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REVIEW ARTICLE

The RANKL–OPG–RANK axis in orthodontic tooth movement: Crosstalk with Wnt/β-catenin and BMP signaling in osteoblast and osteoclast regulation

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Abstract

Mechanically induced osteoclast-mediated bone resorption and osteoblast-mediated bone formation are the forces behind orthodontic tooth movement (OTM). Despite independent research on the RANKL/OPG/RANK axis, Wnt/β-catenin signaling, and BMP signaling, the crosstalk among these pathways in the context of OTM has not been systematically synthesized. The interplay of these pathways in the context of OTM would be crucial in the design of specific biological interventions to maximize the safety and efficacy of treatments. In this review, we mechanistically integrate evidence on the interaction among the RANKL/OPG/RANK axis, Wnt/β-catenin, and BMP signaling pathways to control osteoclastogenesis and osteoblastogenesis in human, animal, and in vitro OTM systems. We searched three databases (PubMed, Cochrane Library, LIVIVO) in April 2026. Following deduplication (n = 20) using Rayyan artificial intelligence, 58 records were screened through PRISMA in two phases. Inclusion criteria included OTM context, defined signaling pathway research with Wnt and/or BMP crosstalk, molecular/cellular outcome data, English language, and peer-reviewed primary research. Narrative synthesis was conducted across 21 studies. RANKL/OPG regulation was universally reported (21/21 studies). The upstream regulator was Wnt/β-catenin signaling (16/21), and the central mechanosensory-molecular mediator of force transduction and osteoclastogenesis in the presence of RANKL was sclerostin (11/21). BMP-2 was also identified as a mechanosensitive pro-osteogenic target (5/21). Compression-tension molecular asymmetry was also continuously observed, and the magnitude and duration of forces further influenced the dynamics of RANKL/OPG. The convergent mechanosensing pathways on the same RANKL/Wnt effector module were Piezo1, α7 nAChR, Ca^{2+} oscillations, and sympathetic β-AR. The RANKL/OPG/RANK axis and Wnt/β-catenin signaling constitute a highly connected regulatory system that regulates OTM bone remodeling. Sclerostin plays a central mechanosensory role in the translation of force to RANKL-mediated osteoclastogenesis. These results offer a molecular rationale to optimize OTM protocols and design specific therapeutics, especially in patients with impaired bone biology.

Keywords: Orthodontic tooth movement; Receptor activator of nuclear factor kappa-B ligand; Osteoprotegerin; Wnt/β-catenin; Sclerostin; Bone morphogenetic protein-2; Mechanotransduction; Signaling crosstalk

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1. Introduction

Orthodontic tooth movement (OTM) is a clinically widespread, biologically complicated process relying on the spatially accurate and temporally synchronized labor of osteoclasts and osteoblasts in the alveolar bone.[1] Osteoclasts resorb mineralized bone matrix at the compression side of a mechanically loaded tooth, while osteoblasts deposit new bone on the opposing tension side.[2] This mechanically guided asymmetric remodeling permits controlled movement of teeth within the bone of the alveoli, and the molecular control of this process defines the effectiveness and safety of orthodontic therapy.[3] Alteration of this balance has been clinically recognized to have adverse effects, such as root resorption, alveolar bone dehiscence, and relapse.[4]

The main mediator of this remodeling is the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B (RANK) axis. RANKL is a ligand expressed by osteoblasts, osteocytes, and periodontal ligament (PDL) cells and binds to RANK on osteoclast precursors to induce their differentiation into fully functional bone-resorbing osteoclasts.[5] Secreted by osteoblasts and osteocytes, OPG is a competitive RANKL decoy receptor that inhibits RANKL binding to RANK.[6] The net resorptive potential at any given site is the ratio of RANKL/OPG and not the absolute concentration of each molecule.[5] The process of directional bone remodeling is produced by the dynamic regulation of this ratio in a spatially asymmetric manner by the mechanical forces during OTM.[7]

Two key upstream signaling pathways have been identified to play a key role in the RANKL/OPG system: the canonical wingless-related integration (Wnt)/β-catenin pathway and the bone morphogenetic protein (BMP) signaling cascade.[8] Canonical Wnt signaling enhances osteoblast differentiation and OPG synthesis and inhibits RANKL.[9] Sclerostin, encoded by the *SOST* gene and expressed by osteocytes, acts as a Wnt antagonist and regulates RANKL, thereby positioning it at the mechanosensory–molecular interface of bone remodeling.[10,11] BMP-2 and its ligands induce osteogenesis by the Smad1/5/8 signaling pathway and have been shown to interact with the Wnt and RANKL pathways.[12] Moreover, several mechanosensory pathways, such as Piezo1 calcium channels, α7 nicotinic acetylcholine receptors (α7 nAChR), and intracellular Ca^{2+} cytoplasmic oscillation pathways, transduce physical orthodontic forces into these molecular signaling cascades.[13,14]

Although each of these pathways has been studied individually in detail, there is no previous systematic review that examines three-way crosstalk among RANKL/OPG, Wnt/β-catenin, and BMP signaling in the context of the complete OTM spectrum of human, animal, and in vitro models. The RANKL/OPG system in OTM, the role of Wnt in overall bone homeostasis, and sclerostin as a pharmacological target in metabolic bone disease have been discussed in the existing reviews,[6,8,10] but none of them have been properly conducted as a systematic synthesis of their mechanistic interaction during OTM. This is a severe gap: the data on individual pathways are not enough to build a mechanobiological model of OTM without knowledge of how these pathways interact, contradict, and mutually support under mechanical loading.

The scientific and medical significance of filling in this gap cannot be overestimated. Mechanistically, the discovery of the key regulatory nodes of the RANKL/OPG-Wnt-BMP network during OTM will allow the design of specific pharmacological interventions, such as anti-sclerostin antibodies, Dickkopf-1 (DKK1) inhibitors, BMP-2 adjuncts, and RANKL inhibitor peptides, to regulate bone remodeling during orthodontic treatment. Such interventions might be clinically effective to decrease resorption of roots, inhibit bone dehiscence, speed up OTM safely, and modify treatment regimens in patients with impaired bone biology, such as osteoporosis, exposure to bisphosphonates, and aging-associated bone loss. This review thus fills a methodological gap with direct translational implications for orthodontic clinical practice. The review also presents an integrated molecular model that synthesizes the multi-tier signaling architecture identified across the included studies.

The research question that guided the research was as follows: In human, animal, and in vitro models of OTM, what is the interaction between the RANKL/OPG/RANK axis and the Wnt/β-catenin and BMP signaling pathways in regulating osteoclastogenesis and osteoblastogenesis?

2. Methods

2.1. Study design

We carried out this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 model.[15] The research question was structured in the population, exposure, outcome (PEO) format because this format is suitable for a mechanistic review, and a comparator group is absent in a clinical trial context: (i) Population: human subjects, animal models, and in vitro cellular systems in the context of OTM; (ii) Exposure: RANKL/OPG/RANK axis and its crosstalk with Wnt and/or BMP signaling; and (iii) Outcome: osteoclastogenesis, osteoblastogenesis, or quantitative molecular/cellular measurements of these processes.

2.2. Search strategy

We conducted a comprehensive multi-database search in April 2026. The search strategy was constructed based on four concept blocks: orthodontic tooth movement (population); RANKL/OPG/RANK axis (exposure); Wnt and BMP signaling pathways (crosstalk exposure); and osteoclastogenesis and osteoblastogenesis (outcome), intersected with the Boolean operator "AND" and synonyms within each block linked with OR.

Three databases were searched: PubMed, Cochrane, and LIVIVO. PubMed was chosen as the primary source due to its extensive, Medical Subject Headings (MeSH)-indexed coverage of biomedical and dental literature and its temporal comprehensiveness for molecular biology studies published from 2005 to 2025. PubMed searches used MeSH terms and "Title/Abstract" tags associated with free-text in all four blocks, and English-language and species filters were used to obtain 34 records. The Cochrane Library was also searched to identify randomized controlled trials; a three-block combination was created because the inclusion of Block 4 (osteoclastogenesis/osteoblastogenesis outcome terms) yielded no results. As Cochrane had limited indexing of basic science molecular studies, we identified only six studies. LIVIVO, the specialist life sciences search service of the ZB MED Information Centre to Life Sciences, was chosen for its specialized use of geographically published literature from biomedical institutions, which is often not available in PubMed or Cochrane, thereby minimizing geographic publication bias. LIVIVO included free-text equivalents for all 4 blocks, yielding 38 distinct records after deleting 3 internal duplicates. We exported 78 studies for deduplication.

2.3. Deduplication and screening

The Rayyan artificial intelligence (AI) systematic review platform uploaded all 78 records and identified 20 duplicate records, which were deleted, leaving 58 distinct records to undergo two-step screening. Phase 1 (title and abstract screening) resulted in 22 direct inclusions and 7 undecided studies, which were subjected to full-text review. A total of 29 studies were excluded on the basis of non-OTM population context, no defined signaling pathways, non-OTM clinical or radiographic outcomes, non-English language, or incorrect study design. Phase 2 (full-text screening) eliminated 8 additional articles: 2 of them contained full-text data in Chinese, 2 articles reported RANKL/OPG in humans but lacked any data on Wnt or BMP experiments (within the crosstalk criterion), 2 articles were narrative reviews (without primary data), and 2 additional articles contained radiographic-only data (without any molecular data). Figure 1 features the PRISMA flow diagram.

2.4. Inclusion and exclusion criteria

The studies were included as they all met the following requirements:

(i) Population: Human subjects, animal models, or in vitro cellular systems that had been subjected to or simulated orthodontic mechanical forces.
(ii) Exposure: At least one of the three RANKL, OPG, or RANK was investigated directly.
(iii) Crosstalk: Wnt/β-catenin and/or BMP signaling has been experimentally studied with respect to the RANKL/OPG system.
(iv) Outcome: Molecular or cellular data on outcome (gene expression, protein levels, signaling pathway activation, osteoclast/osteoblast counts) were reported in either a quantitative or qualitative manner.
(iv) Language: English.
(v) Type of study: Peer-reviewed original research article (not reviews, editorials, letters, theses, conference abstracts, or protocols).

The studies were excluded based on the following:

(i) Focused on non-OTM bone conditions without an orthodontic background.
(ii) Reported clinical (tooth movement distance, anchorage loss, canine retraction rate) or radiographic (cone-beam computed tomography bone dimensions, root length measurements) outcomes only.
(iii) Investigated signaling pathways not within the specified criteria.
(iv) Are narrative reviews, case reports, editorials, letters, unpublished protocols, or theses.

2.5. Data extraction

A preset standardized framework was used to extract data, which included: author(s) and year; journal; study design; population and sample size; OTM protocol and force parameters; signaling pathways under investigation; crosstalk type; outcome measures; methods; RANKL/OPG/Wnt/BMP individual findings; direction of overall effect; key conclusions; and study limitations. The full texts were extracted and put into a structured extraction table.

