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Mapping the global landscape of PTH1R agonists in osteoporosis: a bibliometric analysis

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Research Article

Keywords: PTH1R agonists, teriparatide, abaloparatide, osteoporosis, bibliometric analysis

Posted Date: May 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9351870/v1

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Additional Declarations: No competing interests reported.

Abstract

PTH1R agonists are cornerstone osteoanabolic therapies for osteoporosis, yet the intellectual structure and pharmacological evolution of this field have not been systematically characterized. In this bibliometric analysis, publications on PTH1R agonists in osteoporosis from 2001 to 2025 were retrieved from the Web of Science Core Collection and analyzed using Bibliometrix, VOSviewer, and CiteSpace. Among 1,775 eligible publications, annual output peaked in 2021. The United States led both publication output and citation impact, followed by Japan and China. Eli Lilly was the most influential institution, and leading contributors included Felicia Cosman and Fernando Marin. Osteoporosis International and Journal of Bone and Mineral Research were the core journals. Neer et al. and Miller et al. showed the strongest citation bursts, highlighting the foundational roles of teriparatide and abaloparatide trials in defining the field. Keyword clustering identified nine major themes, whereas overlay and burst analyses revealed a transition from early efficacy validation toward ligand-specific pharmacological differentiation, treatment sequencing, safety refinement, and oral formulations such as EB613. Taken together, the field has evolved from establishing intermittent PTH1R activation as an anti-fracture anabolic principle to refining receptor-informed therapeutic positioning and sequence-based optimization. This study provides a data-driven framework for understanding the landmark pharmacological literature, collaborative structure, and translational frontiers of PTH1R agonists in osteoporosis.

Introduction

Osteoporosis is a chronic, systemic metabolic bone disease in adults, primarily caused by an imbalance between osteoblastic bone formation and osteoclastic bone resorption, which results in the deterioration of bone microarchitecture and progressive bone loss (US Preventive Services Task Force [USPSTF], 2025). Epidemiological studies have demonstrated that half of women and one-fifth of men aged 50 years and older will experience an osteoporotic fracture during their lifetime (Van et al. 2001). An osteoporotic fracture is defined as a fracture induced by minimal or non-traumatic force, arising from the significant reduction in bone mineral density and bone strength characteristic of primary osteoporosis (Friedman and Mendelson, 2014). Such fractures not only impair patients' quality of life but also impose a substantial burden on healthcare systems and society at large. Against the backdrop of global population aging, a comprehensive understanding of this disease, coupled with further in-depth research in the field, is of paramount importance.

Parathyroid hormone type 1 receptor (PTH1R) is a pivotal regulator of bone metabolism, with its primary target tissues being the skeleton and kidney. In the kidney, PTH enhances the tubular reabsorption of calcium and promotes renal phosphate excretion. In the skeleton, PTH stimulates bone turnover and mobilizes calcium into the circulation to maintain serum calcium homeostasis (Fuggle et al. 2025). As a class B G protein-coupled receptor, PTH1R exists in two distinct conformational states, R^0 and R^G, which serve as the molecular basis for determining the direction of bone metabolism, mediating catabolic and anabolic effects, respectively (Gardella and Vilardaga, 2015; Zhao et al. 2023). Imaging studies have confirmed that therapeutic activation of parathyroid hormone (PTH) receptors can promote cortical bone

formation and improve trabecular bone microarchitecture in patients with osteoporosis (Dempster et al. 2001). Both parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) are critical regulators of calcium and phosphate homeostasis, and they exert their biological effects primarily by activating PTH1R expressed on the surface of osteoblasts (Khosla and Hofbauer, 2017). Teriparatide is an analog of the first 34 amino acids of PTH, while abaloparatide is structurally analogous to PTHrP. These two agents are currently the only marketed injectable therapies that act via activation of PTH1R. Due to their distinct binding affinities and the different receptor conformations they preferentially stabilize, the downstream cellular and skeletal responses to these drugs differ (Hattersley et al. 2016; Weidler et al. 1999). Nevertheless, both agents can rapidly stimulate bone formation. A large body of clinical trial evidence supports their application in the treatment of osteoporosis (Neer et al. 2001; Miller et al. 2016; Tabatabai et al. 2025; Beaudart et al. 2025), which has led to their inclusion in the recommended therapeutic regimens for this condition.

Bibliometrics is a quantitative discipline that evaluates academic achievements, providing insights into research performance, knowledge dissemination, and decision support (Ninkov et al. 2022). Accordingly, a focused bibliometric evaluation of PTH1R agonists is needed not only to describe publication trends but also to reconstruct the pharmacological logic by which this field has matured. In contrast to broader osteoporosis bibliometrics, the PTH1R agonist literature is anchored by a relatively small number of landmark mechanistic and clinical studies that established intermittent PTH1R activation as a therapeutic anabolic principle, differentiated ligands within the class on the basis of receptor-state preference and signaling duration, and repositioned these agents within sequence-dependent treatment paradigms. From this perspective, bibliometric analysis can serve as a bridge between knowledge mapping and pharmacological interpretation by identifying the studies that define the field's evidence backbone and by clarifying how research attention has shifted from proof of anti-fracture efficacy toward receptor-informed differentiation, consolidation strategies, long-term safety reassessment, and formulation innovation. Therefore, this study aimed to delineate the global research landscape, core knowledge structure, and emerging frontiers of PTH1R agonists in osteoporosis, with particular emphasis on the most influential pharmacological papers that shaped the field's evolution.

Material and methods

Information sources and eligibility criteria

We used the Web of Science Core Collection (WoSCC) as the data source for literature retrieval and analysis. WoSCC is a widely used multidisciplinary database with strong citation-tracking capability and broad coverage of high-impact biomedical journals, making it well suited to bibliometric research (AlRyalat et al. 2019).A structured keyword search was performed to identify relevant publications published between January 1, 2001 and December 31, 2025. The search was conducted on March 2, 2026. Eligible records were limited to original articles and review articles available in full text. Non-English publications and studies unrelated to the topic were excluded.

Search strategy and selection process

The WoSCC search strategy was as follows: TS=("Osteoporosis, Postmenopausal" OR "Osteoporosis" OR "Posttraumatic Osteoporosis" OR "Senile Osteoporosis" OR "Age Related Bone Loss" OR "Age Related Osteoporosis") AND TS=("parathyroid hormone receptor agonist*" OR "PTH1 receptor agonist*" OR "PTH1R agonist*" OR "teriparatide" OR "PTH 1–34" OR "abaloparatide"), with publication years restricted to 2001.01.01–2025.12.31. The initial search yielded 3,154 records. Two independent investigators (Yongchao Huang and Xin Zhang) screened all records for relevance, and disagreements were resolved by a third investigator (Shengtao Wang). After exclusion of unrelated studies, 1,775 publications on PTH1R agonists in osteoporosis treatment were included in the final bibliometric analysis. The detailed selection process is shown in Fig. 1.

Software for visualization analysis

This study used the Bibliometrix package in R software (version 5.2.0) (Zhai et al. 2026), VOSviewer (version 1.6.2) (Li et al. 2022), CiteSpace (version 6.4 R1 Advanced) (Wu et al. 2025), and Microsoft Excel (2019) for bibliometric analysis and the creation of scientific knowledge maps (Ding et al. 2024).The parameter settings of VOSviewer were as follows: (1) For the author collaboration network, only countries with at least 5 published literatures were included; (2) For the sources co-citation analysis, only literatures with at least 20 citations were considered; (3) For the references co-citation analysis, only literatures with at least 20 citations were taken into account; (4) For the author keywords co-occurrence analysis, only keywords with an occurrence frequency of at least 30 times were included (synonyms were calculated collectively).The parameters of CiteSpace were set as follows: the time slicing was set from 2001 to 2025 with a 1-year slice length. The selection criteria were defined as g-index (k = 25), LRF = 3.0, L/N = 10, LBY = 5, and e = 1.0. The nodes on the map represent various elements, such as countries/regions, journals, and keywords. The strength of the associations was represented by links between elements, with the total link strength (TLS) indicating connection strength. The top 25 keywords with the strongest citation bursts were chosen for detailed analysis.The sole authoritative source of the Impact Factor (IF) and JCR Quartiles is the 2025 latest edition of the Journal Citation Reports (JCR) published by Clarivate.

