding ($P \leq 0.001$), which was 1 mo shorter in normal vitamin D3 group (23.53% faster), and the improvement percentage was significantly higher in all periods when compared to the CG ($P \leq 0.001$). The amount of EARR was not significantly different between groups; however, pain during the first three days of alignment was significantly less in normal vitamin D3 group ($P < 0.05$). |
| Al-Hasani et al. (2011)[22] | International Journal of Pharmacy and Pharmaceutical Sciences | Prospective study | Iraq | Total: n = 15; M/F = N/A | Total: range, 17–28 | Group 1: injection of 0.2 mL of calcitriol in DMSO containing 15 pg/mL of calcitriol into the periodontal ligament of the left canines (distal side). The injections were repeated 3 times for every subject (T0, T1, T2). The distalizing orthodontic forces were about 150 g.<br>Group 2: injection of 0.2 mL of calcitriol in DMSO containing 25 pg/mL of calcitriol into the periodontal ligament of the left canines.<br>Group 3: injection of 0.2 mL of calcitriol in DMSO containing 40 pg/mL of calcitriol into the periodontal ligament of the left canines. | Right canine: injection of 0.2 mL of DMSO. | Tooth movement | T0 (baseline), T1 (7 days), T2 (14 days), T3 (21 days), T4 (28 days) | The results showed no statistically significant differences in OTM between control and experimental sides, and among the 3 groups. From a clinical point of view, the dose of 25 pg of calcitriol produced about 51% faster rate of experimental canine movement compared to control, whereas 15 pg and 40 pg doses resulted in about 10% accelerated OTM. |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Azizi et al. (2022)[37] | International Journal of Dentistry | Retrospective cohort study | Iran | Total: n = 80; M/F = N/A | Total: range, 12–30 | Fixed orthodontic treatment | | - Serum level of vitamin D<br>- EARR<br>- Root length | T0 (baseline) | A reduction in root length was noted in all patients, which was significant ($P < 0.0001$); 75% of patients showed EARR in at least one maxillary incisor. The EARR had no significant correlation with the serum level of vitamin D ($P = 0.423$). |
| Iosub Ciur et al. (2016)[23] | Revista medico-chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi | Prospective study | France | Total: n = 6; M/F = 3/3 | Total: 18 | Injection of 0.2 mL of vitamin D3 in DMSO containing 42 pg/mL of vitamin D3 into the periodontal ligament of the experimental canine was administered, once a week, for 3 wk. Canine distalization was achieved using a closed Niti spring of 12 mm which generated a force of 150 g. | The control canine received only conventional orthodontic treatment. | Tooth movement | T0 (baseline), T1 (1 mo) | Results showed an average of 70% more tooth movement for the experimental teeth compared to control ones. The differences between the control and the experimental sides were statistically significant ($P = 0.0313$). |
| Collins and Sinclair (1988)[24] | American Journal of Orthodontics and Dentofacial Orthopedics | Animal study | USA | Young adult cats<br>Total: n = 5; M/F = N/A | Total: N/A | Injection of 0.1 mL of 1.25 D in DMSO containing 50 pg/mL of $1.25(OH)_2D_3$ into the periodontal ligament of the left canines. The orthodontic forces were delivered using a light-wire retraction spring. | The right canines received an injection of 0.1 mL of DMSO only. The orthodontic forces were delivered using a light-wire retraction spring. | Cumulative amounts of tooth movement, weekly increments of tooth movement, numbers of mononuclear osteoclasts | T0 (baseline), and T1 (21 days) | After 21 days of canine retraction with a light-wire retraction spring, the teeth that had received weekly intraligamentous injections of 1.25 D had moved 60% further than matched control teeth ($P < 0.05$). At the histologic level, increased numbers of mononuclear osteoclasts were recruited and activated, resulting in greater amounts of alveolar bone resorption on the pressure side of the periodontal ligament. |