The specific cell types studied in each investigation (osteocytes, PDL fibroblasts [PDLFs], PDL stem cells [PDLSCs], pre-osteoblasts, cementocytes, bone marrow-derived osteoclast precursors, and monocytic cells) were also noted, because cell-type-specific signaling responses represent an important biological dimension of OTM mechanobiology (summarized in Section 3.7).

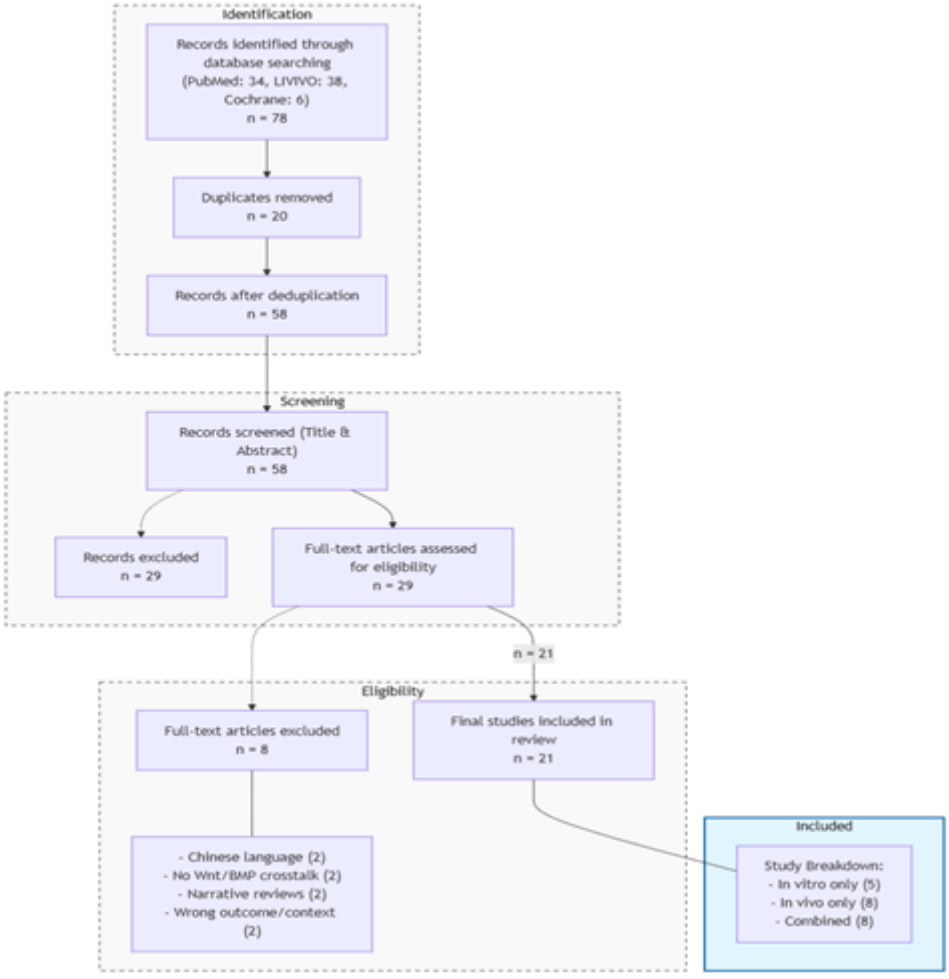

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart of literature screening

2.6. Quality assessment and risk of bias

The quality assessment was conducted using study-design-appropriate, validated instruments, selected because no instrument was suitable for all preclinical research designs. All in vivo animal studies were subjected to the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias (RoB) Tool, because it was created to tackle the specific sources of bias found in animal studies, such as housing conditions, random outcome measurement, and selection of animals to measure outcome, which general clinical trial tools, such as Cochrane RoB 2.0, do not address.[16] The Toxicological Data Reliability Assessment Tool (ToxRTool) was used for in vitro studies because it is specifically designed to assess cell-based experimental research and measures test system characterization, exposure delivery, reliability of endpoint measurements, and transparency in reporting, which are not included in SYRCLE.[17] In mixed in vitro and in vivo experiments, each tool was used on its own in each experiment, and the results were generalized to an overall rating.[16,17] Ratings were classified as low, low-moderate, or moderate; no study was excluded based on quality, but ratings were used to contextualize evidence confidence in Section 4. Results of quality assessment are provided in Section 3 (see Table 1).

2.7. Data synthesis

Given the substantial methodological heterogeneity across studies—different species, different force protocols, different time points, different cell types, and different molecular detection methods—quantitative meta-analysis was not possible. A narrative synthesis was used, with findings organized according to the signaling axes (RANKL/OPG, Wnt/β-catenin, BMP, and mechanosensing

pathways). In cases where studies had directionally conflicting results on the same molecule, the experimental context was considered to determine whether the conflict could be resolved within a biologically coherent context.

3. Results

3.1. Overview of included studies

A total of 21 studies published between 2005 and 2025 were included. Study designs comprised: in vitro only (n = 5), in vivo only (n = 8), and combined in vitro plus in vivo (n = 8). Animal models used were rat (Sprague-Dawley, n = 10), mouse (C57BL/6J, ICR, transgenic, n = 8), and beagle dog (n = 1). The in vitro models used human PDL cells and PDLFs, human PDLSCs from deciduous and permanent teeth, and murine pre-osteoblast cells (MC3T3-E1, MLO-Y4). Sixteen articles were rated as EIII (in vivo animal or combined design), and five as EIV (in vitro only). One study had a low risk of bias, as it used a genetic knockout design with strong causal evidence and adequate controls;[18] low-moderate risk of bias in 15 studies; and moderate risk of bias in 5 studies (all in vitro only or large-animal RNA sequencing [RNA-seq] designs). None of the studies was rated as high risk of bias. Tables 1 and 2 show quality assessment and characteristics of the study, respectively.

3.2. The RANKL/OPG/RANK axis: Consistent direction across all studies

The RANKL/OPG axis was the only molecular endpoint found to be universal—seen in all studies—ensuring its status as the irreducible molecular core of OTM bone remodeling. Through the evidence base, there was a consistent spatial distribution: compression-side environments had RANKL elevation, OPG suppression, and a higher RANKL/OPG ratio to support osteoclastogenesis, whereas tension-side environments had the opposite. This spatial consistency was replicated in rat, mouse, and human PDL cell models, indicating that it is a conserved mechanobiological principle rather than a species- or model-specific phenomenon.

Table 1. Quality assessment and risk of bias

No.	Author(s)	Design	Tool	OTM model/force	Evidence level	Key limitation	Risk of bias
1	Nitzsche *et al.* (2024)[19]	In vitro	ToxRTool	Compressive force simulated (not OTM spring)	Level IV (in vitro only)	Primarily in vitro, no in vivo validation	Moderate
2	Zhang *et al.* (2016)[20]	Combined	SYRCLE + ToxRTool	In vivo rat OTM + 100 kPa static pressure	Level III (in vivo/ combined)	The static pressure model may not replicate dynamic OTM spring forces; limited to two time points (1 h and 12 h)	Low–moderate
3	Wei *et al.* (2022)[21]	In vivo	SYRCLE	Rat: two force magnitudes (10 g/50 g)	Level III (in vivo/ combined)	Lacks tension-side analysis	Low–moderate
4	Qi *et al.* (2024)[22]	In vivo	SYRCLE	Mouse; BMP-2 + RANKL inhibitor injection	Level III (in vivo/ combined)	Standard protocol not yet established	Low–moderate
5	Tabatabaei *et al.* (2023)[23]	In vitro	ToxRTool	Human PDL cells; tensile + compressive + PBM	Level IV (in vitro only)	In vitro; Wnt is not directly mechanistically studied	Moderate
6	Zhu *et al.* (2021)[24]	Combined	SYRCLE + ToxRTool	Rat OTM; 6-shogaol; mouse BMMs	Level III (in vivo/ combined)	Upstream 6-shogaol regulator unknown	Low–moderate
7	Uchibori *et al.* (2020)[25]	In vivo	SYRCLE	SHR rats; β-AR blockers (3 types + control)	Level III (in vivo/ combined)	SHR sympathicotonia may not represent normotensive orthodontic patients; OPG is not directly measured	Low–moderate
8	Wu *et al.* (2023)[26]	In vitro	ToxRTool	MC3T3-E1; cyclic strain; DKK1 siRNA + TNF-α	Level IV (in vitro only)	Murine pre-osteoblast cell line (MC3T3-E1) may not recapitulate primary osteoblast behavior; ERK–RANKL crosstalk requires in vivo validation	Moderate

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Table 1. (*Continued*)

No.	Author(s)	Design	Tool	OTM model/force	Evidence level	Key limitation	Risk of bias
9	Odagaki *et al.* (2018)[27]	Combined	SYRCLE + ToxRTool	ICR mice; PDL-osteocyte indirect co-culture	Level III (in vivo/ combined)	PDL heterogeneity limitation	Low–moderate
10	Kang *et al.* (2024)[13]	In vitro	ToxRTool	MC3T3-E1; 15% cyclic stretch; Piezo1 modulation	Level IV (in vitro only)	15% stretch level may not reflect physiological OTM magnitudes; Piezo1-independent BMP-2 pathway not fully characterized	Moderate
11	Lee *et al.* (2018)[28]	In vivo	SYRCLE	Beagle dogs; osteoperforation; RNA-seq	Level III (in vivo/ combined)	Small RNA-seq sample; beagle-to-human gap	Moderate
12	Lim *et al.* (2014)[18]	In vivo	SYRCLE	*OCN*-Cre;*Wls*(fl/ fl) cKO mice; developmental model	Level III (in vivo/ combined)	No active OTM force applied	Low
13	Jeon *et al.* (2022)[29]	In vivo	SYRCLE	*DMP1* CRE+. *IFT80*f/f transgenic mice	Level III (in vivo/ combined)	Anatomic cilia deflection limits	Low–moderate
14	Chen *et al.* (2019)[14]	In vitro	ToxRTool	Human PDLSCs; hydraulic pressure; α7 nAChR + DKK1	Level IV (in vitro only)	Deciduous tooth context; no in vivo validation	Moderate
15	Silva *et al.* (2024)[30]	In vivo	SYRCLE	OVX mice; bovine MEV treatment; OTM	Level III (in vivo/ combined)	OVX bone loss not reversed; MEV mechanism unclear	Low–moderate
16	Nam *et al.* (2022)[31]	Combined	SYRCLE + ToxRTool	SD rats; adaptable vs heavy force; microarray	Level III (in vivo/ combined)	SOST-OC discordance needs clarification	Low–moderate
17	Ahn *et al.* (2024)[32]	In vivo	SYRCLE	OVX SD rats; romosozumab anti-SOST Ab	Level III (in vivo/ combined)	Histological only; mechanisms need more work	Low–moderate
18	Ei Hsu Hlaing *et al.* (2019)[33]	Combined	SYRCLE + ToxRTool	ICR mice; human PDLFs; Ca^{2+} live imaging	Level III (in vivo/ combined)	The Ca^{2+} heterogeneity mechanism is unclear	Low–moderate
19	Shu *et al.* (2017)[11]	Combined	SYRCLE + ToxRTool	35 rats + 50 WT/*SOST*-KO mice; MLO-Y4; RAW264.7	Level III (in vivo/ combined)	Single time point focus; hypoxia complexity	Low–moderate
20	Ohori *et al.* (2019)[34]	Combined	SYRCLE + ToxRTool	WT + *TNFR*sKO mice; primary GFP-sorted osteocytes	Level III (in vivo/ combined)	Culture variability; in vitro milieu mismatch	Low–moderate
21	Xue *et al.* (2013)[35]	Combined	SYRCLE + ToxRTool	SD rats; LIPUS; Ni-Ti spring OTM	Level III (in vivo/ combined)	Day 3 vs. day 5 threshold unexplained	Low–moderate