Result

General landscapes of global publications

Based on the search strategy, a total of 3,154 unique publications were collected from WoSCC. After excluding studies unrelated to the topic, 1,775 publications were finally identified. The annual publication output demonstrated a clear upward trajectory, particularly after 2010, reflecting the growing clinical interest in osteoanabolic therapies and the introduction of new PTH1R-targeting agents. From 2001 to 2009, the number of articles remained relatively stable, marking the initial exploratory phase of this

research topic, during which studies mainly focused on the basic mechanism of PTH1R activation and the preliminary efficacy of teriparatide. After 2010, the research scale entered a period of rapid expansion, reflecting the growing academic focus on the clinical application of PTH1R agonists and the development of novel agonists. Despite short-lived fluctuations in individual years, the annual scientific production maintained an overall dynamic momentum and peaked in 2021 at roughly 10 times the output recorded in 2001 (Fig. 2).

Contribution of publications volume and collaboration in countries and regions

Based on country-level analysis of bibliometric metadata using the Bibliometrix R-package, a total of 78 countries/regions have contributed scientific publications to the field of Parathyroid Hormone Type 1 Receptor Agonist (PTH1R agonists) for osteoporosis treatment. The United States (U.S.) emerged as the leading contributor, accounting for the largest share of scientific output (n = 590, 33.2%), Japan (n = 227, 12.8%) and China (n = 186, 10.5%) formed the second tier of productive nations, collectively reflecting a marked geographical concentration of research activity in this domain, with the U.S. maintaining a dominant position as the core contributor (Table 1).

Analysis of the corresponding authors' countries of affiliation confirmed the U.S. as the primary contributing nation (n = 590), followed by Japan (n = 227) and China (n = 186). As illustrated in Fig. 3A, multi-country publications (MCPs) accounted for 27.1% of all publications from the U.S., 9.7% from Japan, and 10.2% from China, indicating substantial variability in international collaboration propensity across leading research nations. In terms of citation impact, the U.S. also led with the highest total citations (n = 34,303), followed by the United Kingdom (n = 6,750) and Japan (n = 4,467).

The international collaboration network (Fig. 3B) visualized the collaborative landscape of PTH1R agonists research in osteoporosis treatment, revealing a "one superpower, multiple major players" structure. Nodes are proportional to publication volume, and the thickness of connecting lines denotes the intensity of collaborative ties. The U.S. functioned as the absolute core hub of this network, while European countries, China, Japan, and Australia constituted key secondary nodes. These entities are interconnected by dense collaborative links, forming a global research network that spans continents and is predominantly led by institutions from North America, Europe, and the Asia-Pacific region.

Table 1
The top 10 productive countries/regions related to PTH1R agonists research in osteoporosis treatment

No	Country	Articles	Articles %	SCP	MCP	MCP %	Total cites
1	USA	590	33.2	430	160	27.1	34303
2	JAPAN	227	12.8	205	22	9.7	4467
3	CHINA	186	10.5	167	19	10.2	3529
4	UNITED KINGDOM	97	5.5	53	44	45.4	6750
5	ITALY	69	3.9	55	14	20.3	1798
6	GERMANY	49	2.8	30	19	38.8	1901
7	DENMARK	47	2.6	28	19	40.4	2348
8	KOREA	44	2.5	40	4	9.1	585
9	CANADA	43	2.4	24	19	44.2	2758
10	FRANCE	39	2.2	28	11	28.2	1280

Analysis of institutions and authors

A total of 501 institutions conducted research on PTH1R agonists in osteoporosis treatment.Eli Lilly ranked first in the number of publications (n = 153), followed by Columbia University (n = 118) and Lilly Research Laboratories (n = 97). To further explore inter-institutional collaborative patterns in this field, a co-authorship analysis was performed using CiteSpace software (**Fig. 4A**). Eli Lilly exhibited the highest centrality value of 0.2, with other prominent institutions including the University of California System (centrality = 0.13), Lilly Research Laboratories (centrality = 0.11), and the University of Sheffield (centrality = 0.1) also showing notable network centrality. This distribution pattern is primarily attributed to the fact that Eli Lilly is the original research and development pharmaceutical company of teriparatide—the first approved PTH1R agonists for the treatment of osteoporosis. Concomitantly, a collaborative framework characterized by industrial leadership from pharmaceutical enterprises and academic support from universities has been formed in this research domain, with Eli Lilly serving as the core pharmaceutical entity and supported by multiple renowned academic institutions such as the University of California System and the University of Sheffield.

Table 2 presents the top 10 authors with the highest publication output regarding PTH1R agonists research in osteoporosis treatment. Cosman Felicia ranked first with 43 publications, followed by Marin Fernando with 33 publications; notably, Marin Fernando was the most-cited author in this field, with a total of 3,116 citations. Figure 4B depicts the co-authorship cluster network of researchers, which visually represents the collaborative relationships among core scholars. A total of 237 authors were

categorized into 13 clusters, with each cluster centered on the high-yield authors in this research domain.

Table 2
The top 10 authors with the most publications on PTH1R agonists in osteoporosis treatment research

No	Author	Documents	Citations	Total link strength
1	cosman, felicia	43	3007	133
2	marin, fernando	33	3116	172
3	miller, paul d.	30	3028	164
4	leder, benjamin z.	29	2186	100
5	dempster, david w.	26	1428	161
6	lewiecki, e. michael	25	1562	133
7	krege, john h.	22	1503	109
8	zhou, hua	17	776	129
9	shane, elizabeth	16	1280	90
10	langdahl, berte l.	15	887	90

Journals and co-cited journals

This study included 1,775 articles published in 413 journals.

Table 3 lists the top 10 journals ranked by publication quantity and their latest 2025 impact factors (IF). These include *Osteoporosis International* (n = 200, IF = 5.4), *Journal of Bone and Mineral Research* (n = 132, IF = 5.9), *Bone* (n = 124, IF = 3.6), *Journal of Bone and Mineral Metabolism* (n = 68, IF = 3.2), and *Calcified Tissue International* (n = 67, IF = 2.9). Notably, the limited presence of publications in top-tier journals for PTH1R agonists in osteoporosis treatment achievements suggests the need to improve the quality of research in this field.

Source titles from the co-citation analysis were examined using VOSviewer, with only journals having at least 20 citations included. A total of 321 journals were identified according to their total link strength (Fig. 5). The top five journals ranked by total link strength were as follows: Journal of Bone and Mineral Research (total link strength = 533,508), Osteoporosis International (total link strength = 426,905), The Journal of Clinical Endocrinology & Metabolism (total link strength = 270,876), Bone (total link strength = 255,968), and New England Journal of Medicine (total link strength = 227,348). Although the New England Journal of Medicine published a relatively small number of articles in this field, it exhibited a

high total link strength due to its publication of several landmark randomized controlled trials on PTH1R agonists for the treatment of osteoporosis.

Table 3
The top 10 productive journals related to PTH1R agonists in osteoporosis treatment research

No	Publication Titles	IF(2025)	JCR(2025)	Record Count
1	OSTEOPOROSIS INTERNATIONAL	5.4	Q1	200
2	JOURNAL OF BONE AND MINERAL RESEARCH	5.9	Q1	132
3	BONE	3.6	Q2	124
4	JOURNAL OF BONE AND MINERAL METABOLISM	3.2	Q3	68
5	CALCIFIED TISSUE INTERNATIONAL	2.9	Q3	67
6	JOURNAL OF CLINICAL ENDOCRINOLOGY METABOLISM	5.1	Q1	60
7	ARCHIVES OF OSTEOPOROSIS	2.8	Q2	53
8	CURRENT MEDICAL RESEARCH AND OPINION	2.2	Q2	30
9	CURRENT OSTEOPOROSIS REPORTS	4.2	Q1	22
10	BMC MUSCULOSKELETAL DISORDERS	2.4	Q2	21

Co-cited references and reference bursts

The top 10 most-cited publications were listed in Table 4. The publication titled “Osteoporosis” received 1,860 citations, followed by “Romosozumab Treatment in Postmenopausal Women with Osteoporosis” (1,300 citations) and “The clinician's guide to prevention and treatment of osteoporosis” (846 citations).