Table 2. Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Cui et al. (2016)[25] | Journal of Molecular Histology | Animal study | China | Wistar rats<br>Total: n = 30; M/F = 30/0<br>Group 1: n = 12; M/F = 12/0<br>Group 2: n = 12; M/F = 12/0<br>Group 3: n = 6; M/F = 6/0 | 7-week-old | Group 1: experimental group to examine the effect of 1α,25(OH)$_2$D$_3$ (n = 6) and normal saline (n = 6) on HMGB1 at day 7.<br>Group 2: experimental group to examine the effect of 1α,25(OH)$_2$D$_3$ (n = 6) and normal saline (n = 6) on HMGB1 at day 28.<br>The orthodontic forces were delivered using a nickel-titanium coil spring with (force level of 0.5 N) for 5 days.<br>Vitamin D administration: (100 ng/kg body weight) by gavage once every other day.<br>Saline: identical volume and frequency. | Group 3: control group to determine basal HMGB1 protein expression | TNF-α, IL-6, and HMGB1 | T0 (after 5 days of application of mechanical loading to the tooth), T1 (after 7 days), and T2 (after 28 days) | Expression of IL-6 and TNF-α were time-dependently reduced in the 1α,25(OH)$_2$ vitamin D group compared with the control group at each time point ($P < 0.01$). Similarly, expression of HMGB1 was decreased over time in both the 1α,25(OH)$_2$ vitamin D and normal saline groups, and 1α,25(OH)$_2$ vitamin D administration enhanced this decline ($P < 0.01$). |
| Fontana et al. (2012)[26] | American Journal of Orthodontics and Dentofacial Orthopedics | Prospective study | Brazil | Total: n = 377; M/F = 169/208<br>Group 1: n = 160; M/F = 74/86<br>Group 2: n = 179; M/F = 80/99<br>Group 3: n = 38; M/F = 15/23 | Total: 14.9; range, 8–21<br>Group 1: 14.50 ± 3.01 (8–21)<br>Group 2: 15.33 ± 2.64 (9.9–20)<br>Group 3: 16.46 ± 1.93 (11–19) | Group 1: patients treated with edgewise or straight-wire techniques, with EARR ≤ 1.43 mm.<br>Group 2: patients treated with edgewise or straight-wire techniques, with EARR > 1.43 mm.<br>EARR of the maxillary incisors was evaluated on periapical radiographs. | Group 3: untreated subjects | EARR, genotype and allele distribution of the VDR TaqI polymorphism, protective effect of allele C | T0 (baseline), and T1 (6 mo) | Differences were observed in VDR Taq1 polymorphism genotype frequency ($P = 0.051$) between groups. It was observed a weak protective effect of allele C against EARR (CC + CT × TT [OR, 0.29; 95% CI, 0.07–1.23; $P = 0.091$]) in treated patients compared with control group. |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Gratton et al. (2022)[38] | American Journal of Orthodontics and Dentofacial Orthopedics | Animal study | Canada | Sprague Dawley rats<br>Total: n = 32; M/F = 32/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0<br>Group 3: n = 8; M/F = 8/0<br>Group 4: n = 8; M/F = 8/0 | N/A | Group 1: experimental gavage - daily solution of vitamin D (50 ng/mL) by gavage.<br>Group 2: experimental injection-submucosal injection of solution of vitamin D solution, every 2 days in the anterior and palatal region of the maxillary right first molar (volume of 20 mL, vitamin D $1 \times 10^{-10}$ M, injected at each dose).<br>A closed nickel-titanium coil of 50 cN force was bonded between the maxillary right first molar and the incisors of each rat at T1, for 7 days. | Group 3: control gavage - daily solution of PBS solution (0.1 M, pH 7.2) by gavage<br>Group 4: control injection - submucosal injection of solution of PBS solution, every 2 days in the anterior and palatal region of the maxillary right first molar (volume of 20 mL injected at each dose).<br>A closed nickel-titanium coil of 50 cN force was bonded between the maxillary right first molar and the incisors of each rat at T1, for 7 days. | - Tooth movement<br>- Bone morphometry | T0 (baseline), T1 (10 days), T2 (17 days), T3 (24 days), T4 (47 days) | The systemic vitamin D group showed a lower OTM rate and a lower relapse than the control ($P < 0.05$).<br>It also demonstrated increased bone mineral density, bone volume/total volume, and a decrease in total porosity ($P < 0.05$). The bone structure appeared more fragmented and presented a lower connectivity density than the control ($P < 0.05$).<br>No statistical difference was found between vitamin D local administration and the other groups for the rate and stability of OTM or bone morphometry. |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Kale et al. (2004)[27] | American Journal of Orthodontics and Dentofacial Orthopedics | Animal study | Turkey | Sprague Dawley rats<br>Total: n = 37; M/F = 37/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0<br>Group 3: n = 8; M/F = 8/0<br>Group 4: n=8; M/F= 8/0<br>Group 5: n = 5; M/F = 5/0 | 6-week-old | Group 1: appliance control group; orthodontic appliances alone<br>Group 2: DMSO group; 20 μL injection of DMSO on days 0, 3, and 6.<br>Group 3: 1.25-dihydroxy-cholecalciferol (1.25-DHCC) group; orthodontic appliances + single injection of 20 μL of $10^{-10}$ mol/L, given on days 0, 3, and 6.<br>Group 4: PGE2 group; orthodontic appliances + a single injection of 0.1 mL of 0.1 μg PGE2 on the day of appliance placement.<br>Injections were administered with a microsyringe to the gingiva distal to the maxillary incisors. | Group 5: no treatment | Tooth movement, numbers of Howship's lacunae and capillaries, number of osteoblasts | T0 (baseline), and T1 (9 days) | There was no significant difference in tooth movement between the PGE2 and the 1.25-DHCC groups ($P > 0.05$). Both PGE2 and 1.25-DHCC enhanced the amount of tooth movement significantly when compared with the control group ($P < 0.001$). The numbers of Howship's lacunae and capillaries on the pressure side were significantly greater in the PGE2 group than in the 1.25-DHCC group (Howship's lacunae: $P < 0.001$; capillaries: $P < 0.005$). Compared to the DMSO group and Control, the number of capillaries in the pressure side in the 1.25-DHCC group remains significantly higher ($P < 0.001$). On the other hand, the number of osteoblasts on the external surface of the alveolar bone on the pressure side was significantly greater in the 1.25-DHCC group than in the PGE2 group ($P < 0.001$). |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Kawakami and Takano-Yamamoto (2004)[28] | Journal of Bone and Mineral Metabolism | Animal study | Japan | Wistar rats<br>Total: n = 16; M/F = 16/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0 | 7-week-old | Group 1: a piece of orthodontic elastic band (0.5-mm thickness) was inserted bilaterally between the first and second maxillary molars.<br>Twenty microliters of $10^{-10}$ M $1.25(OH)_2D_3$ was injected locally in the submucosal palatal area of the root furcation of the right molar, using a 30-gauge needle, once every 3 days (tooth movement [TM] $1.25(OH)_2D_3$). The left side was injected with vehicle (TM phosphate-buffered saline-PBS). | Group 2: rats without the insertion of elastic bands were injected with the same dose of $1.25(OH)_2D_3$ on the right side (non-TM $1.25(OH)_2D_3$) and with vehicle on the left side (non-TM PBS). | Histomorphometric indices on the distal and mesial sides of the inter radicular septum of the maxillary first molar | T0 (baseline), T1 (7 days), and T2 (14 days) | Histomorphometric analysis revealed that tooth movement without application of $1.25(OH)_2$ vitamin D decreased the mineral appositional rate (MAR) on the compression area at 7 days ($P < 0.05$). Repeated injections of $1.25(OH)_2$ vitamin D in the orthodontically treated animals distinctly stimulated alveolar bone formation on the mesial side at 14 days. There was a significant increase in MAR associated with elevated osteoblast surface value on the tension surface ($P < 0.05$). |

Table 2. Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Khalaf and Almudhi (2022)[29] | Saudi Dental Journal | Animal study | Saudi Arabia | Wistar rats<br>Total: n = 16; M/F = 16/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0 | 8–9-week -old | Group 1: rats with induced vitamin D deficiency.<br>This condition was achieved using an injection of 0.1 mL of Saline and paricalcitol injected 3 times per week for 2 wk for each rat.<br>An additional week of inactivity was observed, totaling the time to three weeks before commencement of the OTM procedures.<br>Orthodontic appliances were fixed to initiate tooth movement. | Group 2: rats with average vitamin D serum level. Orthodontic appliances were fixed to initiate tooth movement at T0. | Tooth movement | T0 (baseline, for Group 1 after 3 wk from first injection), T1 (7 days), T2 (14 days), and T3 (21 days) | The overall OTM was compared between groups and showed no statistically significant differences at 0–7 days ($P = 0.709$), 0–14 days ($P = 0.313$), or 0–21 days ($P = 0.359$). The OTM over time was compared separately, and for both groups significant changes were observed over time. In group 1 the pairwise comparisons found significant differences between 0–7 days and 0–14 days ($P = 0.013$), 0–7 days, and 0–21 days ($P < 0.001$). Similar results were found in the 2 groups, with significant differences between 0–7 days and 0–14 days ($P = 0.014$), 0–7 days, and 0–21 days ($P = 0.001$). The repeated measures ANOVA found the differences to be significant when considered for time ($F = 29.9$, $P < 0.001$). There was a significant drop in the OTM over time in both groups. Results showed that vitamin D deficiency did not affect rate of OTM. |
| Khalaf and Almudhi (2022)[30] | Journal of Oral Biology and Craniofacial Research | Animal study | Saudi Arabia | Wistar rats<br>Total: n = 16; M/F = 16/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0 | Total: N/A | Group 1: rats with induced vitamin D deficiency.<br>This condition was achieved using injection of 0.1 mL of Saline and paricalcitol injected 3 times per week for 2 wk.<br>An additional week of inactivity was observed, totaling the time to three weeks before commencement of the OTM procedures.<br>Orthodontic appliances were fixed to initiate tooth movement. | Group 2: normal rats. Orthodontic appliances were fixed to initiate tooth movement at T0. | Vitamin D, serum level of RANKL concen-tration, OPG concen-tration, and RANKL/OPG ratio | T0 (baseline, for Group 1 after 3 weeks from first injection), and T1 (21 days) | A statistically significant decrease in serum RANKL concentration ($P < 0.001$) and RANKL/OPG ratio ($P < 0.001$) on day 21 were seen in the experimental group compared to the control group. |