Abbreviations: α7 nAChR: α7 nicotinic acetylcholine receptor; BMM: Bone marrow-derived monocyte; BMP-2: Bone morphogenetic protein 2; cKO: Conditional knockout; DKK1: Dickkopf-1; DMP1: Dentin matrix protein 1; ERK: Extracellular signal-regulated kinase; FACS: Fluorescence-activated cell sorting; IF: Immunofluorescence; IFT80: Intraflagellar transport protein 80; IHC: Immunohistochemistry; ISH: In situ hybridization; LIPUS: Low-intensity pulsed ultrasound; MEV: Milk extracellular vesicle; NC: No change; OCN: Osteocalcin; OPG: Osteoprotegerin; OTM: orthodontic tooth movement; OVX: Ovariectomized; PBM: Photobiomodulation; PDLFs: Periodontal ligament fibroblasts; PDLSCs: Periodontal ligament stem cells; RANKL: Receptor activator of nuclear factor kappa-B ligand; RNA-seq: RNA sequencing; SD: Sprague-Dawley; SHR: Spontaneously hypertensive rat; SOST: Sclerostin; SYRCLE: Systematic Review Centre for Laboratory Animal Experimentation; TNF-α: Tumour necrosis factor-alpha; TNFRsKO: *TNFR* knockout; ToxRTool: Toxicological data Reliability Assessment Tool; WB: Western blot; Wls: Wntless.

Table 2. Summary of included studies: Author, design, pathways, and key findings

No.	Author(s), year	Design	Pathways	Direction of effect	Key findings
1	Nitzsche *et al.* (2024)[19]	In vitro	RANKL/OPG; GDF15/BMP	RANKL↓; OPG↑; GDF15↑	*GDF15* knockdown amplifies the anti-resorptive effect of ZOL in mechanically stressed PDLFs
2	Zhang *et al.* (2016)[20]	Combined	RANKL/OPG; Wnt/β-catenin; DKK1	1 h: RANKL/OPG↓; 12 h: RANKL/OPG↑	Wnt/β-catenin regulates RANKL/OPG biphasically in PDLSCs under static pressure
3	Wei *et al.* (2022)[21]	In vivo	RANKL/OPG; Wnt/SOST	Low force: RANKL/OPG↓; High force: RANKL/OPG↑	Cementocytes regulate RANKL/OPG via force-magnitude-dependent SOST modulation
4	Qi *et al.* (2024)[22]	In vivo	RANKL; BMP-2	RANKL↓ (inhibited); BMP-2↑	BMP-2 + RANKL inhibitor prevents bone dehiscence while maintaining OTM
5	Tabatabaei *et al.* (2023)[23]	In vitro	RANKL/OPG; SOST (Wnt)	Pressure: RANKL↑ SOST↑; Tension: RANKL↓ OPG↑	PBM + OTM forces produce site-specific RANKL/OPG/SOST regulation in human PDL cells
6	Zhu *et al.* 2021[24]	Combined	RANKL/OPG; Wnt/SOST; JNK-NFATc1	RANKL↑; SOST↑; OTM accelerated	6-Shogaol accelerates OTM via JNK-NFATc1-SOST-RANKL cascade
7	Uchibori *et al.* (2020)[25]	In vivo	RANKL; Wnt/SOST	RANKL↓; SOST↓; Bone volume↑	β-AR blockers suppress OTM-induced SOST and RANKL via the sympathetic pathway
8	Wu *et al.* (2023)[26]	In vitro	RANKL/OPG; Wnt/DKK1; ERK	DKK1 silencing: RANKL/OPG↓; TNF-α addition: reversed	DKK1/TNF-α/ERK crosstalk under mechanical stress regulates osteoblast RANKL/OPG
9	Odagaki *et al.* (2018)[27]	Combined	RANKL/OPG; Wnt/SOST	RANKL↑; OPG↓; SOST↑ (PDL→osteocyte)	Paracrine SOST from PDL cells activates osteocytic SOST to drive RANKL
10	Kang *et al.* (2024)[13]	In vitro	BMP-2; RANKL; Piezo1	BMP-2↑; Runx2↑; RANKL partially independent	Piezo1 channel drives BMP-2/osteoblastogenesis; BMP-2 partially Piezo1-independent
11	Lee *et al.* (2018)[28]	In vivo	RANKL/OPG; Wnt (RNA-seq)	RANK↑; Wnt↓; OTM↑	Osteoperforation upregulates RANK and transcriptomically downregulates *Wnt* (RNA-seq)
12	Lim *et al.* (2014)[18]	In vivo	Wnt; RANKL/OPG	Wnt↓→RANKL↑; OPG↓→root resorption	Genetic *Wnt* loss alone is sufficient to cause RANKL elevation and spontaneous root resorption
13	Jeon *et al.* (2022)[29]	In vivo	RANKL; Wnt/SOST; IFT80	NC (null finding)	IFT80 primary cilia NOT required for RANKL/SOST regulation in vivo
14	Chen *et al.* (2019)[14]	In vitro	RANKL/OPG; Wnt/β-catenin; α7 nAChR	RANKL↑; OPG↓; Wnt activated; reversed by DKK1	α7 nAChR → Wnt/β-catenin → RANKL/OPG under hydraulic pressure in PDLSCs
15	Silva *et al.* (2024)[30]	In vivo	RANKL/OPG; Wnt/SOST	RANKL↓; OPG↑; SOST↑	Bovine MEVs reduce OTM via anti-resorptive RANKL/OPG-Wnt axis in OVX mice
16	Nam *et al.* (2022)[31]	Combined	RANKL/OPG; Wnt/SOST	Adaptable: SOST↑ (brake); Heavy: SOST absent → unregulated resorption	SOST is a force-magnitude-dependent Wnt-mediated homeostatic brake on osteoclastogenesis
17	Ahn *et al.* (2024)[32]	In vivo	RANKL/OPG; Wnt/SOST	RANKL↓; OPG/RANKL↑; SOST↓; Biphasic OTM	Romosozumab activates Wnt → reduces RANKL/OPG ratio; biphasic OTM response

(*cont'd...*)

Table 2. (*Continued*)

No.	Author(s), year	Design	Pathways	Direction of effect	Key findings
18	Ei Hsu Hlaing (2019)[33]	Combined	RANKL/OPG; Wnt/SOST; Ca^{2+}	Ca^{2+}↑ → RANKL↑; OPG↓; SOST↑	Ca^{2+} oscillations initiate early bone remodeling via RANKL and Wnt/SOST cascade
19	Shu *et al.* (2017)[11]	Combined	RANKL/OPG; Wnt/SOST	SOST↑ (compression); RANKL↑; SOST-KO: TRAP+↓	SOST causally promotes osteoclastogenesis by directly upregulating RANKL in osteocytes
20	Ohori *et al.* (2019)[34]	Combined	RANKL/OPG; Wnt/SOST; TNF-α	TNF-α→SOST↑→RANKL↑; TNFRsKO reversed	TNF-α→SOST→RANKL: sequential inflammatory-Wnt-resorptive cascade confirmed
21	Xue *et al.* (2013)[35]	Combined	RANKL; BMP-2/HGF/Runx2	RANKL↑; BMP-2↑; Runx2↑ (from day 5)	LIPUS activates HGF/Runx2/BMP-2 and RANKL to accelerate OTM via coupled remodeling

Abbreviations: AR: Adrenergic receptor; BMP-2: Bone morphogenetic protein 2; DKK1: Dickkopf-1; GDF15: Growth differentiation factor 15; HGF: Hepatocyte growth factor; IFT80: Intraflagellar transport protein 80; JNK: c-Jun N-terminal kinase; LIPUS: Low-intensity pulsed ultrasound; MEV: Milk extracellular vesicle; NFATc1: Nuclear factor of activated T-cells 1; OPG: Osteoprotegerin; OTM: orthodontic tooth movement; OVX: Ovariectomized; PBM: Photobiomodulation; PDLSCs: Periodontal ligament stem cells; PDLFs: Periodontal ligament fibroblasts; RANKL: Receptor activator of nuclear factor kappa-B ligand; SOST: Sclerostin; TNF-α: Tumor necrosis factor-alpha; *TNFR*sKO: *TNFR* knockout; TRAP: Tartrate-resistant acid phosphatase; Wnt: Wingless-related Integration; ZOL: Zoledronic acid.

In addition to spatial consistency, two modulatory dimensions emerged from cross-study synthesis. First, the force magnitude: dose-dependent RANKL/OPG regulation in cementocytes—low dose (10 g) of intrusion force decreased the ratio, whereas high dose (50 g) of force increased the ratio significantly.[21] Another study independently supported this observation by demonstrating that compared with heavy forces, adaptive forces (40 centinewton [cN] vs. 120 cN) elicited qualitatively different profiles of RANKL/OPG and that heavy forces abolished the homeostatic sclerostin brake but allowed unopposed ratio elevation.[31] Second, temporal profile: the temporal occupational pattern in human PDLSCs was characterized by a 1-hour static pressure that decreased the RANKL/OPG ratio (pro-osteogenic), and a 12-hour sustained force, which augmented it substantially (pro-resorptive).[20] Such a biphasic reaction indicates that the same signaling pathway can generate diametrically opposite responses to the same mechanical stimulus, depending on its duration. This is significant for designing intermittent versus continuous force regimens in clinical orthodontics.[20,32]

Pharmacological treatments consistently affected the RANKL/OPG ratio in predictable ways. RANKL inhibition (OP3–4 peptide) blocked osteoclastogenesis but not OTM, showing that RANKL is a therapeutic target that can be successfully inhibited without biological blockage of tooth movement.[22] The OPG/RANKL ratio was enhanced, besides generating a biphasic OTM response—early acceleration followed by a decreasing rate—indicating that Wnt pathway stimulation through sclerostin inhibition elicits complicated downstream RANKL/OPG interactions.[22,32] Physical stimulation modalities (low-intensity pulsed ultrasound [LIPUS], photobiomodulation [PBM]) also induced context-specific changes in RANKL. LIPUS co-upregulated RANKL with BMP-2, which is a coupled stimulation between resorption and formation[35] while PBM induced site-selective upregulation at the pressure side and downregulation at the tension side, increasing but not overriding the inherent mechanical asymmetry.[23]

3.3. Wnt/β-catenin signaling: Dominant upstream regulator of RANKL/OPG

Wnt/β-catenin signaling was reported in 16 of 21 studies and can be regarded as the major upstream signaling pathway that controls the balance between RANKL/OPG during OTM. In various experimental systems, genetic conditional knockouts, pharmacological inhibition and activation, mechanical loading models, and cell-specific paracrine systems, a directional effect was identified: canonical Wnt activity downregulates RANKL and upregulates OPG (pro-osteogenic),[14,18,20] and Wnt inhibition upregulates RANKL and downregulates OPG (pro-resorptive).[26,28,29] This two-way regulatory loop offers a mechanistic description as to why RANKL and OPG vary inconsistently during OTM.