Co-cited references were analyzed using VOSviewer to identify the most influential publications (Fig. 6A). Additionally, CiteSpace software was employed to identify the most significant citation bursts associated with PTH1R agonists in osteoporosis treatment. This analysis generated 460 references with the strongest citation bursts, 25 of which are illustrated in Fig. 6B. Among these references, two studies stand out as the pivotal clinical trials for teriparatide and abaloparatide, namely, “Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis” (burst strength: 48.57) and “Effect of Parathyroid Hormone (1–34) on Fractures and Bone Mineral Density in Postmenopausal Women with Osteoporosis” (burst strength: 41.61).

Table 4
The top 10 documents with the citations in the field of PTH1R agonists in osteoporosis treatment

No	Article Title	Journal	Publication Year	Times Cited
1	Osteoporosis	LANCET	2019	1860
2	Romosozumab Treatment in Postmenopausal Women with Osteoporosis	NEW ENGLAND JOURNAL OF MEDICINE	2016	1300
3	The clinician's guide to prevention and treatment of osteoporosis	OSTEOPOROSIS INTERNATIONAL	2022	846
4	Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis A Randomized Clinical Trial	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2016	670
5	Postmenopausal osteoporosis	NATURE REVIEWS DISEASE PRIMERS	2016	668
6	Teriparatide or alendronate in glucocorticoid-induced osteoporosis	NEW ENGLAND JOURNAL OF MEDICINE	2007	644
7	Drug therapy for osteoporosis in older adults	LANCET	2022	565
8	The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis	JOURNAL OF BONE AND MINERAL RESEARCH	2003	555
9	Parathyroid hormone and teriparatide for the treatment of osteoporosis: A review of the evidence and suggested guidelines for its use	ENDOCRINE REVIEWS	2005	553
10	Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for 2 years and relevance to human safety	TOXICOLOGIC PATHOLOGY	2002	517

Analysis of keywords and hotspots

To elucidate the current research trends of PTH1R agonists in the treatment of osteoporosis, a total of 652 keywords were extracted from published literature, and a visual network map of keyword clustering was constructed. The results revealed nine distinct clusters, namely PTH (#0), back pain (#1), postmenopausal osteoporosis (#2), strontium ranelate (#3), atypical femoral fracture (#4), spine surgery (#5), glucocorticoid-induced osteoporosis (#6), osteocalcin (#7), and pharmacokinetic (#8). These clusters summarize the research directions of PTH1R agonists in osteoporosis treatment over the past 24 years(Fig. 7A). Figure 7B displays a standardized word cloud depicting the frequency of author

keywords in investigations of PTH1R agonists in the treatment of osteoporosis, emphasizing the core research themes and emerging topic domains within this discipline.

Keyword burst analysis captures the dynamic shifts in research focus over time. Figure 8A shows that the keyword with the highest intensity is mass (19.52), followed by those with intensity greater than 15: estrogen (16.23) and strontium ranelate (15.05).

This network visualization maps the evolving knowledge structure of PTH1R agonists in osteoporosis treatment research from 2014 to 2020 through co-occurrence analysis of author keywords (Fig. 8B). VOSviewer color-coded these co-occurring keywords by their average appearance timing across all papers: blue denotes earlier-emerging terms, while yellow marks those that arose later.

Discussion

The citation structure points to a coherent pharmacological trajectory. Citation bursts and co-citation centrality help identify influential papers, yet they are imperfect markers of pharmacological originality because citations also accumulate around guidelines, broad reviews, safety controversies, comparator debates, and widely used methods. We therefore used the bibliometric network as a map for close reading and weighted primary pharmacological studies more heavily than citation prominence alone.

Neer et al. mark the first decisive turning point in this field, especially when their trial is read against the earlier distinction between intermittent and continuous PTH exposure (Neer et al. 2001). The study established that pulse-like PTH1R activation could deliver a clinically useful anabolic effect in humans and reduce vertebral and nonvertebral fractures (Kaufman et al. 2005). That result gave therapeutic credibility to a concept that had already been emerging from experimental work. Jilka then clarified the biological basis of this principle by showing that intermittent PTH expands osteoblast number, limits osteoblast apoptosis, promotes differentiation, and can reactivate quiescent lining cells (Jilka, 2007). In retrospect, this was the moment when intermittent PTH ceased to be a physiological observation and became a viable pharmacological strategy (Orwoll et al. 2003; Saag et al. 2007).

A second advance came from a more exact account of receptor pharmacology. Gardella and Vilardaga showed that PTH1R, as a class B G protein-coupled receptor, cannot be understood adequately through affinity alone. Ligands differ in conformational preference, signaling location, and signaling duration. The familiar R^0 and R^G states are therefore best treated as a compact description of temporal pharmacology. Ligands that favor prolonged stabilization of R^0 generally support longer cAMP signaling and greater calcemic liability, whereas ligands with greater R^G preference tend to produce a shorter signaling pulse. This framework has remained one of the most useful organizing concepts in the field (Gardella and Vilardaga 2015; Winzenrieth et al. 2021).

Hattersley et al. supplied the key bridge between receptor theory and clinical pharmacology. Their work showed that abaloparatide, a PTHrP analog, has greater selectivity for the RG conformation of PTH1R than PTH(1–34) and generates a more transient cAMP response. The result supports a model of

temporal and conformational bias within a shared receptor system. It does not imply separate anabolic pathways. Teriparatide and abaloparatide act on the same receptor and retain broad mechanistic overlap. The important difference lies in signaling kinetics, and that distinction proved clinically consequential (Hattersley et al. 2016; Hong et al. 2023).

Clinical differentiation became clearer in ACTIVE (Miller et al. 2016). Alongside the major reductions in vertebral and nonvertebral fractures, the trial showed a lower frequency of hypercalcemia with abaloparatide than with teriparatide (Cosman et al. 2020; Miller et al. 2007). That finding deserves more attention than it usually receives because it is one of the clearest clinical expressions of ligand-specific PTH1R pharmacology. Eastell et al. extended this interpretation by showing that abaloparatide produced an early rise in bone formation markers with a comparatively restrained increase in resorption markers (Eastell et al. 2019). The literature is persuasive here, although ACTIVE did not fully resolve how much of this difference arises from receptor-state bias itself and how much reflects broader exposure kinetics in vivo.

At the signaling level, the field has also moved beyond a one-pathway account of osteoanabolism. Gardella and Vilardaga emphasized that the dominant axis remains Gs-adenylyl cyclase-cAMP-PKA-CREB signaling, yet PTH1R can also engage Gq/PLC/PKC, beta-arrestin-associated processes, and trafficking-dependent signaling from internalized receptor compartments (Gardella and Vilardaga 2015). Martin further argued that, in osteoblast-lineage cells, the osteoanabolic response depends on the integration of signaling duration, cell-state context, and downstream transcriptional timing. That broader view is important because it explains why modest changes in ligand kinetics can lead to clinically visible differences without requiring entirely distinct receptors or pathways (Martin, 2022).

Attention then shifted from stand-alone efficacy to therapeutic sequencing. This was a genuine maturation of the field. PTH1R agonists began to be understood within treatment history, skeletal compartment, and remodeling state. Leder et al. in DATA-Switch showed that women moving from teriparatide to denosumab continued to gain bone density, whereas the reverse sequence produced transient bone loss at the spine and hip and progressive loss at the radius (Leder et al. 2015). Tsai et al. strengthened that observation with HR-pQCT data showing deterioration in cortical volumetric bone mineral density, cortical thickness, and estimated strength, together with increased cortical porosity, after transition from denosumab to teriparatide (Tsai et al. 2017). ACTIVExtend then demonstrated that gains achieved with abaloparatide could be consolidated and extended by subsequent alendronate therapy (Bone et al. 2018).

These studies indicate that the pharmacodynamic meaning of a PTH1R agonist depends in part on the skeletal state created by prior therapy (Kendler et al. 2018). Denosumab induces profound remodeling suppression through RANKL inhibition. When teriparatide is introduced after that condition, remodeling may reactivate before cortical consolidation has recovered, leaving a temporary imbalance between formation and resorption. The opposite sequence is more favorable because teriparatide first builds new bone and raises turnover, after which denosumab or alendronate can preserve the accrued structural

gain (Papapoulos and Makras 2008). This sequence literature is clinically convincing, although the evidence remains stronger for bone density and microarchitectural endpoints than for fracture-endpoint validation.