Table 2. Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Leszczyszyn et al. (2021)[31] | Nutrients | Prospective study | Poland | Total: n = 114; M/F = 61/53<br>Group 1: n = 86; M/F = 57/29<br>Group 2: n = 28; M/F = 4/24 | Total: 36.5 ± 11.8 (18–50) | Group 1: vitamin D deficiency | Group 2: no vitamin D deficiency | 25(OH) vitamin D serum levels, malocclusion development ratio | T0 (baseline) | In about 42.1% of patients, the presence of a skeletal defect was found, and in 46.5% of patients, dentoalveolar malocclusion. The most common defect was transverse constriction of the maxilla with a narrow upper arch (30.7%). The concentration of vitamin 25(OH) D in the study group was on average 23.6 ± 10.5 (ng/mL). Vitamin D deficiency was found in 86 subjects (75.4%). Our research showed that vitamin D deficiency could be one of the important factors influencing maxillary development. Patients had a greater risk of a narrowed upper arch (OR = 4.94), crowding (OR = 4.94), and crossbite (OR = 6.16). |
| Marañón-Vásquez et al. (2023)[39] | European Journal of Oral Sciences | Retrospective study | Germany | Total: n = 143; M/F = 71/72 | Total: 13.5 ± 4.5 | Orthodontic treatment<br>A sample of cheek cells (buccal cells) was collected for DNA analysis | | - Vitamin-D-related genes (VDR, GC, CYP27B1, and CYP24A1)<br>- EARR<br>- Root length | T1 (initial treatment radiograph), and T2 (final treatment adiograph) | Individuals carrying the AA genotype in VDR rs2228570 had a 21% higher $EARR_{mol}$ than those having AG and GG genotypes (95% CI: 1.03,1.40).<br>$EARR_{mol}$ in heterozygous rs2228570, was 12% lower than for homozygotes (95% CI: 0.78–0.99). Participants with the CCG haplotype (rs1544410-rs7975232-rs731236) in VDR had an $EARR_{mol}$ 16% lower than those who did not carry this haplotype.<br>Regarding CYP27B1 rs4646536, $EARR_{inc}$ in participants who had at least one G allele was 42% lower than for homozygotes AA (95% CI: 0.37–0.93). |

Table 2. Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Moradinejad et al. (2022)[40] | American Journal of Orthodontics and Dentofacial Orthopedics | Animal study | Iran | Wistar rats<br>Total: n = 32; M/F = 32/0<br>Group 1: n = 8; M/F = 8/0<br>Group 2: n = 8; M/F = 8/0<br>Group 3: n = 8; M/F = 8/0<br>Group 4: n = 8; M/F = 8/0 | N/A | Group 1: vitamin D3 intraperitoneal injection, once every 2 wk for 3 times (2 times [21 days and 7 days] before the appliance placement and 1 time [7 days] after it), each dose of 0.6 mg/kg body weight equivalent to 24,000 IU/kg.<br>Group 2: alendronate solution, once a week and for a total of 5 times (21, 14, and 7 days before the appliance placement, the day of placement, and 7 days after placement) at a dosage of 7 mg/kg of body weight per week by gavage.<br>Group 3: alendronate + vitamin D (same doses) Orthodontic appliances: the incisors were distalized at 30 g of force for 2 weeks. | Group 4: only orthodontic appliances | - Tooth movement<br>- Capillaries, lacunae, osteoclasts, and osteoblasts | T0 (21 days before the appliance placement)<br>T1 (14 days before the appliance placement)<br>T2 (7 days before the appliance placement)<br>T3 (the day of placement)<br>T4 (7 days after placement) | The OTMs in the groups vitamin D3, ALN+D3, ALN, and control were 1.900 ± 0.237, 1.629 ± 0.219, 0.975 ± 0.145, and 1.565 ± 0.324 mm ($P < 0.001$), respectively.<br>The OTM in the ALN group was smaller than all other groups ($P < 0.001$). The OTM in the D3 group was greater than in the control group ($P = 0.054$). The ALN+D3 group had greater OTM than the ALN group ($P < 0.001$) but was not significantly different from the D3 ($P = 0.153$) or control ($P = 0.951$) groups.<br>All histologic variables were significantly different across groups ($P < 0.001$). All the markers in the D3 group were more frequent than those of the other groups ($P < 0.001$). There were fewer markers in the ALN group than in the control group ($P \leq 0.001$). The ALN + D3 group had more markers than the ALN group in terms of capillaries, osteoclasts, and osteoblasts ($P \leq 0.007$). The ALN + D3 group was similar to the control group regarding capillaries, osteoclasts, and osteoblasts ($P \geq 0.382$). |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Takano-Yamamoto et al. (1992)[32] | Journal of Dental Research | Animal study | Japan | Wistar rats<br>Total: n = 60; M/F = 60/0<br>Group 1: n = 30; M/F = 30/0<br>Group 2: n = 30; M/F = 30/0 | Group 1: 7-week-old<br>Group 2: 28-week-old | The right maxillary first molar was moved buccally with a fixed appliance. The appliances delivered forces ranging from 5 to 20 g.<br>Twenty gL of $1.25(OH)_2D_3$ ($10^{-10}$ and $10^{-8}$ mol/L) was injected locally into the submucosal palatal area of the root bifurcation of the right first molar. | The left side was injected with PBS. | Tooth movement, calcium, phosphate, and alkaline phosphatase activity | T0 (baseline), and T1 (21 days) | In young rats receiving $10^{-10}$ mol/L $1.25(OH)_2D_3$ every three days, tooth movement significantly increased to 126% of that in PBS-injected control rats on day 20. In $1.25(OH)_2D_3$-injected mature rats, tooth movement was stimulated markedly and increased by 245% after $10^{-10}$ mol/L of $1.25(OH)_2D_3$, while a dose of $10^{-8}$ mol/L of $1.25(OH)_2D_3$ increased of 154% tooth movements compared to PBS-injected controls.<br>PBS-injected rats had a plateau stage where tooth movement did not occur at all, while there was no such lag-time in the $1.25(OH)_2D_3$-injected group which showed continuous tooth movement. The local injection of $1.25(OH)_2D_3$ did not change serum calcium, phosphate, and alkaline phosphatase activity, and there were no apparent clinical or microscopic side effects. |
| Tashkandi et al. (2021)[33] | BMC Oral Health | Prospective study | USA | Total: n = 73; M/F = 30/43<br>Group 1: n = 18; M/F = 9/9<br>Group 2: n = 37; M/F = 15/22<br>Group 3: n = 18; M/F = 6/12 | Total: 21.5 ± 11.1 (8–63)<br>Group 1: 22.78 ± 7.89<br>Group 2: 20.05 ± 11.74<br>Group 3: 23.72 ± 12.39 | Group 1: low VitDBP | Group 2: normal VitDBP<br>Group 3: high VitDBP | VitDBP, ALP | T0 (baseline), and T1 (6 mo) | VitDBP is a biological marker for bone apposition and clinical tooth movement. Both low (< 2.75 ng/mL) and high (> 6.48 ng/mL) VitDBP levels were associated with reduced tooth movement. Significant ($P < 0.05$) seasonal changes in VitDBP using a 2-season year model was found with lower levels observed in the summer (Apr–Sep) than in the winter (Oct–Mar). |