The genetic model in Lim *et al.*[18] provided the strongest causal evidence because genetic deletions of the *Wls* gene in osteoblasts and odontoblasts caused spontaneous RANKL upregulation, OPG downregulation, osteoclast overactivation, and cementum loss, inducing root resorption without the need for mechanical force.

This genetic evidence confirms that Wnt signaling is not simply linked to the balance of RANKL/OPG but is causally required to sustain it.[18] The confirmation of the inverse RANKL–Wnt relationship at the RNA-sequencing level in a large-animal model using genome-wide Wnt pathway downregulation and RANK osteoclast pathway upregulation corroborates transcriptomic evidence of osteoperforation-accelerated OTM.[28]

The DKK1 protein was found to be the major Wnt inhibitor that mediates Wnt–RANKL crosstalk under mechanical loading.[26] DKK1 was upregulated in the presence of cyclic compressive/tensile strain of MC3T3-E1 pre-osteoblasts, and silencing with DKK1 small-interfering RNA had a significant effect in lowering the RANKL/OPG ratio and increasing β-catenin, Wnt5a, Runx2, and osterix.[26] All these positive effects were reversed by TNF-α addition via the ERK signaling pathway, demonstrating that DKK1/TNF-α/ERK constitutes an ERK signaling axis activated by mechanical stimulus.[26] In human PDLSCs subjected to hydraulic pressure, pharmacological inhibition of DKK1 reversed the mechanical stress-induced upregulation of RANKL and restored the expression of OPG and RUNX2,[14] supporting the causal relationship between Wnt and RANKL in two independent in vitro systems.

Wnt pathway downregulation and rapid OTM were seen in osteoperforation-treated beagle dogs,[28] which might seem to contradict the Wnt-protective model. Yet the biological rationale behind this observation makes sense. Osteoperforation purposefully induces a local temporary resorptive state to hasten tooth displacement,[28] and Wnt downregulation is a pro-resorptive molecular aftermath of cortical disruption of homeostatic regulation, but not the other way around.[18,28] The Wnt inhibition here has resorptive effects, accelerating OTM, and is in agreement with the general model of Wnt inhibition, which results in osteoclast-stimulating environments.[18,28]

3.4. Sclerostin as a pivotal mechanosensory–Wnt–RANKL mediator

The most commonly mentioned molecular mediator throughout the review was sclerostin, which was mentioned in 11 of 21 studies. Its intersection with Wnt/β-catenin inhibition and RANKL activation positions it as the molecular hub through which mechanical force is converted into an osteoclastogenic signal.[29-31] More importantly, sclerostin in OTM is not just another Wnt antagonist, which inhibits bone formation: it has been causally shown to trigger the transcription of RANKL in osteocytes, which facilitates osteoclastogenesis, which is not dependent on its anti-Wnt properties.[30]

The causal evidence was given in the form of *SOST*-knockout mice: the number of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts at the compression side was significantly reduced in *SOST*-deficient animals, and the direct induction of an increase in the *RANKL* mRNA level in the MLO-Y4 osteocyte-like cells by recombinant sclerostin was obtained in vitro.[11] Wnt inhibition and RANKL upregulation are dual actions that render sclerostin a highly powerful pro-resorptive mediator at the compression face of OTM.[11,30,31] Compressive force on PDL cells triggers sclerostin secretion that parabolically diffuses to nearby osteocytes, which respond to sclerostin expression and enhance the RANKL signal in a PDL–osteocyte paracrine cascade.[27] This observation reconsiders the PDL, not as a passive transmission medium, but as a mechanosensory-signaling organ.[27]

Several sclerostin upstream regulatory signals were discovered. TNF-α, a pro-inflammatory cytokine that increases in OTM, induces sclerostin osteocyte expression, and genetic *TNFR* knockout mice decrease compression-side sclerostin and osteoclastogenesis.[34] This confirms a TNF-α–sclerostin–RANKL molecular cascade that magnifies inflammatory resorptive signaling during the inflammatory stage of OTM.[24,34] Mechanical compression of PDLFs elicits intracellular Ca^{2+} oscillations, which in turn increase the levels of sclerostin and RANKL (placing calcium mechanotransduction as another upstream activator of sclerostin).[33]

The extent of force was the decisive factor in the functionality of sclerostin, and the seeming controversy between the studies needs to be resolved. Adaptive forces (40 cN) maintained sclerostin at the PDL compression surface as an osteoclastogenesis-moderating homeostatic regulatory molecule, whereas heavy forces (120 cN) eliminated PDL sclerostin expression, depleting this homeostatic brake and allowing unchecked RANKL-mediated resorption.[31] In case of pathological or maximal force conditions, the pro-resorptive effects of sclerostin were demonstrated by Shu *et al.* and Ohori *et al.*[11,34] These observations are not opposing, as they outline a force-magnitude-dependent biphasic sclerostin response: at physiologically relevant forces, sclerostin is a balancer; under excessive forces or inflammation, it is a pro-resorptive amplifier.[11,30,31,34] This force-magnitude threshold model offers a molecular interpretation of the clinical finding, indicating that under heavy forces of orthodontic treatment, there is disproportionate bone resorption.

The sclerostin–Wnt–RANKL axis is pharmacologically tractable, and romosozumab (anti-sclerostin antibody) treatment of ovariectomized rats decreased sclerostin, stimulated Wnt, improved the OPG/RANKL ratio, improved bone microarchitecture, and induced an

initial increase of OTM followed by a rate decrease as bone quality enhanced.[32] This biphasic OTM response is consistent with the dual role of sclerostin: early deletion of the pro-resorptive RANKL stimulus (slowing OTM), and a long-lasting lack of this stimulus that activates Wnt-mediated bone formation (enhancing bone quality).[20,32] A β-adrenergic receptor blocker experiment also substantiated that activation of the sympathetic nervous system controls sclerostin and RANKL in osteocytes and added a neuroendocrine facet to the Wnt–RANKL control during OTM.[25]

3.5. BMP signaling: Mechanosensitive pro-osteogenic axis with RANKL crosstalk

In 5 of 21 studies, BMP signaling was directly explored, which is the least well-characterized of the three major axes of signaling in OTM. However, the evidence continually placed BMP-2 as a mechanosensitive proosteogenic target, and there were significant interactions with RANKL.[35] Three articles gave mechanistic details of the stimulation of BMP-2 by physical stimulation.[19,23,35] Brain-derived neurotrophin factor (BDNF) stimulation in response to LIPUS was observed on day 5 of treatment,[35] Piezo1 channel activation in the presence of cyclic stretch induced BMP-2, with Runx2 and osteocalcin,[13] and growth differentiation factor 15 (GDF15), a TGF-β/BMP superfamily member, in response to compressive force in treatment with bisphosphonate-treated PDLFs showed RANKL/OPG regulation.[19]

Xue *et al*.[35] demonstrated that LIPUS co-upregulates BMP-2 (pro-osteogenic) and RANKL (pro-resorptive), which are physiological activities of bone formation and resorption in accelerated OTM: both are synergistically stimulated to accelerate tooth movement, with no net bone loss. In comparison, Qi *et al*.[22] proved that prophylactic BMP-2 injection combined with RANKL inhibition was an effective method to prevent bone dehiscence through bone formation and selective limiting resorption. These results do not contradict each other: physiological OTM is a physiological linkage between BMP-2 and RANKL, but in the therapeutic setting, it is possible to deliberately decouple them and rebalance the balance toward bone preservation. This clinical difference has direct implications for patients receiving orthodontic care with poor bone structure.[22,35]

Activation of Piezo1 channels by cyclic stretch regulated BMP-2, but was only partially dependent on Piezo1: GsMTx4 (Piezo1 blocker) had no ability to fully prevent BMP-2 upregulation, confirming that BMP-2 is regulated by parallel mechanosensory pathways that converge on the same effector.[13] Such redundancy in BMP-2 regulation via multiple mechanosensory pathways suggests a well-developed, robust osteogenic response to mechanical loading that is not heavily reliant on a single mechanosensor.

3.6. Mechanosensing pathways: Parallel upstream regulators converging on RANKL/Wnt

Seven of the 21 studies described particular mechanosensory functions that convert orthodontic mechanical force into RANKL/OPG and/or Wnt/BMP signaling molecules. Instead of one large dominant mechanosensory pathway, the evidence is all pointing towards a redundant, multi-pathway mechanosensory network with heavy convergence on common downstream effectors. The cross-study synthesis determines four main mechanosensory nodes. One is intracellular Ca^{2+} oscillations, which are induced by mechanical compression in PDLFs and increase the mRNA levels of *RANKL* and *SOST*, one of the first measurable molecular responses to the application of force. Secondly, the Piezo1 mechanosensitive ion channel, which is triggered by cyclic stretch in osteoblasts and promotes the BMP-2/Runx2 osteogenic cascade as well as modulates osteoclast signaling via NF-κB p65. Third, the α7 nAChR mechanoreceptor, triggered by the hydraulic pressure of the PDLSCs, initiates canonical Wnt/β-catenin RANKL/OPG signaling, and DKK1 pharmacological blockage verifies the causal cascade. Fourth, β-adrenergic receptor signaling, where sympathetic nervous system stimulation enhances sclerostin and RANKL in osteocytes, and β-adrenergic blockade suppresses both, with a systemic neuroendocrine contribution to local osteocyte OTM molecular biology.