Comparator studies with romosozumab also sharpened the therapeutic profile of PTH1R agonists within the broader anabolic landscape (Guyer et al. 2025; Ebina et al. 2025). In STRUCTURE, Langdahl et al. reported greater gains at the total hip and femoral neck with romosozumab than with teriparatide in women previously treated with oral bisphosphonates (Langdahl et al. 2017). Chavassieux et al. and Eriksen et al. help explain that pattern through histomorphometric and translational data showing modeling-based bone formation together with reduced resorption under romosozumab (Chavassieux et al. 2019; Eriksen et al. 2022). These studies are informative because they clarify where PTH1R agonists are relatively strong and where they are more context-dependent. They should not, however, obscure the distinct pharmacology of this class, which remains centered on remodeling-linked osteoanabolism rather than simultaneous high-level formation and antiresorptive suppression.

That distinction matters most at cortical-rich skeletal sites. Modeling-enriched formation with concurrent suppression of resorption is particularly advantageous at the hip, where cortical thickness and porosity have major biomechanical consequences. Responses to PTH1R agonists at these locations appear more sensitive to prior antiresorptive exposure and remodeling history. Safety became the next major phase of refinement. Postmarketing analyses by Gilsenan et al. and mechanistic reassessment by Krege et al. substantially weakened the earlier concern that teriparatide might increase osteosarcoma risk in adults (Gilsenan et al. 2021; Krege et al. 2022; Abdulelah et al. 2023). The field benefited from this correction, although the episode remains a useful reminder that preclinical toxicology signals require careful species-level interpretation before they are translated into durable clinical caution.

The most recent translational frontier is formulation innovation, represented most clearly by oral PTH(1–34). Tripto-Shkolnik et al. reported increases in bone formation markers, a reduction in CTX, and significant 6-month gains in lumbar spine, total hip, and femoral neck bone mineral density with the highest-dose tablet (Tripto-Shkolnik et al. 2024). The study is promising, but its mechanistic implications should be stated carefully. Receptor-level signaling was not measured directly. Even so, the pattern is consistent with the idea that oral delivery may impose a shorter systemic exposure window than subcutaneous injection. Choi et al. provide a plausible mechanistic context for that interpretation, having shown that shorter versus longer PTH exposure can differentially regulate primary response genes such as Nurr1 and RANKL (Choi et al. 2018). In my view, this line of work may become particularly important if future studies can connect exposure shape, marker kinetics, and fracture efficacy in a single development program.

Taken together, the PTH1R agonist literature reads as a sequence of pharmacological consolidations. Neer et al. established intermittent PTH1R activation as a clinically effective anti-fracture principle. Gardella and Vilardaga, together with Hattersley et al., provided the receptor framework needed to distinguish ligands within the class. Miller et al. showed that these mechanistic differences can appear

at the bedside as divergent safety and turnover profiles. DATA-Switch, Tsai et al., and ACTIVExtend repositioned PTH1R agonists within sequence-based treatment logic. Later safety and formulation studies normalized long-term risk assessment and opened a new discussion about exposure engineering. This developmental line is unusually coherent for an osteoanabolic field and helps explain why a relatively compact set of papers continues to anchor the literature (Neer et al. 2001; Gardella and Vilardaga 2015; Hattersley et al. 2016; Miller et al. 2016; Tsai et al. 2017; Wang et al. 2017).

From this perspective, the next phase of PTH1R agonist research will depend less on re-establishing that the class is anabolic and more on defining when, for whom, and in what sequence each ligand should be used. The most informative studies will integrate receptor-state pharmacology, cortical versus trabecular response, transition biology after potent antiresorptives, long-term human safety, and fracture-endpoint evidence for emerging formulations. My expectation is that the field will move toward a more explicit coupling of pharmacokinetics, receptor signaling duration, and skeletal compartment response. If that happens, PTH1R agonists may ultimately be selected less as a class and more as deliberately differentiated anabolic tools.

Strengths and limitations

Several limitations should nevertheless be acknowledged. First, this analysis relied on the Web of Science Core Collection and English-language publications only, which may have excluded relevant studies indexed elsewhere or published in other languages. Second, citation bursts and co-citation centrality are informative but not pure measures of mechanistic originality. Highly cited nodes may reflect guidelines, broad reviews, safety warnings, comparator debates, or methodological utility as much as true pharmacological breakthroughs (Aksnes et al. 2019). For that reason, the present interpretive discussion required manual re-reading of the underlying primary literature and should still be regarded as a synthesis layered onto, rather than inherent in, the bibliometric network itself. Third, more recent topics such as oral formulations and late safety reassessment may still be underrepresented in citation-based analyses because of limited accumulation time. Even so, bibliometric mapping remains useful for identifying the knowledge structure of the field and, when combined with critical pharmacological reading, for clarifying how landmark studies shaped its evolution.

Conclusion

In conclusion, this bibliometric analysis shows that the PTH1R agonist literature was led predominantly by the United States and strongly shaped by Eli Lilly. After critical reading of the underlying literature rather than simple reliance on citation counts alone, the citation structure suggests that the field progressed from validation of intermittent PTH1R activation, to ligand-specific differentiation, to sequence-dependent deployment, and more recently to safety normalization and exposure-profile refinement. The next phase should determine which signaling profile is optimal for particular skeletal compartments and prior-treatment states, how post-anabolic consolidation can be further optimized,

and whether formulation-driven control of exposure can widen the therapeutic window without compromising fracture efficacy.

Declarations

Authors' contributions

Yongchao Huang made substantial contributions to the conception and design of the study, analyzed the data, and drafted the manuscript. Xin Zhang and Shengtao Wang participated in data collection and interpretation. Yuhan Sui, Xinni Yang, Jun Liu, and Hong Liu contributed to the study design and data analysis. Zhaoxu Li contributed to the study conception, drafted the manuscript, and revised it critically. The authors declare that all data were generated in-house and that no paper mill was used.

Funding

This study was supported by the Guangxi Medical and Health Key Cultivation Discipline Construction Project.

Acknowledgments

The authors thank Prof. Chao-Mei Chen, developer of CiteSpace, for providing access to the software and supporting its academic use.

Data Availability Statement

The data analyzed in this study were derived from publicly accessible sources. All data supporting the findings of this study are included in the article and its Supplementary Materials.

Competing interests

The authors declare no competing interests.

Statements of Ethics

Because this study was based exclusively on bibliometric analysis of publicly available literature and involved no human participants, animals, or identifiable personal data, ethics approval was not required.

Clinical trial number

Not applicable.