**Table 2.** Continued

| Authors | Journal | Design | Nationality | Population | Age (yr) | Intervention | Comparator | Outcome | Time points | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Tehranchi et al. (2017)[34] | Dental Research Journal | Cross-sectional study | Iran | Total: n = 34; M/F = 8/26 | Total: 16.63 ± 2.84 (12–23) | Group 1: mild vitamin D deficiencies (25-OHD 20–30 ng/mL) Patients were treated with fixed orthodontic treatment. | Group 2: moderate vitamin D deficiencies (25-OHD 10–20 ng/mL) Group 3: severe vitamin D deficiencies (25-OHD < 10 ng/mL) | Vitamin D status, EARR | T0 (baseline), and T1 (end of orthodontic treatment) | The Pearson coefficient between vitamin D status and observed EARR was determined about 0.15 ($P$ = 0.38). Regression analysis revealed that vitamin D status of the patients demonstrated no significant statistical correlation with EARR, after adjustment of confounding variables using linear regression model ($P$ > 0.05). |
| Varughese et al. (2019)[35] | The Journal of Contemporary Dental Practice | Randomized controlled trial | India | Total: n = 15; M/F = N/A | Total: 22.5; range, 15–30 | Injection of 0.2 mL of 1.25 vitamin D in DMSO containing 50 pg/mL of 1.25 D into the periodontal ligament of the experimental canine was administered at monthly intervals for duration of three months. Canine distalization was achieved using a closed Niti spring, which generated a force of 150 g. | Injection of 0.2 mL placebo gel into the periodontal ligament of the control canine. | Tooth movement and anchorage loss | T0 (baseline), T1 (4 wk), and T2 (8 wk), T3 (12 wk) | About total amount of canine distalization the results showed statistically significant difference ($P$ = 0.000) between experimental and control sides over a period of 3 mo. About the amount of anchorage loss, no statistically significant results were shown. |

Values are presented as mean ± standard deviation and maximum-minimum (range).
M, male; F, female; N/A, not applicable; DMSO, dimethylsulfoxide; OTM, orthodontic tooth movement is correct; HMGB1, high mobility group box 1; EARR, external apical root resorption; VDR, vitamin D receptor; PBS, phosphate-buffered saline; PGE2, prostaglandin E2; RANKL, receptor activator of nuclear factor-kappa B ligand; OPG, osteoprotegerin; OR, odds ratio; $EARR_{mol}$, external apical root resorption of lower first molars; $EARR_{inc}$, external apical root resorption of upper central incisors; CI, confidence interval; ALN, alendronate; VitDBP, vitamin D binding protein; ALP, alkaline phosphatase.

15 patients with pre-adjusted fixed appliances and performed maxillary canine retraction with a distalizing force of 150 g. They administered an injection of 0.2 mL of DMSO containing vitamin D3 (calcitriol) into the periodontal ligament of the left canines (distal side). The patients were randomly treated with 15 pg, 25 pg, or 40 pg/0.2 mL vitamin D, and no statistical differences among the 3 groups regarding the rate of orthodontic tooth movement.

Iosub Ciur et al.[23] treated 6 patients with fixed appliances and performed maxillary canine retraction (distalizing force: 150 g). They administered an injection of 0.2 mL DMSO containing 42 pg/mL of vitamin D3 into the periodontal ligament of the experimental canine, and was administered weekly for 3 weeks. A significant difference was reported regarding tooth movement between the experimental and control canines ($P = 0.0313$).

Fontana et al.[26] investigated the association between VDR TaqI gene polymorphism and EARR during orthodontic treatment in 377 participants. They evaluated the amount of EARR on periapical radiographs taken before and after 6 months of orthodontic fixed treatment. They concluded that the polymorphism was associated with higher EARR.

In 2021, Leszczyszyn et al.[31] evaluated the relationship between vitamin D deficiency and skeletal malocclusion in 114 participants. They found that hypovitaminosis D might increase the risk of crossbite (odds ratio [OR] = 6.16), crowding (OR = 4.94), and narrowed upper arch (OR = 4.94).

In the same year, Tashkandi et al.[33] demonstrated that low (< 2.75 ng/mL) and high (> 6.48 ng/mL) levels of vitamin D binding protein were associated with a reduction of tooth movement in 73 orthodontic patients. The study confirmed that optimal vitamin D binding protein saliva levels could only be associated with an adequate rate of orthodontic tooth movement.

In 2023, Marañón-Vásquez et al.[39] explored the association between single-nucleotide polymorphisms in vitamin-D-related genes (i.e., VDR, GC, CYP27B1, and CYP24A1) and the amount of EARR subsequent orthodontic treatment in 143 individuals. They reported that

**Table 3.** Joanna Briggs Institute Critical Appraisal for quasi-experimental studies

| Authors | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Total score |
|---|---|---|---|---|---|---|---|---|---|---|
| Al-Hasani et al. (2011)[22] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Azizi et al. (2022)[37] | Y | Y | Y | N | N | Y | Y | Y | Y | 7 |
| Iosub Ciur et al. (2016)[23] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Collins and Sinclair (1988)[24] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Cui et al. (2016)[25] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Fontana et al. (2012)[26] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Gratton et al. (2022)[38] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Kale et al. (2004)[27] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Kawakami and Takano-Yamamoto (2004)[28] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Khalaf and Almudhi (2022)[29] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Khalaf and Almudhi (2022)[30] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Leszczyszyn et al. (2021)[31] | Y | Y | Y | Y | N | Y | Y | Y | Y | 8 |
| Marañón-Vásquez et al. (2023)[39] | Y | Y | Y | N | Y | Y | Y | Y | Y | 8 |
| Moradinejad et al. (2022)[40] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Takano-Yamamoto et al. (1992)[32] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 8 |
| Tashkandi et al. (2021)[33] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Tehranchi et al. (2017)[34] | Y | Y | Y | N | Y | Y | Y | Y | Y | 8 |

Q1 = Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?; Q2 = Were the participants included in any comparisons similar?; Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4 = Was there a control group?; Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure?; Q6 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q7 = Were the outcomes of participants included in any comparisons measured in the same way?; Q8 = Were outcomes measured in a reliable way?; Q9 = Was appropriate statistical analysis used?
N, no; Y, yes.

 https://doi.org/10.4041/kjod23.064 

**Table 4.** Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials

| Authors | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Al-Attar and Abid (2022)[36] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 13 |
| Varughese et al. (2019)[35] | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 13 |

Q1 = Was true randomization used for assignment of participants to treatment groups?; Q2 = Was allocation to treatment groups concealed?; Q3 = Were treatment groups similar at the baseline?; Q4 = Were participants blind to treatment assignment?; Q5 = Were those delivering treatment blind to treatment assignment?; Q6 = Were outcomes assessors blind to treatment assignment?; Q7 = Were treatment groups treated identically other than the intervention of interest?; Q8 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q9 = Were participants analyzed in the groups to which they were randomized?; Q10 = Were outcomes measured in the same way for treatment groups?; Q11 = Were outcomes measured in a reliable way?; Q12 = Was appropriate statistical analysis used?; Q13 = Was the trial design appropriate, and any deviations from the standard randomized controlled trial design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?
Y, yes.

the AA genotype in VDR rs2228570 was associated with 21% higher EAAR than those with AG and GG genotypes. As a result, they concluded that vitamin-D-related genes might be significantly associated with orthodontic treatment effects.