All these mechanosensory pathways rely on specific molecular machineries, which should be described in detail. The Piezo1 channel is a mechanically activated non-selective cation channel that is present in the plasma membrane;[36] upon mechanically induced plasma membrane deformation, Piezo1 opens and leads to influx of Ca^{2+} into the cell, activating calcineurin/nuclear factor of activated T-cells 1 (NFATc1) and BMP-2/Runx2 transcriptional programs.[13] The pharmacological validation of these activities can be seen in osteoblast models using Piezo1 and Yoda1, as well as GsMTx4 (peptide antagonist).[13,36,37] The α7 nAChR, historically considered a neuronal receptor, is now known to be a mechanosensitive receptor in PDLSCs; evidence of coupling between the α7 nAChR and canonical Wnt/β-catenin signaling, involving glycogen synthase kinase-3 beta (GSK-3β) phosphorylation and pharmacologically blocked with α-bungarotoxin, confirms the sequential signaling pathway.[20,38]

The mechanically gated channels trigger the initiation of oscillations, which are sustained by endoplasmic reticulum Ca^{2+} release mediated by the inositol 1,4,5-trisphosphate

(IP3) receptor; the frequency of the oscillations, but not the level of Ca^{2+} released, represents the intensity of the mechanical stimulus. There is also a systemic neuroendocrine input: the activity of the sympathetic nervous system releases catecholamines, which bind to the osteocyte surface β1- and β2-adrenergic receptors (β-AR) and stimulate cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling, promoting the upregulation of sclerostin and RANKL.[14,27] Three different pharmacological preparations are used for the three receptors: atenolol, a β1-selective preparation; butoxamine, a β2-selective preparation; and propranolol, a non-selective preparation;[39] all are individually able to suppress OTM-induced sclerostin and RANKL induction, indicating both receptors play a role and that the systemic sympathetic state influences local OTM biology.[25] Importantly, these mechanosensory pathways are not exclusive: oscillations in Ca^{2+}, Piezo1, and α7 nAChR can all act on shared downstream targets to produce redundancy and signal amplification that contribute to the robust nature of OTM bone remodeling under normal forces.[13,40]

Notably, Jeon *et al.*[29] reported an imperative result that disproves the hypotheses and also guides us toward correctly omitting a candidate mechanism. During OTM, IFT80-regulated primary cilia in osteocytes were not required for RANKL/sclerostin regulation in the transgenic conditional knockout mouse model. This negative finding is mechanistically revealing, as it excludes one previously anticipated mechanosensory pathway and therefore focuses on the residual candidate systems. This finding, established on two time points (5 and 12 days of force) using various validated outcome measures, switches the focus of mechanosensing research to Ca^{2+}, Piezo1, and α7 nAChR systems as the major mechanosensors of RANKL/WNT regulation in OTM.[13,14,32] The overlap shown in these parallel pathways confirms the existence of many mechanosensory systems converging on common RANKL/Wnt effectors—a redundancy that is visually consolidated in all signaling axes and experimental conditions in Figure 2.

3.7. Cell-type-specific signaling patterns

Across the included studies, seven main periodontal cell populations were examined together, and the RANKL/OPG/Wnt/BMP signaling network operates differently in each of these populations. Osteocytes—the largest mechanosensory cells of the skeleton—were the most consistently involved cell type in sclerostin production and RANKL-driven osteoclastogenesis at the compression side.[11,28,29,34] Causality was demonstrated using a genetic *SOST*-knockout in osteocytes (OTM), which decreased TRAP+ osteoclast numbers (Figure 3).

A unique mechanosensory profile characterized by Ca^{2}+-based mechanotransduction and secretion of sclerostin, a paracrine factor, was uncovered in PDLFs.[19,23,27,31] The PDLFs are the predominant cell type in the periodontal space and are the first cells responding to the orthodontic force; compression-induced Ca^{2+}-oscillations cause sclerostin secretion, which in turn leads to RANKL activation in osteocytes, thus creating a PDLF → osteocyte paracrine axis unique in the PDL space (Figure 4).[19,23,27,31] Various molecular inputs modulate PDLF responses. The inflammatory cytokine TNF-α gives the inflammatory signal, while cellular stress induces GDF15, an endogenous growth factor pertaining to the TGF-β/BMP superfamily. The bisphosphonate zoledronate hinders the bone resorptive properties of osteoclasts by adhering to alveolar bone hydroxyapatite and dismantling

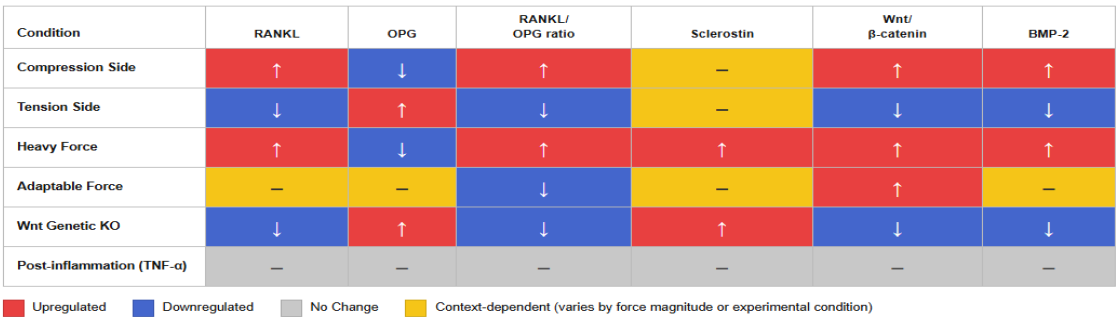

Figure 2. Heatmap synthesizing the direction of molecular effect across all included studies. Notes: Rows represent experimental contexts; columns represent key molecules. Cells indicate consensus direction: ↑ upregulated, ↓ downregulated, – no change/not reported, ~ context-dependent (varies by force magnitude or experimental condition).
Abbreviations: BMP-2: Bone morphogenetic protein 2; KO: Knockout; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor kappa-B ligand; SOST: Sclerostin; TNF-α: Tumor necrosis factor alpha; Wnt: Wingless-related integration.

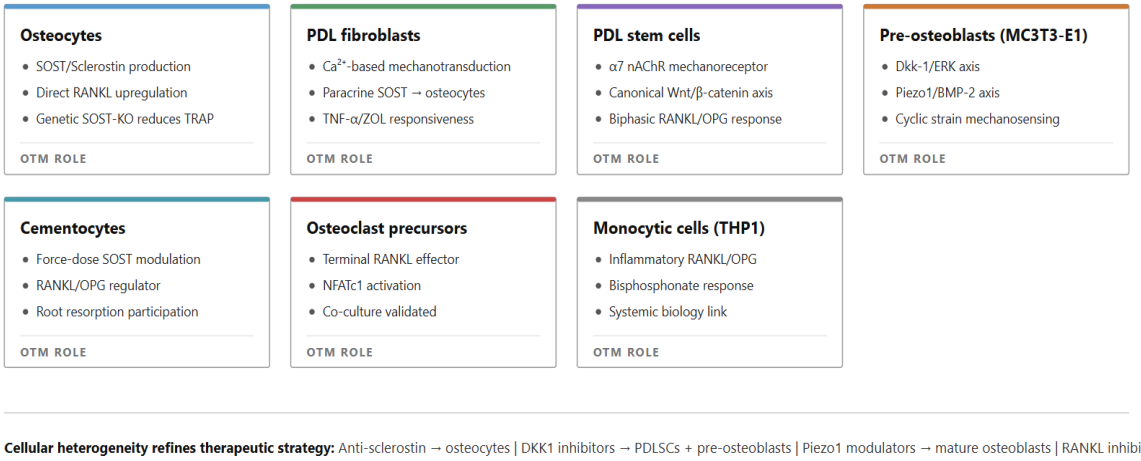

Figure 3. Cell-type-specific signaling patterns. Seven panels showing the dominant signaling pathway in each of the seven cell types.
Abbreviations: α7 nAChR: α7 nicotinic acetylcholine receptor; BMP-2: Bone morphogenetic protein 2; DKK1: Dickkopf-1; ERK: Extracellular signal-regulated kinase; KO: Knockout; OPG: Osteoprotegerin; OTM: Orthodontic tooth movement; PDL: Periodontal ligament; PDLSC: PDL stem cell; RANKL: Receptor activator of nuclear factor kappa-B ligand; TNF-α: Tumor necrosis factor alpha; TRAP: Tartrate-resistant acid phosphatase; Wnt: Wingless-related integration; ZOL: Zoledronic acid.

the mevalonate pathway in resident osteoclasts. This mechanical, inflammatory, and pharmacological amalgam shows the integrative function of PDLFs in the biology of OTM.[19]

Periodontal ligament stem cells showed a context-dependent biphasic RANKL/OPG response, which was primarily Wnt/β-catenin regulated. Wnt/β-catenin pathway facilitates osteogenesis differentiation and inhibits RANKL/OPG under short-duration static pressure; RANKL/OPG predominates under sustained pressure.[14,20] The stem cell-specific pathway is different from Piezo1, a mechanosensor known to activate the canonical Wnt signaling pathway in mature osteoblasts, and involves activation of the α7 nAChR in PDLSCs.[14,20]

The DKK1/ERK mechanosensory axis and the Piezo1/BMP-2 mechanosensory axis were discovered in pre-osteoblasts and the murine cell line MC3T3-E1.[13,26] These cells become mechanically strained, leading to increased DKK1 expression and, in turn, an increased RANKL/OPG ratio (via ERK signaling).[13,26] Concurrently, BMP-2 is upregulated by Piezo1 channel activation in a Wnt-pathway-independent manner, implying parallel mechanosensing of pro-osteogenic pathways in mature osteoblast lineage cells.[13] The other understudied cell type, cementocytes, displayed force-magnitude-dependent modulation of RANKL/OPG by sclerostin, suggesting they may be actively involved in regulating root resorption rather than merely passive cells within the matrix.[21] The downstream integration of the RANKL signal was confirmed in co-culture experiments using bone marrow-derived osteoclast precursors and RAW264.7 cells as osteoclastogenesis effector cells.[11,24] Finally, as to the THP1 monocytic cells, the inflammatory and bisphosphonate-induced modulation of RANKL/OPG was found to be conserved throughout the monocytic cell lineage beyond the immediate periodontium, with implications in the field of orthodontic biology for immunocompromised patients and patients undergoing pharmacological therapy.[19]

These cell-type-specific patterns strongly suggest that interventions targeting the RANKL-OPG-RANK axis should account for cellular context. The anti-sclerostin drugs target signaling from osteocytes: DKK1 inhibitors target both PDLSCs/pre-osteoblasts and mature osteoblasts, while Piezo1 modulators target only mature osteoblasts, and RANKL inhibitor peptides target the universal effector layer, independent of cell source. The cellular multiplicity offers a mechanism for combinatorial therapies and further develops the integrated molecular model proposed in Section 4.1.