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Figures

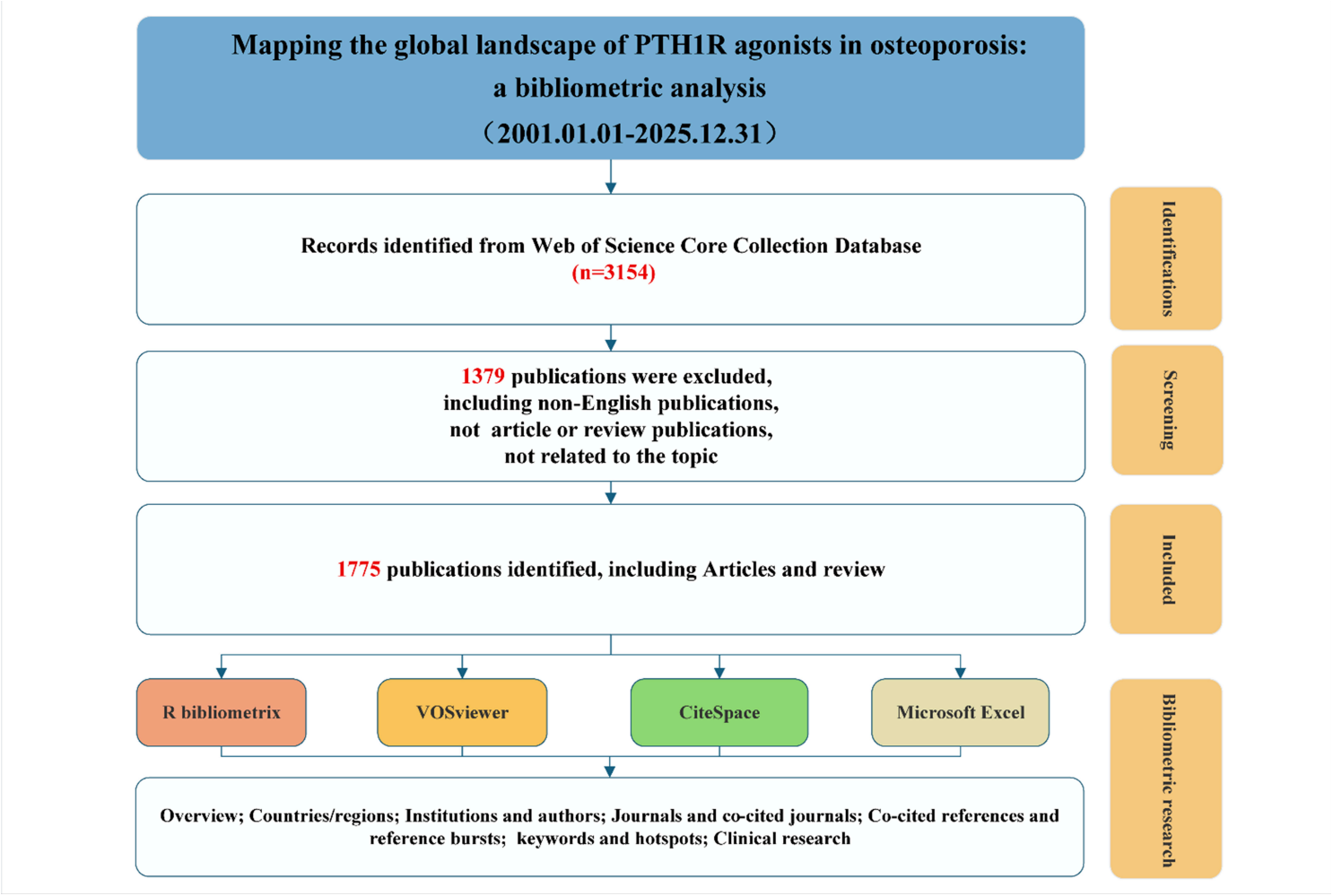


Figure 1

Flowchart of study selection and analysis

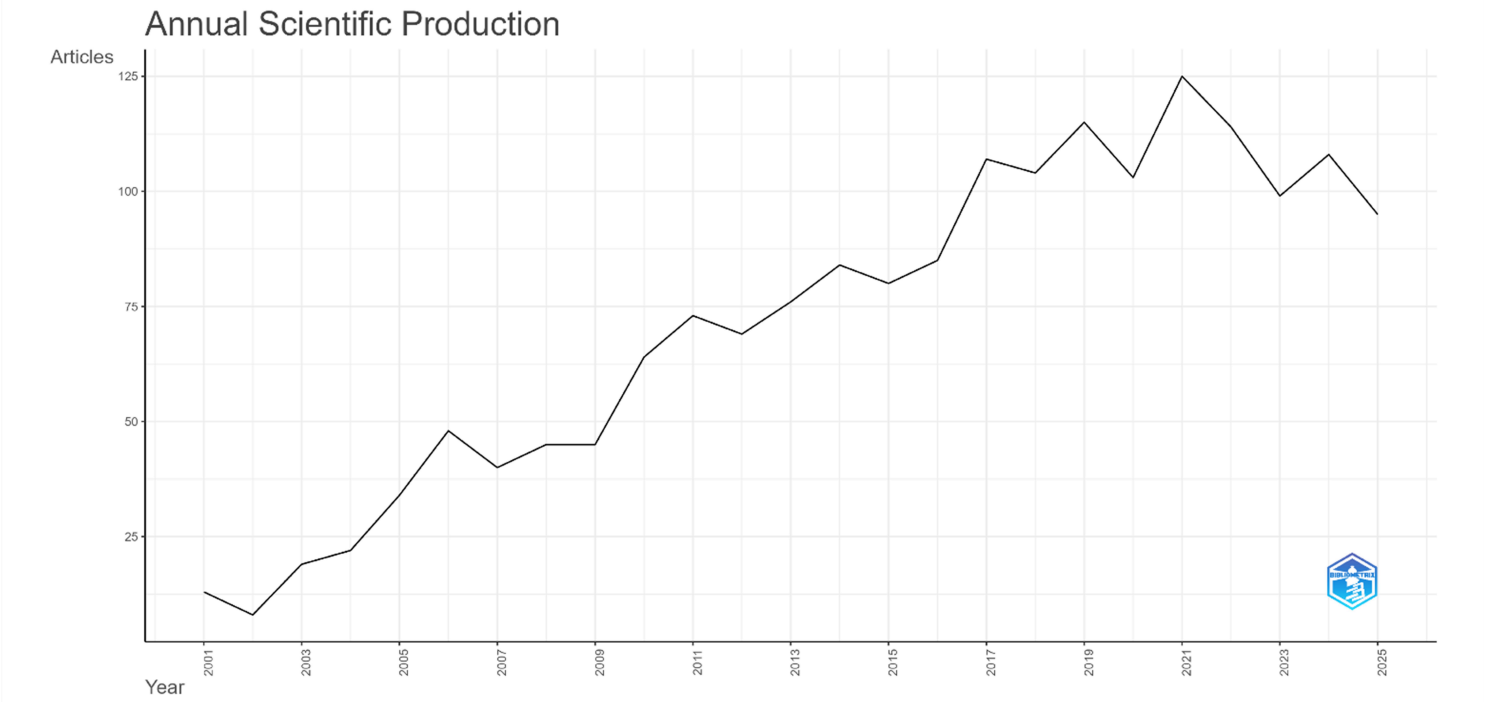


Figure 2

The annual number of publications on PTH1R agonists in osteoporosis treatment from 2001 to 2025