On the other hand, Tehranchi et al.[34] analyzed 34 patients with mild, moderate, and severe vitamin D deficiency treated with fixed orthodontic appliance. They found no significant differences between groups regarding EARR ($P > 0.05$). Similarly, in 2022, Azizi et al.[37] reported no significant correlation ($P = 0.423$) between EARR and vitamin D serum levels in 50 patients treated with the same fixed orthodontic appliance.

Al-Attar and Abid[36] assessed the effect of vitamin D3 levels on the alignment of mandibular anterior teeth in 33 patients. They found statistically significant advantages in patients with normal vitamin D3 levels regarding the resolution time of mandibular incisors crowding ($P \leq 0.001$). In contrast, there was no significant between-group difference regarding the amount of EARR. However, the pain reported by patients during the first 3 days of treatment was significantly lower in the normal vitamin D3 levels group ($P < 0.05$).

Varughese et al.[35] evaluated the total amount of canine distalization using a closed Niti spring (distalizing force: 150 g) in 15 patients. An injection of 0.2 mL of $1.25(OH)_2$ vitamin D in DMSO, containing 50 pg/mL of vitamin D3, was administered into the periodontal ligament of the experimental canine once a month for 3 months. In contrast, a 0.2 mL placebo gel was injected into the periodontal ligament of the control canine. Statistically significant differences ($P = 0.000$) were observed between the experimental and control groups over a period of 3 months.

### Quality assessment

Fifteen studies (78.95%)[22-30,32,33,35,36,38,40] did not present serious risks of bias, whereas 4 studies (21.05%)[31,34,37,39] reported at least 1 serious risk of bias, in accordance with the Joanna Briggs Institute Critical Appraisal.[41] The main issues regarding study quality included the lack of a control group[34,37,39] and multiple measurements of the outcome both pre and post-intervention/exposure.[31,37] Tables 3 and 4 describes a detailed quality assessment according to the Joanna Briggs Institute Critical Appraisal.[41]

## DISCUSSION

This systematic review aimed to evaluate the correlation between vitamin D levels and the rate of tooth movement, EARR, bone biomarker expression, and bone remodeling. Ten studies[22-24,27,28,30,35,36,38,40] investigated the effect of local (injections were administered in periodontal ligament or submucosal area) and systemic administration (oral supplementation) of vitamin D3 on the rate of tooth movement. The remaining 9 studies[25,26,29,31-34,37,39] investigated the relationship among EARR, bone turnover, bone remodeling markers, and vitamin D.

### Vitamin D3 and orthodontic tooth movement

Among the animal studies, 5[24,27,28,30,38] evaluated the effects of injections of $1.25(OH)_2D_3$ into the periodontal ligament[24] or the submucosal area of rat teeth.[27,28,30,38] Four studies reported a significant improvement in the rate of orthodontic tooth movement,[24,27,28,30] which was increased from 60% to 245%. Only 1 study[38] did not report a significant increase in orthodontic tooth movement compared to the controls.

Among the human studies, 3[22,23,35] evaluated the effects of injection of 0.2 mL of DMSO containing vitamin D3 into the periodontal ligament, on tooth movement. Two studies[23,35] reported a significant difference regarding tooth movement between the experimental and control teeth, and the amount of administered vi-


https://doi.org/10.4041/kjod23.064

tamin D3 ranged from 42 pg/mL[23] to 50 pg/mL.[35] Only 1 study[22] compared different concentrations of injected vitamin D3 (15 pg, 25 pg, and 40 pg), and found no statistical differences among the 3 groups regarding tooth movement; however, the authors did not compare the amount of tooth movement to a control group. The only randomized controlled trial (RCT)[35] performed on humans showed a significant increase in canine distalization with a local administration of vitamin D3, suggesting the potential role of vitamin D as an innovative approach to accelerate tooth movement in orthodontic patients.

Most of the included studies supported the idea that local injection of vitamin D3 during an orthodontic treatment might increase the rate of tooth movement and might potentially reduce the time required to achieve treatment results. However, the non-uniform study designs might have negatively influenced the results in both animal and human studies. Although the results show that vitamin D3 accelerates orthodontic tooth movement, the protocol and outcome methods revealed substantial differences, making it difficult to draw reliable conclusions.

A recent systematic review by Arqub et al.[18] investigated the impact of biological agents on orthodontic tooth movement. The study confirmed that vitamin D showed variable effects on bone turnover, possibly related to the different stages of osteoblast maturation. The authors reported that vitamin D might decrease the RANKL/OPG ratio in mature osteoblasts, but increase the RANKL/OPG ratio in less-mature osteoblasts, thus stimulating osteoclastic bone resorption.

In this scenario, genetic polymorphisms in RANK, RANKL, OPG, COX-2 and IL-6 could be involved in the individual rate of orthodontic tooth movement and also with the expression of RANKL, OPG, COX-2 and IL-6 by the human periodontal ligament.[42]

On the other hand, a recent meta-analysis on the impact of calcitriol on orthodontic tooth movement reported a substantial discrepancy in the level of evidence, highlighting inadequate sample size in the study.[19]

Only 2 studies evaluated the effects of systemic supplementation of vitamin D3 on tooth movement.[38,40] Gratton et al.[38] evaluated the effects of oral supplementation and reported a lower tooth movement rate and relapse in animals receiving systemic vitamin D supplementation compared to control. In contrast, Moradinejad et al.[40] showed significant differences in orthodontic tooth movement between groups, with significant advantages for groups treated with intraperitoneal administration of vitamin D3. Thus, a lack of consensus has been reported regarding the effects of systemic vitamin D supplementation on tooth movement.

### Vitamin D receptor polymorphism, vitamin D serum levels, and external apical root resorption

Four human studies evaluated the correlation between VDR polymorphism, vitamin D serum levels, and EARR.[26,34,36,39] Marañón-Vásquez et al.[39] suggested a potential association between AA genotype in VDR polymorphism (rs2228570) and EARR. Similarly, Fontana et al.[26] evaluated the frequency of the VDR TaqI polymorphism genotype in patients treated with fixed orthodontic appliances to determine its correlation with EARR. The findings showed no significant protective effect of allele C against EARR. Furthermore, the authors concluded that VDR TaqI polymorphism (rs731236), initial root length, and age might be correlated to the EARR.

On the other hand, results from the present systematic review may not support a relationship between serum levels of vitamin D and EARR after orthodontic treatment. Tehranchi et al.[34] divided the subjects in the study into three groups according to the grade of hypovitaminosis D and evaluated the EARR of maxillary incisors on periapical radiographs. The results showed that the prevalence of hypovitaminosis D did not change in patients with higher EARR. Al-Attar and Abid[36] divided patients into a normal vitamin D3 level group and a control group (unknown vitamin D levels). The authors found a significant reduction in root length after treatment compared to baseline for both groups and no significant difference between the groups.