4. Discussion

4.1. An integrated molecular model of orthodontic-tooth-movement bone remodeling

The combination of results of our studies allows us to construct a hierarchical, multi-layered model of molecular remodeling of OTM bone. At the top is a group of mechanosensory receptors (Piezo1, α7 nAChR, Ca^{2+} oscillators, and the sympathetic β-AR pathway), which respond to and convert mechanical force into intracellular molecules.[13,14,25,32] These culminate in an intermediate regulatory layer that is prevalent with Wnt/β-catenin signaling and its major antagonist, sclerostin.[25,27]

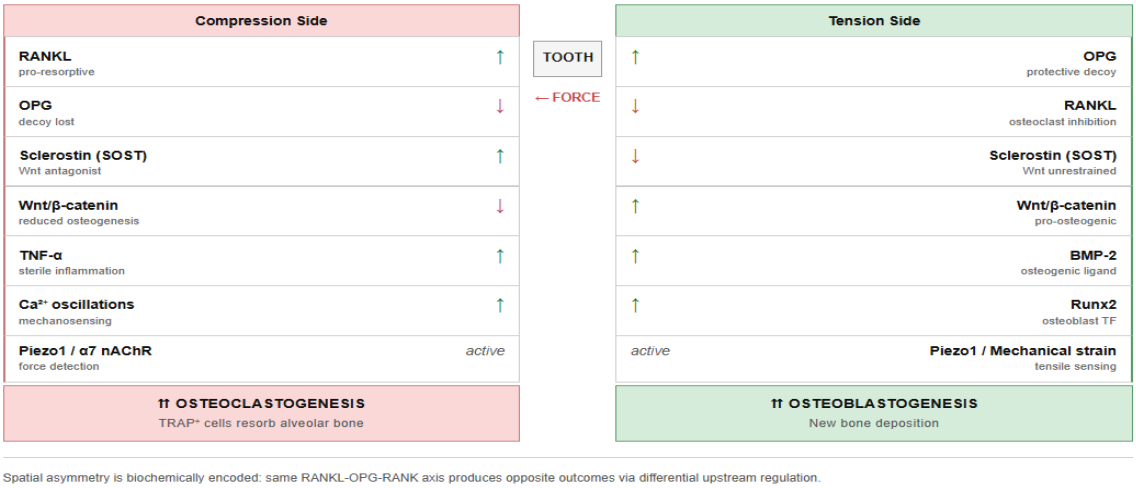

Figure 4. Compression vs. tension side molecular asymmetry. A schematic diagram of a tooth under orthodontic force showing the alveolar bone and periodontal ligament on both sides.
Abbreviations: α7 nAChR: α7 nicotinic acetylcholine receptor; BMP-2: Bone morphogenetic protein 2; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor kappa-B ligand; TNF-α: Tumor necrosis factor alpha; TRAP: Tartrate-resistant acid phosphatase; Wnt: Wingless-related integration.

Sclerostin serves as the key intermediary in the essential process of force sensing and RANKL regulation with two mechanistically reinforcing roles: Wnt pathway suppression (lowering OPG)[27,41] and direct RANKL expression in osteocytes.[27,31] All this carries the RANKL/OPG ratio to the downstream effector module, which ultimately washes out to a balance between osteoclasts and osteoblasts on both sides of the periodontium.[23,31,33] BMP-2 is a parallel pro-osteogenic axis that intersects both the mechanosensory layer (Piezo1, LIPUS)[13,35] and the RANKL layer (therapeutic decoupling), offering an additional regulatory dimension to facilitate tension-side bone formation and can be pharmacologically utilized to prevent compression-side bone loss (Figure 5).[24,25,42]

The compression-tension molecular asymmetry—the one that is persistently replicated in all models—provides mechanistic support for the idea that the directionality of OTM is not just mechanical but also biochemically determined. Three similarly parallel pathways enable the compression side to generate a pro-resorptive environment, reinforcing itself: Ca^{2+} oscillations and α7 nAChR activation upregulate sclerostin and RANKL;[14,33] sclerostin turns down Wnt and directly increases RANKL;[11,27] and TNF-α inflammatory signals produced by the sterile inflammatory response augment sclerostin expression, intensifying the cascade.[34] The tension side forms a reciprocal pro-formative space by Wnt stimulation, OPG stimulation, and BMP-2 discharge of the resorbed bone compartment, jointly supporting osteoblast differentiation and new bone deposition (Figure 4).[20,23,31,35,43]

4.2. Implications of evidence quality for interpretation

The quality evaluation of our studies indicates a generally satisfactory, though not consistently strong, evidence base. The best causal evidence in the review is the single low-risk-of-bias study,[18] which appeals to genetic conditional knockout with suitable littermate controls and multi-method outcome assessment, and its observation that Wnt loss alone leads to spontaneous root resorption by dysregulating RANKL/OPG should carry the greatest weight in mechanistic interpretation.[44,45] Most of the studies (15/21) graded low–moderate are well controlled in vivo and use combined designs with the correct comparator groups, validated molecular detectors, and multi-timepoint analysis. Nevertheless, there are a number of constraints to trust in particular findings.

Five studies had a risk of bias of Moderate (in vitro only) because they used established murine cell lines instead of primary human cells. Although these lines provide regularized mechanistic data, they may not fully capture the heterogeneous biology of primary periodontal cells in clinical OTM settings. The identified mechanistic pathways Piezo1/BMP-2, DKK1/ERK/RANKL, α7 nAChR/Wnt/RANKL, etc., should then be considered as mechanistic hypotheses that have to be validated in vivo instead of being real physiological facts. The beagle dog RNA-seq research[28] is classified as moderate risk because of the small sequencing sample size (n = 8) and the translational species-human gap; its transcriptomic results are very enlightening but need confirmation in rodents and humans.

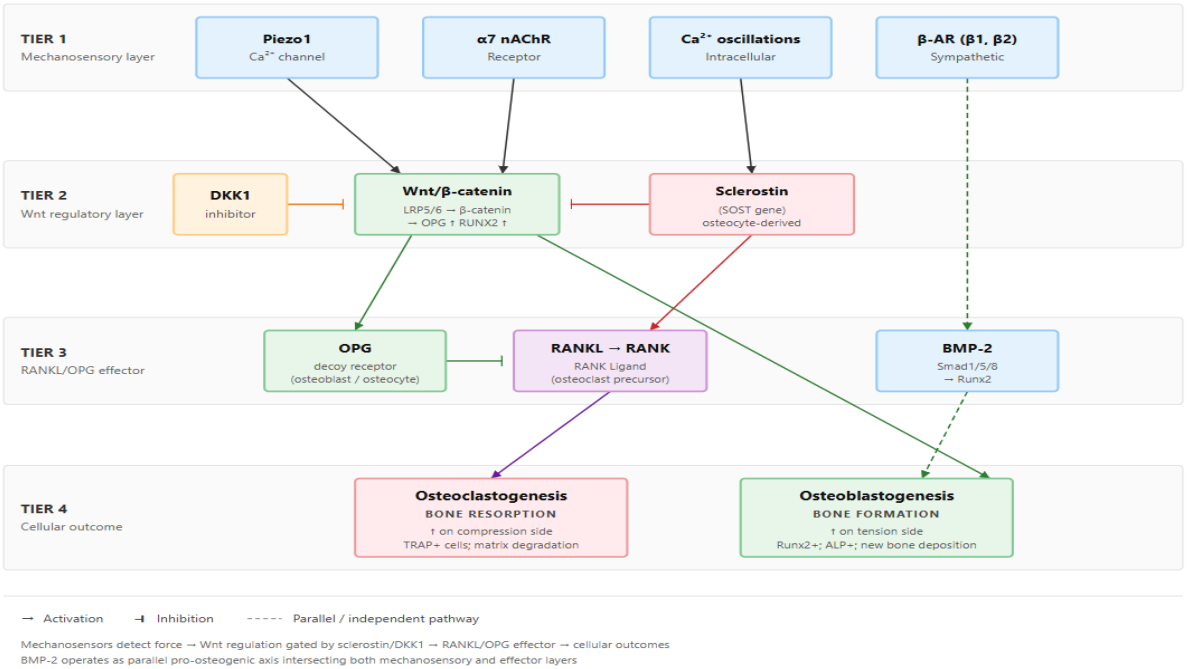

Figure 5. Integrated molecular model of OTM bone remodeling. A four-tier hierarchical pathway diagram showing the mechanosensory layer, Wnt regulatory layer, RANKL/OPG effector layer, and cellular outcome layer. BMP-2 signaling is shown as a parallel pro-osteogenic axis with Smad1/5/8 → Runx2 cascade. Arrows depict activation (→) and inhibition (⊣).
Abbreviations: α7 nAChR: α7 nicotinic acetylcholine receptor; AR: Adrenergic receptor; BMP-2: Bone morphogenetic protein 2; DKK1: Dickkopf-1; OPG: Osteoprotegerin; OTM: Orthodontic tooth movement; RANKL: Receptor activator of nuclear factor kappa-B ligand; TRAP: Tartrate-resistant acid phosphatase; Wnt: Wingless-related integration.

4.3. Therapeutic implications

Our mechanistic synthesis suggests a number of therapeutic targets that can be clinically implemented. Initial acceleration, followed by an enhancement in bone quality and a decrease in RANKL/OPG ratio, was shown with romosozumab, an anti-sclerostin therapy, in ovariectomized rats—a biphasic OTM response.[32,46] This trend has significant clinical implications: it indicates that inhibition of sclerostin can be most effective in preserving bone in OTM in osteoporotic patients, rather than solely accelerating treatment.[47] Wnt activation via sclerostin inhibition improved bone volume/tissue volume (BV/TV), trabecular number (Tb.N), and trabecular thickness (Tb.Th), which can be applied directly to postmenopausal patients who receive orthodontics.[32] It is important to note that this finding aligns with the evidence presented by Shu *et al.*[11] and Ohori *et al.*[34] that sclerostin has a pro-resorptive effect, implying that, at least in the case of adaptable forces, sclerostin is a homeostatic brake. This seemingly contradictory situation can be resolved by considering the clinical context: in ovariectomized bone with low bone mineral density and high resorption, the net effect of sclerostin is pathologically pro-resorptive, and its inhibition is thus protective;[48] in healthy bone at physiological levels of force, sclerostin regulates the resorptive response adequately.[31] The clinical practice message is that anti-sclerostin therapy should not be applied universally, but rather in the context of bone biology.

The proof-of-concept evidence for preventing OTM-induced bone dehiscence is provided by the dual BMP-2 and RANKL inhibitor approach,[22] which promotes bone formation and inhibits excessive resorption. This can best be compared with the LIPUS findings, where LIPUS co-upregulated both BMP-2 and RANKL,[35] seemingly linking the two pathways. The major difference is that LIPUS is an intentional, contextually-specific stimulation of the physiologically coupled resorption-formation response that accelerates healthy bone OTM,[35,49] whereas BMP-2 injection and RANKL inhibitor therapy are therapeutic decoupling of the two pathways to preserve damaged bone but permit OTM.[22] The two strategies are biologically valid, but are used in different clinical applications—a difference that is currently being mechanistically narrowed in the molecular evidence base.