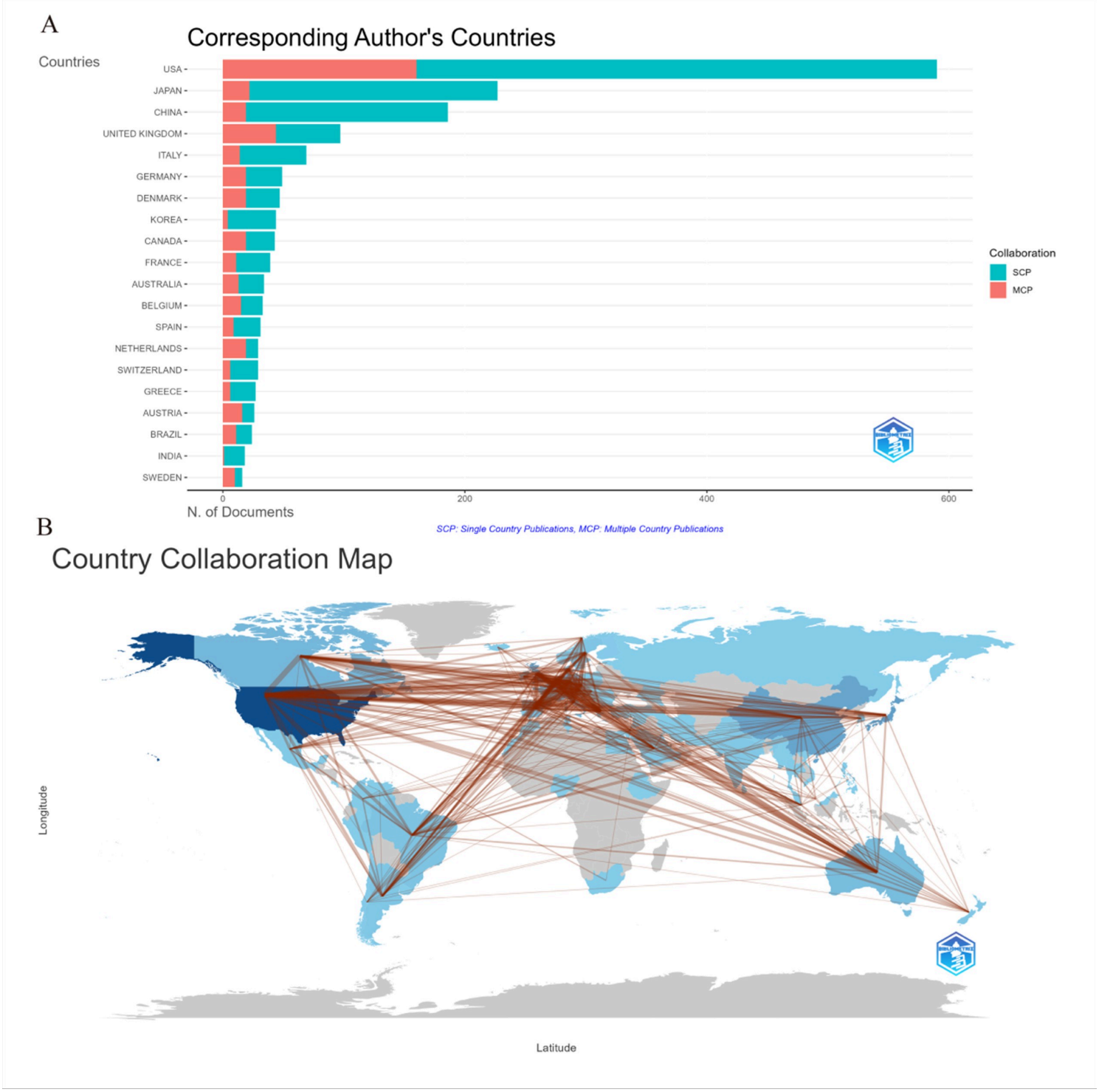


Figure 3

Global trends and countries/regions contributing to the research field regarding PTH1R agonists in osteoporosis treatment from 2001 to 2025. **(A)**The top 20 countries of total number of publications. **(B)** A visual map for country collaboration

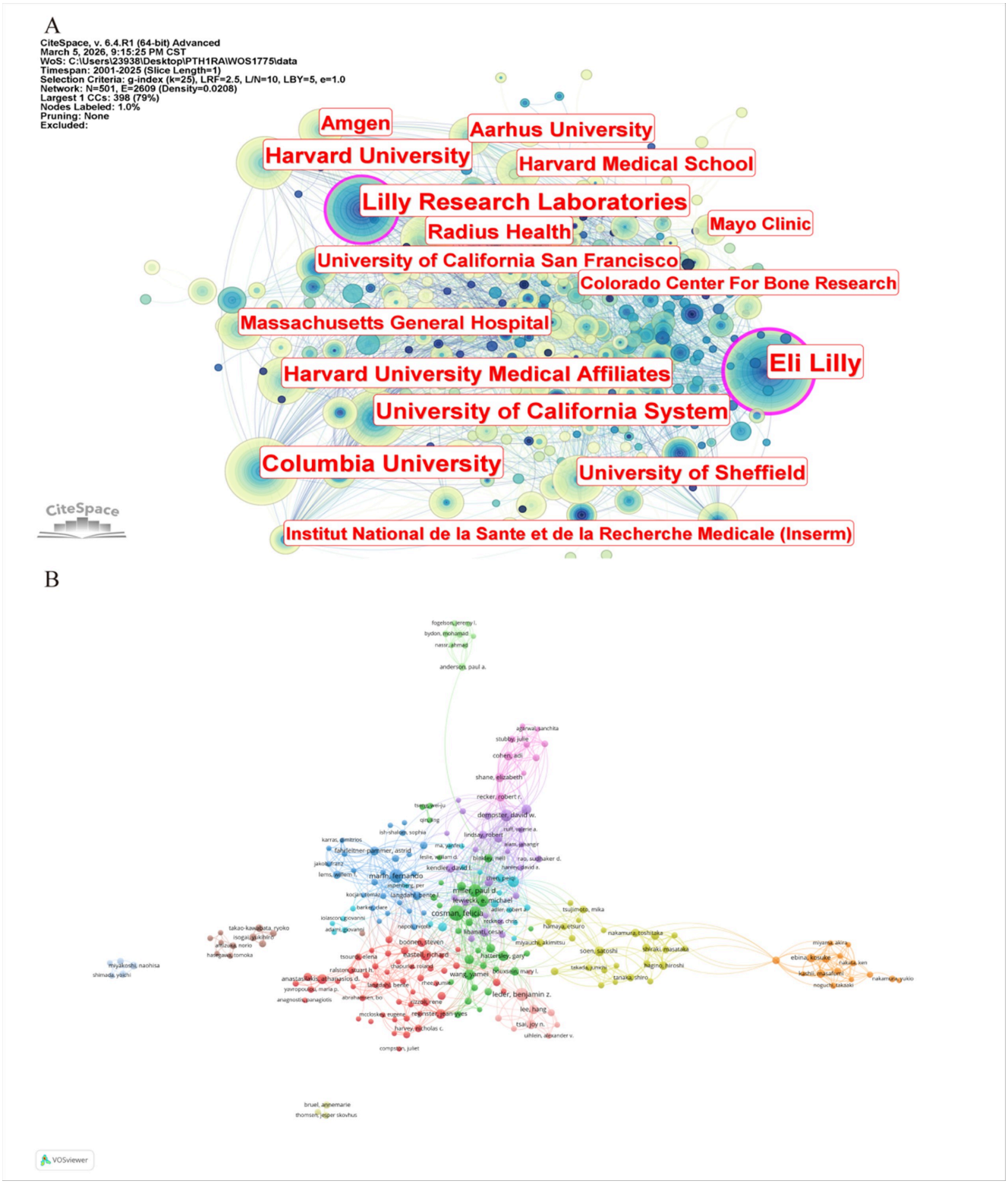


Figure 4

Institutions, authors, and their cooperative relationships in the field of PTH1R agonists in osteoporosis treatment. **(A)** Institutions and their cooperative relationship in the field regarding PTH1R agonists in osteoporosis treatment. **(B)** Authors and their cooperative relationship in the field regarding PTH1R agonists in osteoporosis treatment