Recent investigations have explored the main causes of EARR, suggesting its association with age, dentition, and skeletal maturity during orthodontic treatment.[43-47] However, the etiopathology of EARR remains unclear.[48,49] Booij-Vrieling et al.[50] analyzed the expression of muscle segment homeobox 2 (MSX2), RANKL, and VDR in teeth, assessing the serum levels of vitamin-D metabolites in cats with and without tooth resorption. The authors reported that the vitamin D levels in animals did not differ between groups, whereas the amount of expression of VDR protein differed between groups. Results showed that the VDR was expressed in resorptive lesions of permanent teeth of cats, suggesting that $1.25(OH)_2$ vitamin D might play a role in feline tooth resorption. Moreover, the results suggested that the expression of the VDR by fibroblasts could indicate that vitamin D has an indirect role in the differentiation of odontoclasts, possibly by stimulating RANKL and MSX2 production.

### Vitamin D serum levels and RANK, RANKL, and RANKL/OPG ratio

Among the animal studies, Cui et al.[25] showed that vitamin D3 administered via gavage could down-regulate the expression of HMGB1, which may influence macrophages to secrete RANKL, contributing indirectly to the formation of osteoclasts.

Among human studies, Khalaf and Almudhi[30] correlated the hypovitaminosis D to the serum levels of RANKL/OPG ratio and showed a statistically significant decrease in the concentration of RANKL and RANKL/OPG ratio in patients with hypovitaminosis D compared to the control group.

Vitamin D was reported to affect the RANK/OPG axis, particularly by reducing inflammatory cytokines and modifying the expression of COX-2, OPG, RANKL, and IL-6 genes during orthodontic tooth movement.[13] In this context, Yang et al.[51] showed that RANKL could be produced by periodontal ligament cells in response to orthodontic tooth movement.

The present systematic review also showed the positive role of vitamin D in reducing pro-inflammatory cytokines (e.g., IL-6, TNF-α, and HMGB1), which are synthesized and secreted by the periodontal ligament cells.[25]

These results align with Nebel et al.[52] which demonstrated the role of $1\alpha,25(OH)_2D_3$ in promoting the expression of cytokines in the periodontal ligament cells. In this scenario, HMGB1 was reported to indirectly affect the proliferation and the differentiation of osteoclasts and the release of proinflammatory cytokine in the early phase of tissue remodeling.[25,52] Furthermore, HMGB1 appears to lead the macrophages to produce RANKL and pro-inflammatory cytokines (i.e., IL- 6, IL-8, and TNF-α).[53] Moreover, it has been shown that the IL-6 could be overexpressed during the orthodontic tooth movement and involved in bone resorption.[54-56]

Even though studies have shown the biological effect of vitamin D on bone metabolism, there are insufficient clinical studies and a lack of substantial evidence regarding its influence on orthodontic tooth movement in humans. Well-powered RCT with sufficient sample sizes and extended follow-up periods are needed to evaluate the clinical effects.

### Study limitations

Despite the interesting findings, this systematic review has several limitations. Firstly, the effects of vitamin D administration were analyzed in both animal and human, making it difficult to draw clear clinical conclusions. Moreover, there are no standardized protocols and outcome methods for vitamin D supplementation or the assessment of vitamin D serum levels. Lastly, a meta-analysis could not be performed due to the high heterogeneity of conditions, interventions, and outcomes.

## CONCLUSIONS

The present systematic review evaluated the correlation between vitamin D levels and the rate of tooth movement, EARR, bone biomarker expression, and bone remodeling.

The findings of the included studies supported that vitamin D3 local injections might increase the rate of tooth movement and expedite orthodontic treatment outcomes. However, the non-uniform study designs and different protocols and outcome methods make it challenging to draw reliable conclusions.

Moreover, the results of this systematic review did not support a relationship between VDR polymorphisms, vitamin D serum levels, and EARR. Thus, further investigations are necessary to enhance our understanding on the etiopathology of EARR.

Lastly, it should be taken into consideration that vitamin D might affect the RANK/OPG axis by reducing inflammatory cytokines and modifying the expression of HMGB1, COX-2, OPG, RANKL, and IL-6 genes during orthodontic tooth movement.

In conclusion, due to the low number of high-quality studies involving human, there is a critical need for physicians and scientists to improve the clinical research on the role of vitamin D on orthodontic tooth movement and bone remodeling.

## AUTHOR CONTRIBUTIONS

Conceptualization: MF, AS. Data curation: MF, DC, AS. Formal analysis: MF, DC, LL. Investigation: MF, DC, LL. Methodology: AS. Supervision: AS. Validation: MF, DC, LL. Visualization: FA, MM. Writing–original draft: MF, DC, LL. Writing–review & editing: MI, AG, AS. All authors have read and agreed to the published version of the manuscript.

## CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

## FUNDING

None to declare.

## REFERENCES

1. Kapoor P, Kharbanda OP, Monga N, Miglani R, Kapila S. Effect of orthodontic forces on cytokine and receptor levels in gingival crevicular fluid: a systematic review. Prog Orthod 2014;15:65. https://doi.org/10.1186/s40510-014-0065-6
2. Meikle MC. The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt. Eur J Orthod 2006;28:221-40. https://doi.org/10.1093/ejo/cjl001
3. Masella RS, Meister M. Current concepts in the biology of orthodontic tooth movement. Am J Orthod