This therapeutic context is especially noteworthy for mentioning the osteoperforation concept.[28] RNA-sequencing revealed that OTM accelerated by surgery was accompanied by downregulation of the Wnt pathway,

which would seemingly go against the Wnt-protective theory.[50] This observation, however, represents an artificially induced pro-resorptive condition produced by surgical cortical injury, rather than a pathological breakdown of Wnt homeostasis. Wnt inhibition in this case has the desired clinical outcome of speeding up tooth movement; it aligns with the general model but warns against the general interpretation of all Wnt suppression as necessarily deleterious.[38] The biphasic RANKL/OPG response at 1 hour versus 12 hours also supports the optimization of force protocols in that short-duration forces are pro-osteogenic RANKL/OPG-favoring, and sustained forces are the opposite.[20]

In addition to romosozumab, the molecular network generated here also identifies multiple other druggable targets of interest. A complementary anti-Wnt inhibitor approach would be to neutralize DKK1, since DKK1 was mechanically upregulated in pre-osteoblasts and PDLSCs in the included studies; neutralizing DKK1 could restore the Wnt–OPG axis without completely inhibiting OTM.[26,51] Biologically, clinical-silence-stage anti-DKK1 agents are being evaluated for osteoporosis and multiple myeloma that could be considered for adjunctive clinical orthodontic application to patients with suboptimal bone quality, such as the bispecific anti-DKK1/anti-sclerostin antibody DKK–Scl.[52]

There are strategies for inhibiting RANKL beyond the single small peptide OP3–4.[22] A fully human monoclonal antibody, denosumab, a drug approved for postmenopausal osteoporosis and bone metastases, targets the RANKL effector directly;[53] but locally delivered automatic low-dose RANKL inhibition via scaffold-based prophylactic injection (as done in the murine bone dehiscence model) might present a promising compartmentalized approach, as systemically delivered denosumab during active OTM would have a significant effect on tooth movement.[54] The LIPUS data and the dual-agent prophylactic injection model support the idea of BMP-2 augmentation with controlled-release scaffolds, recombinant injection, and/or gene therapy, although these latter strategies must be mindful of adverse effects at higher doses (heterotopic ossification and inflammation) that have limited BMP-2 use in spine surgery.[55]

The third dimension of therapeutic possibilities is modulation of mechanosensory pathways. Yoda1 and its derivative Jedi1/2 are at the preclinical stage and are promising Piezo1 agonists that may selectively increase the pro-osteogenic tension-side response without increasing the compression-side response globally;[56] α7 nAChR agonists are clinically available compounds for the modulation of cognition and may be repurposed for Piezo1-mediated pro-Wnt OTM in select patients.[14,37] Based on the data available on β-blockers in our included studies, it has been suggested that patients taking a systemic β-blocker on a chronic basis may alter OTM kinetics, a previously underappreciated drug-disease interaction with direct relevance to adult orthodontic practice.[13,25] Non-pharmacological, clinically deployable approaches, including LIPUS and 980 nm diode laser PBM, have also been mechanistically characterized at the molecular level and are suitable for further investigation for evidence-based green-light clinical orthodontic adjuncts.[23] Finally, dietary and biologic agents provide evidence that modulation of the RANKL-Wnt-sclerostin network by these means is biologically plausible, but efficacy data in the clinic are still limited.[24,30]

4.4. Limitations and future research directions

There are significant limitations to this review. Clinical translation is limited by predominantly animal and in vitro evidence, with no human clinical trials specifically examining the mechanistic RANKL/OPG-Wnt-BMP crosstalk in OTM patients. The force magnitude, duration, cell type, and outcome measurement were methodologically heterogeneous and could not be included in a meta-analysis. The temporal dynamics of signaling activation were not consistently reported, and most studies were limited to a single or a few time points.

Another limitation is that the literature search was limited to peer-reviewed publications and did not investigate any primary RNA-seq datasets, e.g., Gene Expression Omnibus (GEO), ArrayExpress, or Sequence Read Archive. As a future task, targeted re-analysis of publicly available transcriptomic data from OTM models could be used to identify additional interactions between pathways that have not previously been reported in the literature. Moreover, the search strategy purposefully focused on a core set of three signaling axes (RANKL/OPG/RANK, Wnt/β-catenin, BMP); molecules with conceptual ties to these axes (e.g., additional Wnts: Wnt5a, Wnt10b, additional BMPs: BMP-7, BMP-9, identified during full-text screening: microRNAs (miRs): miR-138, miR-195-5p, long non-coding RNAs: H19, etc. cytokines beyond TNF-α (interleukin [IL]-1β, IL-6, IL-17) were thus underrepresented. Future systematic reviews could be expanded to include these molecules, further expanding the mechanobiological picture and its relevance to a broader biomedical audience. Lastly, no human randomized controlled trial has been identified that directly explored the "molecular crosstalk" in orthodontic patients, limiting clinical translation, which is the most important target for future research.

Future research directions include longitudinal human clinical research that undertakes extensive molecular profiling of gingival crevicular fluid and PDL tissue at OTM time points, and standardized in vitro force models using primary human PDL cells rather than established cell lines. Moreover, concurrent stimulation of several mechanosensory pathways in the same OTM model (Piezo1, α7 nAChR, Ca^{2+}) to investigate relative activities,[13,14,33] in vivo validation of the DKK1/ERK/RANKL[26] and α7 nAChR/Wnt/RANKL[14] axes found in cell-line models, and randomized controlled trials of anti-sclerostin therapy[32] and BMP-2/RANKL inhibitor dual-modulation[22] in clinical orthodontic cohorts.

5. Conclusion

This systematic review of primary studies shows that the OTM-related bone remodeling is regulated by a hierarchically organized molecular network. At the center of this network, the RANKL/OPG/RANK axis acts as a universal effector. The upstream controllers are the Wnt/β-catenin pathway and its molecular mediator, sclerostin. BMP signaling works as a parallel pro-osteogenic axis. Sclerostin plays a singular role in this network. It functions as a mechanosensory-WNT-RANKL translator produced by osteocytes and PDL cells in response to compressive force, inflammatory signals, and sympathetic activation. It both suppresses Wnt-regulated OPG production and directly increases RANKL expression. Collectively, a self-reinforcing pro-resorptive cascade is established on the compression side of OTM.

The stable compression-tension molecular asymmetry—replicated across all studies irrespective of the experimental model—offers mechanistic support for the directionality of OTM being biochemically programmed by the spatially localized regulation of the RANKL/OPG–Wnt–sclerostin network. The intensity and duration of forces play a critical role in these patterns, and heavy and prolonged forces disorient the homeostatic Wnt-mediated regulatory brake that defends bone integrity in the physiologically relevant OTM.

All of this forms a molecular basis for the development of specific therapeutic modalities—such as sclerostin inhibitors, DKK1, BMP-2, and RANKL inhibitor combinations—to maximize OTM efficacy, reduce adverse effects, and tailor orthodontic therapies to patients with impaired bone biology. The molecular architecture described herein is a conceptual development of current single-pathway analyses and offers a framework for future translational studies linking mechanistic bone biology to clinical orthodontics.

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Conflict of interest

The authors declare no conflicts of interest relevant to this work.

Author contributions

Conceptualization: Feng Yan
Formal analysis: Feng Yan
Investigation: Feng Yan
Methodology: Feng Yan
Writing–original draft: Feng Yan
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable. This review synthesizes data from previously published primary research studies.

Consent for publication

Not applicable.

Availability of data

All data supporting this review are available within the article.

References

1. Alam M, Hajeer M, Aljubab H, Alruwaili E, AlMashhri J, Alruwaili R. Evaluation of Systemic Nonsteroidal Anti-inflammatory Drugs on Orthodontic Tooth Movement Rate: a Clinical and Biomarker-Based Study. *J Pharm Bioallied Sci*. 2026;18(1):22-24.

   doi: 10.4103/jpbs.jpbs_1761_25

2. Nikeghbal D, Rostamzadeh S, Qutaiba Badraldeen S, *et al*. From Bench to Bedside: Translating Research on miR-138 miR-195-5p and Long Non-Coding RNA H19 into Therapeutic Applications of Orthodontic Tooth Movement. *Int J Mol Cell Med*. 2025;14(3).

   doi: 10.22088/IJMCM.BUMS.14.3.949

3. Jeon HH, Teixeira H, Tsai A. Mechanistic Insight into Orthodontic Tooth Movement Based on Animal Studies: A Critical Review. *J Clin Med*. 2021;10(8):1733.

   doi: 10.3390/jcm10081733

4. Teti L, Pérez-Idarraga A, Salcedo-Miranda M, Cacho A, Yeste-Ojeda F, Martin C. Randomised Clinical Trial on the Effect of Intermittent Vibrational Force Application

During Orthodontic Treatment With Aligners on Root Resorption. *Orthod Craniofac Res*. 2025;28(6):1015-1026.

doi: 10.1111/ocr.70028

5. Nakai Y, Praneetpong N, Ono W, Ono N. Mechanisms of osteoclastogenesis in orthodontic tooth movement and orthodontically induced tooth root resorption. *J Bone Metab*. 2023;30(4):297-310.

doi: 10.11005/jbm.2023.30.4.297

6. Suda T, Nagasawa T, Wara-aswapati N, *et al*. Regulatory roles of β-catenin and AP-1 on osteoprotegerin production in interleukin-1α-stimulated periodontal ligament cells. *Oral Microbiol Immunol*. 2009;24(5):384-389.

doi: 10.1111/j.1399-302X.2009.00529.x

7. Kitaura H, Ohori F, Marahleh A, *et al*. The role of cytokines in orthodontic tooth movement. *Int J Mol Sci*. 2025;26(14):6688.

doi: 10.3390/ijms26146688

8. Yuliasih Y, Rachma B, Awalia A, *et al*. A narrative review of bone disease in spondyloarthropathy: molecular mechanisms and emerging advances. *Egypt Rheumatol Rehabil*. 2025;52(1):72.

doi: 10.1186/s43166-025-00363-z

9. Wang X, Tian Y, Liang X, *et al*. Bergamottin promotes osteoblast differentiation and bone formation via activating the Wnt/β-catenin signaling pathway. *Food Funct*. 2022;13(5):2913-2924.

doi: 10.1039/D1FO02755G

10. Lu W, Zhang X, Firth F, *et al*. Sclerostin injection enhances orthodontic tooth movement in rats. *Arch Oral Biol*. 2019;99:43-50.

doi: 10.1016/j.archoralbio.2018.12.011

11. Shu R, Bai D, Sheu T, *et al*. Sclerostin Promotes Bone Remodeling in the Process of Tooth Movement. *PLoS One*. 2017;12(1):e0167312.

doi: 10.1371/journal.pone.0167312

12. Wu LL, Jia YM, Sui YX, *et al*. The effect of BMP2/Smads pathway mediating platelet-rich fibrin on rat bone mesenchymal stem cells. *Eur Rev Med Pharmacol Sci*. 2022;26(15).