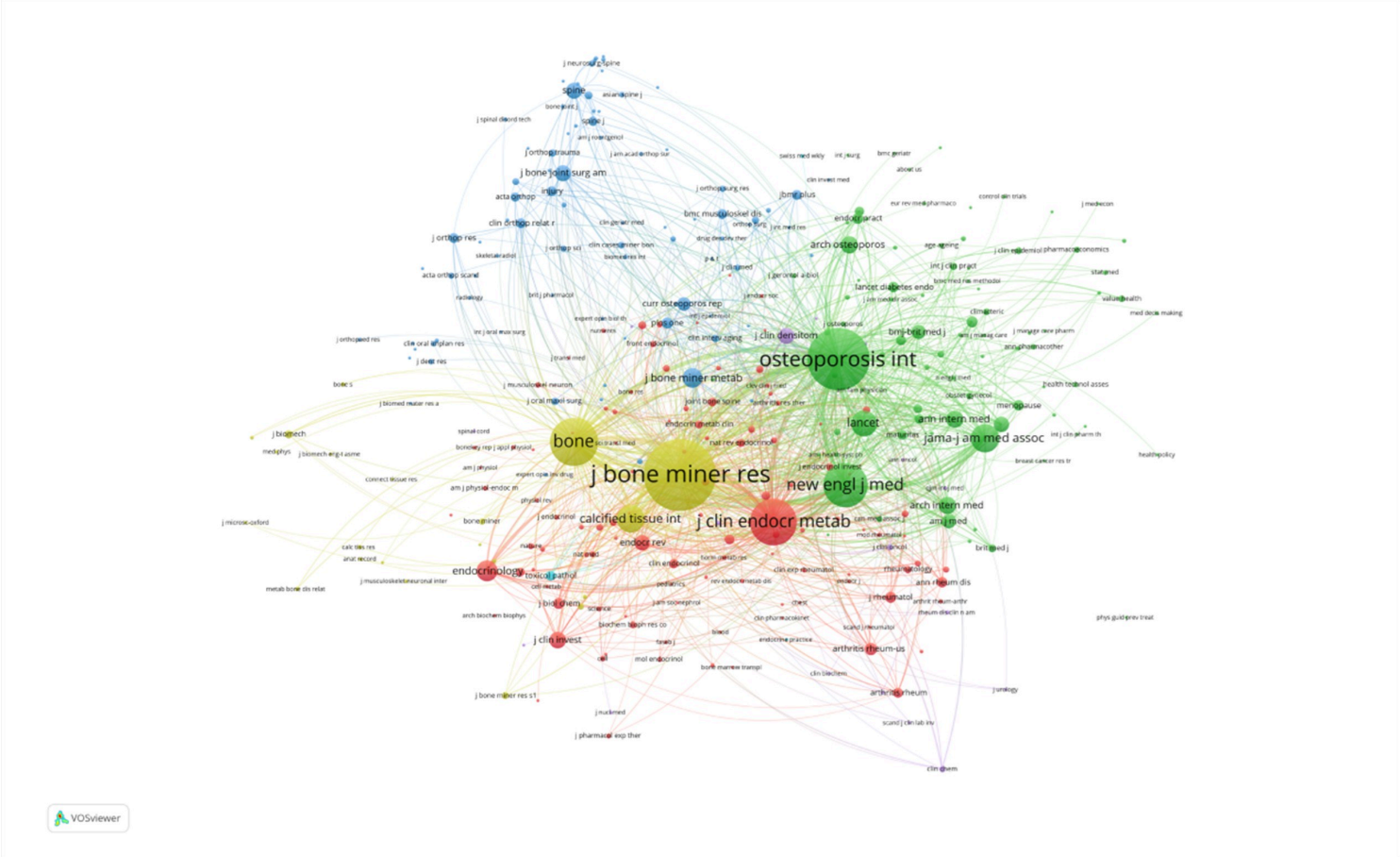
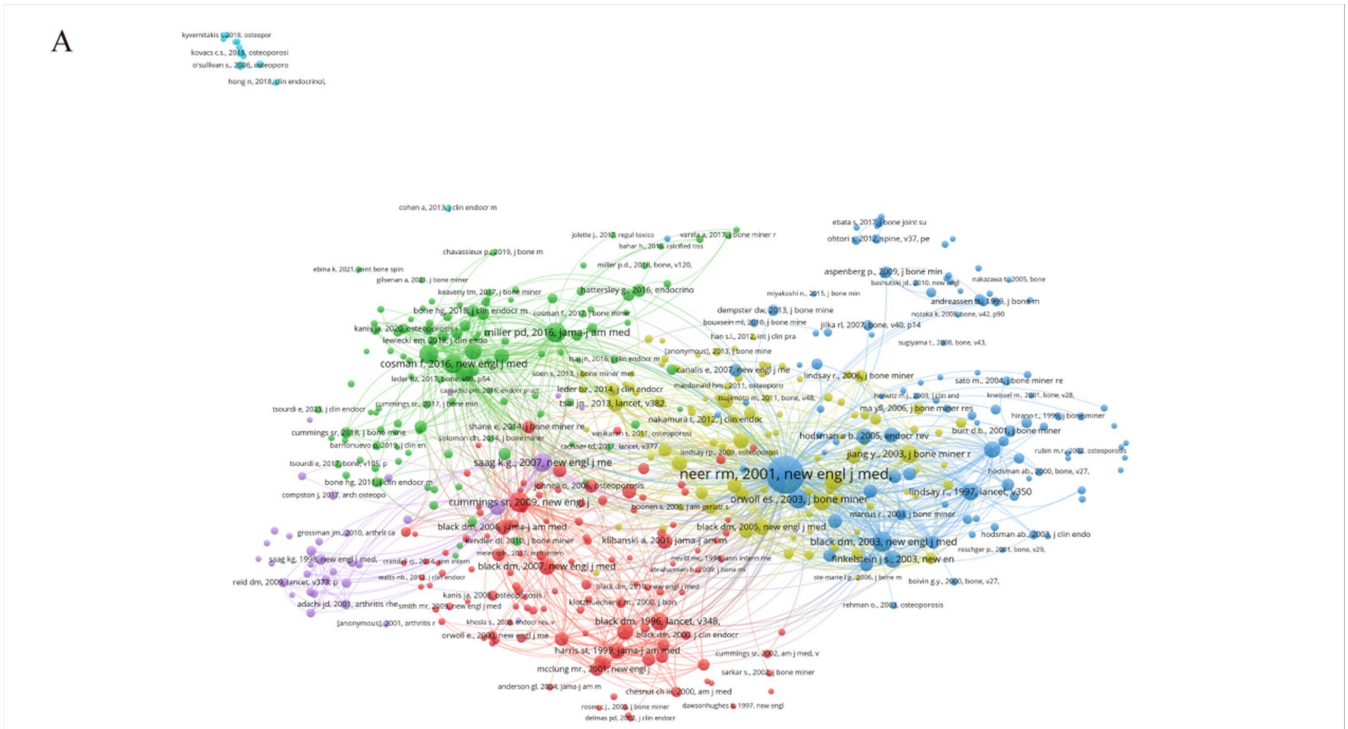


Figure 5

Analysis of Co-cited journal in the field of regarding PTH1R agonists in osteoporosis treatment.



B

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2005 - 2025
Neer RM, 2001, NEW ENGL J MED, V344, P1434, DOI 10.1056/NEJM200105103441904, DOI	2001	41.61	2005	2006	
Black DM, 2003, NEW ENGL J MED, V349, P1207, DOI 10.1056/NEJMoa031975, DOI	2003	37.04	2005	2008	
Orwoll ES, 2003, J BONE MINER RES, V18, P9	2003	26.92	2005	2008	
Finkelstein J S, 2003, NEW ENGL J MED, V349, P1216	2003	25.33	2005	2008	
Ettinger B, 2004, J BONE MINER RES, V19, P745751	2004	24.94	2005	2009	
Jiang Y, 2003, J BONE MINER RES, V18, P1932	2003	23.21	2005	2008	
Donley DW, 2005, ARCH INTERN MED, V165, P1762	2005	27.99	2006	2010	
Hodsman A B, 2005, ENDOCR REV, V26, P688	2005	21.96	2006	2010	
Greenspan SL, 2007, ANN INTERN MED, V146, P326, DOI 10.7326/0003-4819-146-5-200703060-00005, DOI	2007	25.16	2007	2012	
Saag KG, 2007, NEW ENGL J MED, V357, P2028	2007	30.27	2008	2012	
Saag KG, 2009, ARTHRITIS RHEUM-US, V60, P3346	2009	24.89	2010	2014	
Cummings SR, 2009, NEW ENGL J MED, V361, P756, DOI 10.1056/NEJMoa0809493, DOI	2009	22.89	2010	2014	
Cosman F, 2011, J BONE MINER RES, V26, P503	2011	28	2011	2016	
Tsai JN, 2013, LANCET, V382, P50	2013	29.91	2013	2018	
Nakamura T, 2012, J CLIN ENDOCR METAB, V97, P3097, DOI 10.1210/jc.2011-3479, DOI	2012	21.81	2013	2017	
Leder BZ, 2014, J CLIN ENDOCR METAB, V99, P1694	2014	23.09	2014	2019	
Leder BZ, 2015, LANCET, V386, P1147, DOI 10.1016/S0140-6736(15)61120-5, DOI	2015	34.6	2016	2020	
Miller PD, 2016, JAMA-J AM MED ASSOC, V316, P722, DOI 10.1001/jama.2016.11136, DOI	2016	48.57	2017	2021	
Cosman F, 2016, NEW ENGL J MED, V375, P1532, DOI 10.1056/NEJMoa1607948, DOI	2016	33.48	2017	2021	
Hattersley G, 2016, ENDOCRINOLOGY, V157, P141	2016	22.56	2017	2021	
Saag KG, 2017, NEW ENGL J MED, V377, P1417, DOI 10.1056/NEJMoa1708322, DOI	2017	37.45	2018	2022	
Kendler DL, 2018, LANCET, V391, P230, DOI 10.1016/S0140-6736(17)32137-2, DOI	2018	32.97	2018	2023	
Eastell R, 2019, J CLIN ENDOCR METAB, V104, P1595, DOI 10.1210/jc.2019-00221, DOI	2019	22.06	2021	2025	
Kanis JA, 2020, OSTEOPOROSIS INT, V31, P801, DOI 10.1007/s00198-020-05303-5, DOI	2020	21.55	2021	2025	
Camacho PM, 2020, ENDOCR PRACT, V26, P1, DOI 10.4158/GL-2020-0524SUPPL, DOI	2020	29.42	2022	2025	

Figure 6

Analysis results of co-cited references. **(A)** The co-citation network of references. **(B)** Top 25 references with the strongest citation bursts on PTH1R agonists in osteoporosis treatment research