Dentofacial Orthop 2006;129:458-68. https://doi.org/10.1016/j.ajodo.2005.12.013
4. Yamaguchi M. RANK/RANKL/OPG during orthodontic tooth movement. Orthod Craniofac Res 2009;12:113-9. https://doi.org/10.1111/j.1601-6343.2009.01444.x
5. Kobayashi Y, Hashimoto F, Miyamoto H, Kanaoka K, Miyazaki-Kawashita Y, Nakashima T, et al. Force-induced osteoclast apoptosis in vivo is accompanied by elevation in transforming growth factor beta and osteoprotegerin expression. J Bone Miner Res 2000;15:1924-34. https://doi.org/10.1359/jbmr.2000.15.10.1924
6. Epsley S, Tadros S, Farid A, Kargilis D, Mehta S, Rajapakse CS. The effect of inflammation on bone. Front Physiol 2021;11:511799. https://doi.org/10.3389/fphys.2020.511799
7. Uematsu S, Mogi M, Deguchi T. Interleukin (IL)-1 beta, IL-6, tumor necrosis factor-alpha, epidermal growth factor, and beta 2-microglobulin levels are elevated in gingival crevicular fluid during human orthodontic tooth movement. J Dent Res 1996;75:562-7. https://doi.org/10.1177/00220345960750010801
8. Yamaguchi M, Aihara N, Kojima T, Kasai K. RANKL increase in compressed periodontal ligament cells from root resorption. J Dent Res 2006;85:751-6. https://doi.org/10.1177/154405910608500812
9. Xiong J, Piemontese M, Onal M, Campbell J, Goellner JJ, Dusevich V, et al. Osteocytes, not osteoblasts or lining cells, are the main source of the RANKL required for osteoclast formation in remodeling bone. PLoS One 2015;10:e0138189. https://doi.org/10.1371/journal.pone.0138189
10. Küchler EC, Schröder A, Teodoro VB, Nazet U, Scariot R, Spanier G, et al. The role of 25-hydroxyvitamin-D3 and vitamin D receptor gene in human periodontal ligament fibroblasts as response to orthodontic compressive strain: an in vitro study. BMC Oral Health 2021;21:386. https://doi.org/10.1186/s12903-021-01740-8
11. Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 2004;19:265-9. https://doi.org/10.1359/jbmr.2004.19.2.265
12. Iolascon G, Moretti A, de Sire A, Calafiore D, Gimigliano F. Effectiveness of calcifediol in improving muscle function in post-menopausal women: a prospective cohort study. Adv Ther 2017;34:744-52. https://doi.org/10.1007/s12325-017-0492-0
13. Li B, Zhang YH, Wang LX, Li X, Zhang XD. Expression of OPG, RANKL, and RUNX2 in rabbit periodontium under orthodontic force. Genet Mol Res 2015;14:19382-8. https://doi.org/10.4238/2015.December.29.48
14. Yu X, Zong X, Pan Y. Associations between vitamin D receptor genetic variants and periodontitis: a meta-analysis. Acta Odontol Scand 2019;77:484-94. https://doi.org/10.1080/00016357.2019.1597160
15. Ferrillo M, Lippi L, Giudice A, Calafiore D, Paolucci T, Renò F, et al. Temporomandibular disorders and vitamin D deficiency: what is the linkage between these conditions? A systematic review. J Clin Med 2022;11:6231. https://doi.org/10.3390/jcm11216231
16. Ferrillo M, Migliario M, Roccuzzo A, Molinero-Mourelle P, Falcicchio G, Umano GR, et al. Periodontal disease and vitamin D deficiency in pregnant women: which correlation with preterm and low-weight birth? J Clin Med 2021;10:4578. https://doi.org/10.3390/jcm10194578
17. Ferrillo M, Migliario M, Marotta N, Lippi L, Antonelli A, Calafiore D, et al. Oral health in breast cancer women with vitamin D deficiency: a machine learning study. J Clin Med 2022;11:4662. https://doi.org/10.3390/jcm11164662
18. Arqub SA, Gandhi V, Iverson MG, Ahmed M, Kuo CL, Mu J, et al. The effect of the local administration of biological substances on the rate of orthodontic tooth movement: a systematic review of human studies. Prog Orthod 2021;22:5. https://doi.org/10.1186/s40510-021-00349-5
19. Al-Attar A, Abid M, Dziedzic A, Al-Khatieeb MM, Seppala M, Cobourne MT, et al. The impact of calcitriol on orthodontic tooth movement: a cumulative systematic review and meta-analysis. Appl Sci 2021;11:8882. https://doi.org/10.3390/app11198882
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71
21. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13:147-53. https://doi.org/10.1097/XEB.0000000000000054
22. Al-hasani NR, Al-bustani AI, Ghareeb MM, Hussain SA. Clinical efficacy of locally injected calcitriol in orthodontic tooth movement. Int J Pharm Pharm Sci 2011;5:139-43. https://d1wqtxts1xzle7.cloudfront.net/66870183/CLINICAL_EFFICACY_OF_LOCALLY_INJECTED_CA20210504-24281-ddxdes.pdf?1620114250=&response-content-disposition=inline%3B+filename%3DClinical_Efficacy_of_Locally_Injected_Ca.pdf&Expires=1701758593&Signature=d-

ZJgk~ThTLt7nJY7CFIoSpXtJkBtc1S-3ozaAspvEJxRiQXcLNp5oYQ6~NSp-qg8cwWY1co6uWFAi1U7NI-dBg1oiv-CDsi9RxNwGi6w4zw~VQJZyD-Fv-h8z9B3JmxDGbS2FSjetrym~B5J9JxNGQWfcMvSEIdVNEKjUuTmH7FxA2gCl-7VQ2D8b7my61rp8YNfSFCF~X4Q-ypmuDpRFOhg40WHHNy-lFJSiWticvx5JKBZ-wAYKaot7j3EH3B9lAc~FO9-rOntGwWRTGwXJr-54CZDnacoBcOrFMz7VStRUW3wOD-8rEX-dJJjo49TT1NRPJhfIvl2BRLuGJ2bvdPw__&tKey-Pair-Id=APKAJLOHF5GGSLRBV4ZA

23. Iosub Ciur MD, Zetu IN, Haba D, Viennot S, Bourgeois D, Andrian S. Evaluation of the influence of local administration of vitamin D on the rate of orthodontic tooth movement. Rev Med Chir Soc Med Nat Iasi 2016;120:694-99. https://pubmed.ncbi.nlm.nih.gov/30148332/
24. Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. Am J Orthod Dentofacial Orthop 1988;94:278-84. https://doi.org/10.1016/0889-5406(88)90052-2
25. Cui J, Li J, Wang W, Han X, Du J, Sun J, et al. The effect of calcitriol on high mobility group box 1 expression in periodontal ligament cells during orthodontic tooth movement in rats. J Mol Histol 2016;47:221-8. https://doi.org/10.1007/s10735-016-9669-0
26. Fontana ML, de Souza CM, Bernardino JF, Hoette F, Hoette ML, Thum L, et al. Association analysis of clinical aspects and vitamin D receptor gene polymorphism with external apical root resorption in orthodontic patients. Am J Orthod Dentofacial Orthop 2012;142:339-47. https://doi.org/10.1016/j.ajodo.2012.04.013
27. Kale S, Kocadereli I, Atilla P, Aşan E. Comparison of the effects of 1,25 dihydroxycholecalciferol and prostaglandin E2 on orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2004;125:607-14. https://doi.org/10.1016/j.ajodo.2003.06.002
28. Kawakami M, Takano-Yamamoto T. Local injection of 1,25-dihydroxyvitamin D3 enhanced bone formation for tooth stabilization after experimental tooth movement in rats. J Bone Miner Metab 2004;22:541-6. https://doi.org/10.1007/s00774-004-0521-3
29. Khalaf RM, Almudhi AA. Effects of vitamin D deficiency on the rate of orthodontic tooth movement: an animal study. Saudi Dent J 2022;34:129-35. https://doi.org/10.1016/j.sdentj.2021.12.008
30. Khalaf RM, Almudhi AA. The effect of vitamin D deficiency on the RANKL/OPG ratio in rats. J Oral Biol Craniofac Res 2022;12:228-32. https://doi.org/10.1016/j.jobcr.2022.02.004
31. Leszczyszyn A, Hnitecka S, Dominiak M. Could vitamin D3 deficiency influence malocclusion development? Nutrients 2021;13:2122. https://doi.org/10.3390/nu13062122
32. Takano-Yamamoto T, Kawakami M, Kobayashi Y, Yamashiro T, Sakuda M. The effect of local application of 1,25-dihydroxycholecalciferol on osteoclast numbers in orthodontically treated rats. J Dent Res 1992;71:53-9. https://doi.org/10.1177/00220345920710010901
33. Tashkandi N, Zhao Y, Mitchell-Lee G, Stephens D, Patel M, Motro M, et al. Longitudinal assessment of salivary vitamin D binding protein during orthodontic tooth movement. BMC Oral Health 2021;21:332. https://doi.org/10.1186/s12903-021-01689-8
34. Tehranchi A, Sadighnia A, Younessian F, Abdi AH, Shirvani A. Correlation of vitamin D status and orthodontic-induced external apical root resorption. Dent Res J (Isfahan) 2017;14:403-11. https://doi.org/10.4103/1735-3327.218565
35. Varughese ST, Shamanna PU, Goyal N, Thomas BS, Lakshmanan L, Pulikkottil VJ, et al. Effect of vitamin D on canine distalization and alveolar bone density using multi-slice spiral CT: a randomized controlled trial. J Contemp Dent Pract 2019;20:1430-5. https://doi.org/10.5005/jp-journals-10024-2698
36. Al-Attar A, Abid M. The effect of vitamin D3 on the alignment of mandibular anterior teeth: a randomized controlled clinical trial. Int J Dent 2022;2022:6555883. https://doi.org/10.1155/2022/6555883
37. Azizi F, Karami N, Golshah A, Imani MM, Safari-Faramani R. Effect of serum level of vitamin D on external apical root resorption in maxillary anterior teeth in patients under fixed orthodontic treatment. Int J Dent 2022;2022:7942998. https://doi.org/10.1155/2022/7942998
38. Gratton MP, Londono I, Rompré P, Villemure I, Moldovan F, Nishio C. Effect of vitamin D on bone morphometry and stability of orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop 2022;162:e319-27. https://doi.org/10.1016/j.ajodo.2022.08.019
39. Marañón-Vásquez G, Küchler EC, Hermann S, Paddenberg E, Schröder A, Baratto-Filho F, et al. Association between genetic variants in key vitamin-D-pathway genes and external apical root resorption linked to orthodontic treatment. Eur J Oral Sci 2023;131:e12916. https://doi.org/10.1111/eos.12916
40. Moradinejad M, Yazdi M, Mard SA, Razavi SM, Shamohammadi M, Shahsanaei F, et al. Efficacy of the systemic co-administration of vitamin D3 in reversing the inhibitory effects of sodium alendronate on orthodontic tooth movement: a preliminary experimental animal study. Am J Orthod Dentofacial Orthop 2022;162:e17-27. https://doi.org/10.1016/