13. Kang T, Yang Z, Zhou M, *et al*. The role of the Piezo1 channel in osteoblasts under cyclic stretching: A study on osteogenic and osteoclast factors. *Arch Oral Biol*. 2024;163:105963.

doi: 10.1016/j.archoralbio.2024.105963

14. Chen Y, Yang K, Zhou Z, Wang L, Du Y, Wang X. Mechanical stress modulates the RANKL/OPG system of periodontal ligament stem cells via α7 nAChR in human deciduous teeth: an in vitro study. *Stem Cells Int*. 2019;2019(1):5326341.

doi: 10.1155/2019/5326341

15. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

doi: 10.1136/bmj.n71

16. Leenaars CH, Stafleu FR, Häger C, Bleich A. A case study of the informative value of risk of bias and reporting quality assessments for systematic reviews. *Syst Rev*. 2024;13(1):230.

doi: 10.1186/s13643-024-02650-w

17. Camargo K, Wright R, Vist GE, *et al*. A protocol to assess ToxRTool use in peer-reviewed literature. *Evid Based Toxicol*. 2025;3(1):2569331.

doi: 10.1080/2833373X.2025.2569331

18. Lim WH, Liu B, Hunter DJ, Cheng D, Mah SJ, Helms JA. Downregulation of Wnt causes root resorption. *Am J Orthod Dentofacial Orthop*. 2014;146(3):337-345.

doi: 10.1016/j.ajodo.2014.05.027

19. Nitzsche A, Hennig CL, Von Brandenstein K, *et al*. GDF15 Modulates the Zoledronic-Acid-Induced Hyperinflammatory Mechanoresponse of Periodontal Ligament Fibroblasts. *Cells*. 2024;13(2):147.

doi: 10.3390/cells13020147

20. Zhang L, Liu W, Zhao J, *et al*. Mechanical stress regulates osteogenic differentiation and RANKL/OPG ratio in periodontal ligament stem cells by the Wnt/β-catenin pathway. *Biochim Biophys Acta Gen Subj*. 2016;1860(10):2211-2219.

doi: 10.1016/j.bbagen.2016.05.003

21. Wei T, Shan Z, Wen X, Zhao N, Shen G. Dynamic alternations of RANKL/OPG ratio expressed by cementocytes in response to orthodonticinduced external apical root resorption in a rat model. *Mol Med Rep*. 2022;26(1):228.

doi: 10.3892/mmr.2022.12744

22. Qi J, Matsumoto Y, Xie C, Rashed F, Ono T, Aoki K. Prevention of bone dehiscence associated with orthodontic tooth movement by prophylactic injection of bone anabolic agents in mice. *Sci Rep*. 2024;14(1):15749.

doi: 10.1038/s41598-024-66617-6

23. Tabatabaei SN, Hodjat M, Hakimiha N, Akhoundi MSA, Kharazifard MJ. In Vitro Effect of Photobiomodulation Therapy with 980 nm Diode Laser on Gene Expression of Key Regulators of Bone Remodeling by Human Periodontal Ligament Cells under Mild Orthodontic Forces. *Photochem Photobiol*. 2023;99(6):1448-1455.

doi: 10.1111/php.13787

24. Zhu X, Yuan H, Ningjuan O, *et al*. 6-Shogaol promotes bone resorption and accelerates orthodontic tooth movement through the JNK-NFATc1 signaling axis. *J Bone Miner Metab*. 2021;39(6):962-973.

doi: 10.1007/s00774-021-01245-y

25. Uchibori S, Sekiya T, Sato T, *et al*. Suppression of tooth movement-induced sclerostin expression using β-adrenergic receptor blockers. *Oral Dis*. 2020;26(3):621-629.

doi: 10.1111/odi.13280

26. Wu Y, Jing Z, Deng D, *et al*. Dkk-1–TNF-α crosstalk regulates MC3T3E1 pre-osteoblast proliferation and differentiation under mechanical stress through the ERK signaling pathway. *Mol Cell Biochem*. 2023;478(10):2191-2206.

doi: 10.1007/s11010-022-04645-4

27. Odagaki N, Ishihara Y, Wang Z, *et al*. Role of Osteocyte-PDL Crosstalk in Tooth Movement via SOST/Sclerostin. *J Dent Res*. 2018;97(12):1374-1382.

doi: 10.1177/0022034518771331

28. Lee JW, Cha JY, Park KH, Kang YG, Kim SJ. Effect of flapless osteoperforation-assisted tooth movement on atrophic alveolar ridge: Histomorphometric and gene-enrichment analysis. *Angle Orthod*. 2018;88(1):82-90.

doi: 10.2319/061217-388.1

29. Jeon HH, Kang J, Li J, *et al*. The effect of IFT80 deficiency in osteocytes on orthodontic loading-induced and physiologic bone remodeling: In vivo study. *Life*. 2022;12(8):1147.

doi: 10.3390/life12081147

30. Silva FRF, Heredia JE, Duffles LF, *et al*. Protective Effect of Bovine Milk Extracellular Vesicles on Alveolar Bone Loss. *Mol Nutr Food Res*. 2024;68(3):e2300445.

doi: 10.1002/mnfr.202300445

31. Nam YS, Yang DW, Moon JS, *et al*. Sclerostin in periodontal ligament: Homeostatic regulator in biophysical force-induced tooth movement. *J Clin Periodontol*. 2022;49(9):932-944.

doi: 10.1111/jcpe.13624

32. Ahn H, Park W, Choi SH, Hong N, Huh J, Jung S. Effect of anti-sclerostin antibody on orthodontic tooth movement in ovariectomized rats. *Prog Orthod*. 2024;25(1):45.

doi: 10.1186/s40510-024-00544-0

33. Ei Hsu Hlaing E, Ishihara Y, Wang Z, Odagaki N, Kamioka H. Role of intracellular Ca(2+)-based mechanotransduction of human periodontal ligament fibroblasts. *FASEB J*. 2019;33(9):10409-10424.

doi: 10.1096/fj.201900484R

34. Ohori F, Kitaura H, Marahleh A, *et al*. Effect of TNF-α-Induced Sclerostin on Osteocytes during Orthodontic Tooth Movement. *J Immunol Res*. 2019;2019:9716758.

doi: 10.1155/2019/9716758

35. Xue H, Zheng J, Cui Z, *et al*. Low-intensity pulsed ultrasound accelerates tooth movement via activation of the BMP-2 signaling pathway. *PLoS One*. 2013;8(7):e68926.

doi: 10.1371/journal.pone.0068926

36. Vasileva V, Morachevskaya E, Sudarikova A, Negulyaev Y, Chubinskiy-Nadezhdin V. Selective chemical activation of Piezo1 in leukemia cell membrane: Single channel analysis. *Int J Mol Sci*. 2021;22(15):7839.

doi: 10.3390/ijms22157839

37. Liu Y, Xu YQ, Long YY, Xiao H, Ma YY, Li YW. Mechanosensitive channel Piezo1 in calcium dynamics: structure, function, and emerging therapeutic strategies. *Front Mol Biosci*. 2025;12:1693456.

doi: 10.3389/fmolb.2025.1693456

38. Birjandi AA, Sharpe P. Wnt signalling in regenerative dentistry. *Front Dent Med*. 2021;2:725468.

doi: 10.3389/fdmed.2025.1537478

39. Khan MF, Ramos L. Drugs Affecting Adrenergic System. In: *Medicinal Chemistry of Drugs Affecting the Nervous System*. Sharjah, UAE: Bentham Science Publishers; 2020:59-108.

doi: 10.2174/9789811454073120020004

40. Gehlert S, Bloch W, Suhr F. Ca2+-dependent regulations and signaling in skeletal muscle: from electro-mechanical coupling to adaptation. *Int J Mol Sci*. 2015;16(1):1066-1095.

doi: 10.3390/ijms16011066

41. Aryana IGPS, Rini SS, Soejono CH. Importance of sclerostin as bone-muscle mediator crosstalk. *Ann Geriatr Med Res*. 2022;26(2):72.

doi: 10.4235/agmr.22.0036

42. Li L, Ji J, Ren H, *et al*. Transformative biomechanics and mechanobiology breakthroughs shaping the future of health and medicine. *Innovation*. 2026;7(4):101307.

doi: 10.1016/j.xinn.2026.101307

43. Danz JC, Degen M. Selective modulation of the bone remodeling regulatory system through orthodontic tooth movement—A review. *Front Oral Health*. 2025;6:1472711.

doi: 10.3389/froh.2025.1472711

44. Zhou J, Guo L, Yang Y, Liu Y, Zhang C. Mechanical force regulates root resorption in rats through RANKL and OPG. *BMC Oral Health*. 2022;22(1):290.

doi: 10.1186/s12903-022-02327-7

45. Zhang T, Feng Y, Wang W, *et al*. Membrane-bound or soluble, mesenchymal or myeloid: which RANKL drives osteoclastogenesis? *J Transl Genet Genom*. 2026;10(2):74-88.

doi: 10.20517/jtgg.2025.146

46. Chen Y, Zhang C. Role of noncoding RNAs in orthodontic tooth movement: new insights into periodontium remodeling. *J Transl Med*. 2023;21(1):101.

doi: 10.1186/s12967-023-03951-9

47. Liao C, Liang S, Wang Y, Zhong T, Liu X. Sclerostin is a promising therapeutic target for oral inflammation and regenerative dentistry. *J Transl Med*. 2022;20(1):221.

doi: 10.1186/s12967-022-03417-4

48. Carletti A, Gavaia PJ, Cancela ML, Laizé V. Metabolic bone disorders and the promise of marine osteoactive compounds. *Cell Mol Life Sci*. 2023;81(1):11.

doi: 10.1007/s00018-023-05033-x

49. Wei Y, Guo Y. Clinical applications of low-intensity pulsed ultrasound and its underlying mechanisms in dentistry. *Appl Sci*. 2022;12(23):11898.

doi: 10.3390/app122311898

50. Hu Y, Li H. Biological mechanism of surgery-mediated acceleration of orthodontic tooth movement: a narrative review. *J Int Med Res*. 2022;50(9):03000605221123904.

doi: 10.1177/03000605221123904

51. Cao Z, Liu R, Zhang H, *et al*. Osterix controls cementoblast differentiation through downregulation of Wnt-signaling via enhancing DKK1 expression. *Int J Biol Sci*. 2015;11(3):335.

doi: 10.7150/ijbs.10874

52. Gerov V, Gerova D, Micheva I, Nikolova M, Mihaylova G, Galunska B. Dynamics of bone disease biomarkers dickkopf-1 and sclerostin in patients with multiple myeloma. *J Clin Med*. 2023;12(13):4440.

doi: 10.3390/jcm12134440

53. Lu J, Hu D, Zhang Y, Ma C, Shen L, Shuai B. Current comprehensive understanding of denosumab (the RANKL neutralizing antibody) in the treatment of bone metastasis of malignant tumors, including pharmacological mechanism and clinical trials. *Front Oncol*. 2023;13:1133828.

doi: 10.3389/fonc.2023.1133828

54. Dinesh SPS, Sivakumar A, Alshehri A, Awadh W. Evaluating the effect of denosumab in preventing anchorage loss: a split-mouth randomized controlled trial. *J Contemp Dent Pract*. 2022;22:1399-1405.

doi: 10.5005/jp-journals-10024-3256

55. Han JJ, Yang HJ, Hwang SJ. Enhanced bone regeneration by bone morphogenetic protein-2 after pretreatment with low-intensity pulsed ultrasound in distraction osteogenesis. *Tissue Eng Regen Med*. 2022;19(4):871-886.

doi: 10.1007/s13770-022-00457-1

56. Yuan G, Xiong Z, Ke X, Wang G, Liu X, Li Z. Exploring the multifactorial regulation of PIEZO1 in chondrocytes: mechanisms and implications. *Int J Med Sci*. 2025;22(13):3393.

doi: 10.7150/ijms.111082