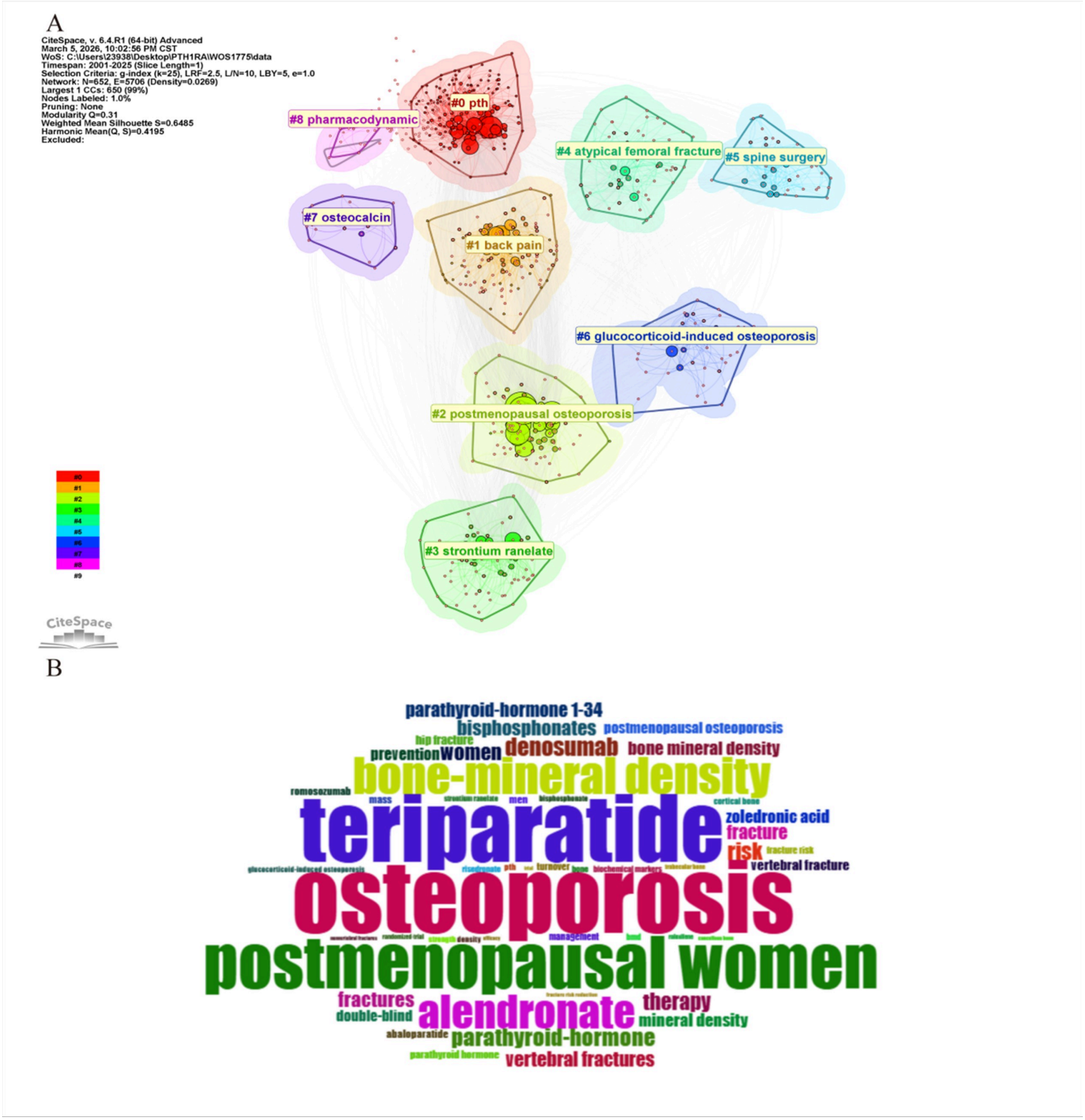


Figure 7

Keywords co-occurrence network and cluster analysis of PTH1R agonists in the treatment of osteoporosis research. **(A)** Clustering analysis of the co-occurrence keywords network based on CiteSpace. (Modularity Q = 0.31, Weighted Mean Silhouette S = 0.6485). **(B)** Word Cloud highlights dominant topics and emerging thematic areas

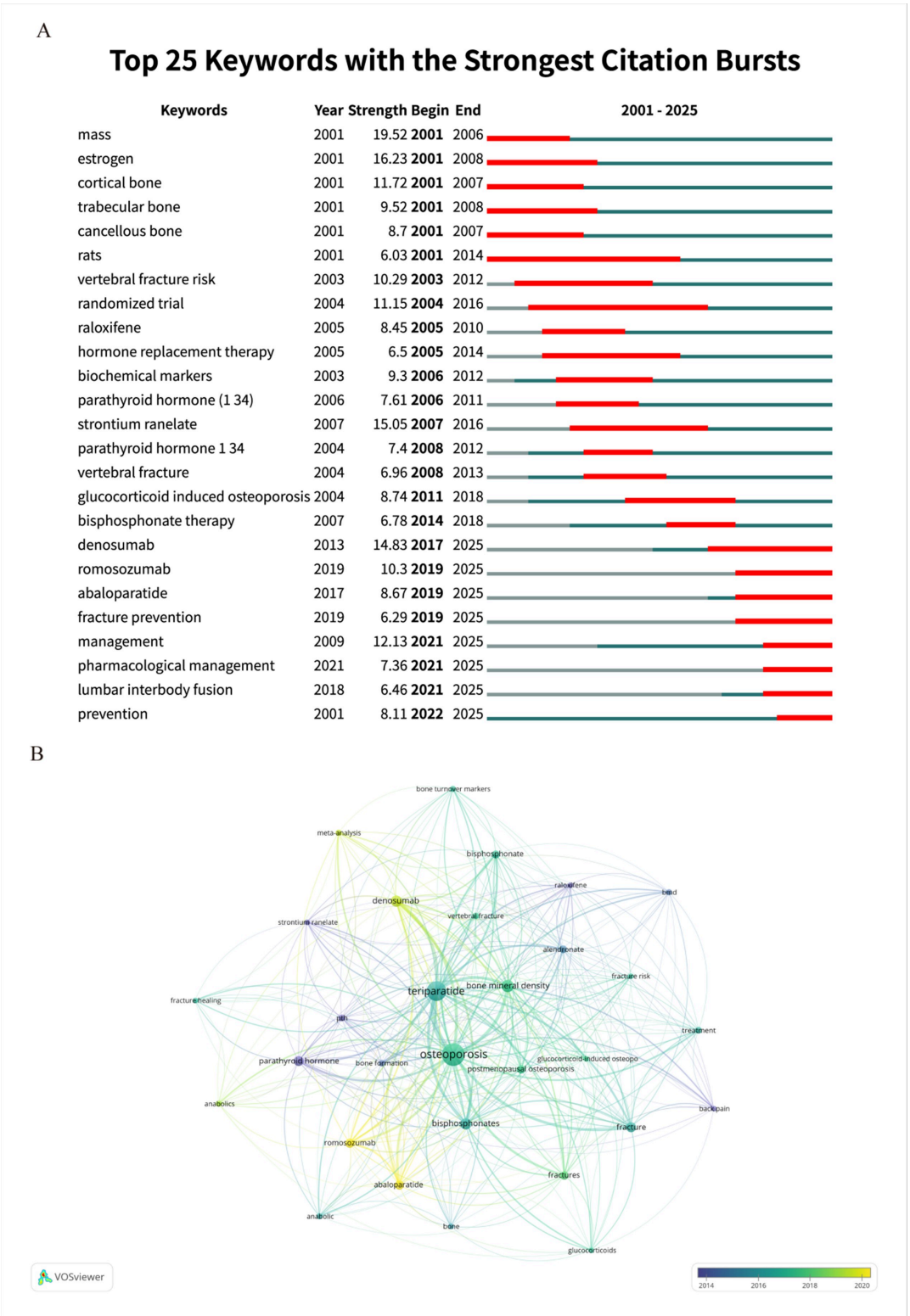


Figure 8

Keywords burst analysis reveals the dynamic evolutionary trends of PTH1R agonists in the treatment of osteoporosisresearch. **(A)** The keywords with the strong citation bursts in articles related to this field. **(B)** Distribution of keywords according to their time of appearance. The blue color represents an earlier appearance and yellow color appeared later.(Items:30; clusters:5; links:328; Total link strength:3,890)