j.ajodo.2021.11.014
41. Institute TJB. JBI critical appraisal tools [Internet]. Adelaide: Institute TJB; 2017 [cited 2023 Sep 21]. Available from: https://jbi.global/critical-appraisal-tools
42. Küchler EC, Schröder A, Corso P, Scariot R, Spanier G, Proff P, et al. Genetic polymorphisms influence gene expression of human periodontal ligament fibroblasts in the early phases of orthodontic tooth movement. Odontology 2020;108:493-502. https://doi.org/10.1007/s10266-019-00475-x
43. Mitsea A, Palikaraki G, Karamesinis K, Vastardis H, Gizani S, Sifakakis I. Evaluation of lateral incisor resorption caused by impacted maxillary canines based on CBCT: a systematic review and meta-analysis. Children (Basel) 2022;9:1006. https://doi.org/10.3390/children9071006
44. Nieto-Nieto N, Solano JE, Yañez-Vico R. External apical root resorption concurrent with orthodontic forces: the genetic influence. Acta Odontol Scand 2017;75:280-7. https://doi.org/10.1080/00016357.2017.1294260
45. Bizzarro M, Generali C, Maietta S, Martorelli M, Ferrillo M, Flores-Mir C, et al. Association between 3D palatal morphology and upper arch dimensions in buccally displaced maxillary canines early in mixed dentition. Eur J Orthod 2018;40:592-6. https://doi.org/10.1093/ejo/cjy023
46. Hasan HS, Elkolaly MA, Elmoazen R, Kolemen A, Al Azzawi AM. Factors that guide the diagnosis and treatment planning for impacted canines using three-dimensional cone-beam computed tomography: a cross-sectional study. Int J Dent 2022;2022:7582449. https://doi.org/10.1155/2022/7582449
47. Ferrillo M, Migliario M, Curci C, Roccuzzo A, Invernizzi M, de Sire A. Reliability of dental calcification compared to hand-wrist X-ray to evaluate skeletal maturation in growing subjects: a systematic review. J Biol Regul Homeost Agents 2021;35:717-23. https://doi.org/10.23812/21-106-L
48. Gonzales C, Hotokezaka H, Yoshimatsu M, Yozgatian JH, Darendeliler MA, Yoshida N. Force magnitude and duration effects on amount of tooth movement and root resorption in the rat molar. Angle Orthod 2008;78:502-9. https://doi.org/10.2319/052007-240.1
49. Küchler EC, Schröder A, Spanier G, Thedei G Jr, Carvalho Ribeiro de Oliveira MB, de Menezes-Oliveira MAH, et al. Influence of single-nucleotide polymorphisms on vitamin D receptor expression in periodontal ligament fibroblasts as a response to orthodontic compression. Int J Mol Sci 2022;23:15948. https://doi.org/10.3390/ijms232415948
50. Booij-Vrieling HE, Ferbus D, Tryfonidou MA, Riemers FM, Penning LC, Berdal A, et al. Increased vitamin D-driven signalling and expression of the vitamin D receptor, MSX2, and RANKL in tooth resorption in cats. Eur J Oral Sci 2010;118:39-46. https://doi.org/10.1111/j.1600-0722.2009.00707.x
51. Yang CY, Jeon HH, Alshabab A, Lee YJ, Chung CH, Graves DT. RANKL deletion in periodontal ligament and bone lining cells blocks orthodontic tooth movement. Int J Oral Sci 2018;10:3. https://doi.org/10.1038/s41368-017-0004-8
52. Nebel D, Svensson D, Arosenius K, Larsson E, Jönsson D, Nilsson BO. 1α,25-dihydroxyvitamin D3 promotes osteogenic activity and downregulates proinflammatory cytokine expression in human periodontal ligament cells. J Periodontal Res 2015;50:666-73. https://doi.org/10.1111/jre.12249
53. Andersson U, Wang H, Palmblad K, Aveberger AC, Bloom O, Erlandsson-Harris H, et al. High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. J Exp Med 2000;192:565-70. https://doi.org/10.1084/jem.192.4.565
54. Kirschneck C, Proff P, Maurer M, Reicheneder C, Römer P. Orthodontic forces add to nicotine-induced loss of periodontal bone: an in vivo and in vitro study. J Orofac Orthop 2015;76:195-212. https://doi.org/10.1007/s00056-015-0283-7
55. Madureira DF, Taddei Sde A, Abreu MH, Pretti H, Lages EM, da Silva TA. Kinetics of interleukin-6 and chemokine ligands 2 and 3 expression of periodontal tissues during orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2012;142:494-500. https://doi.org/10.1016/j.ajodo.2012.05.012
56. Fonseca JE, Santos MJ, Canhão H, Choy E. Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev 2009;8:538-42. https://doi.org/10.1016/j.autrev.2009.01.012