The role of Wnt signalling in osteoporosis: A bibliometric analysis

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ABSTRACT

Osteoporosis has long been a key area of medical research, as the Wnt signalling pathway is essential for bone formation and maintaining bone balance. The purpose of this study was to perform a bibliometric analysis of the literature on osteoporosis and Wnt signalling to identify research trends, hot topics, and emerging areas of interest in this field. A visual analysis of the literature on osteoporosis and Wnt signalling offers a clearer perspective on the current research landscape, highlighting key topics and emerging trends in this area. The present study analysed publications related to osteoporosis and Wnt signalling from January 1, 2002 to December 31, 2021, using data from the Web of Science Core Collection. A total of 1553 publications were examined via tools, such as Microsoft Excel, CiteSpace, Vosviewer, and the Bibliometrics online analysis platform. The findings indicated that China has the highest number of publications in this area, with 489 articles. Warman Mathew's work has the most citations, totalling 1031 articles, and the journal Bone has published the most articles, with 89 publications. Current research in this field has focused primarily on osteogenesis, metabolism, fractures, and osteoblasts. The present study highlights the significant role of Wnt signalling in bone homeostasis and disease, suggesting that future research will explore novel metabolic therapies for osteoporosis by targeting the Wnt signalling pathway with drugs.

Keywords:
Bibliometrics; Bone homeostasis; Osteoporosis; Wnt signalling pathway

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1. Introduction

Bone is an active tissue rather than a fixed structure. Under the influence of hormones, exercise, nutrition and other conditions, bone is constantly redecomposed and reconstructed, in which osteoclasts promote bone absorption and osteoblasts promote the formation of new bones.[1] Osteoporosis is a systemic bone disease caused by multiple factors, such as low bone mass, bone structure degradation, bone microstructure destruction, and increased bone fragility, making bones prone to fracture.[2] Fracture is the most serious complication of osteoporosis. Approximately 70–80% of middle-aged and elderly fractures are caused by osteoporosis, resulting in medical costs of more than 10 billion dollars. Osteoporosis fracture has become one of the main causes of fracture, which seriously affects the quality of life of patients, places a heavy burden on families, and imposes high operating costs on society.[3,4] With increasing research on osteoporosis, an increasing number of signalling pathways and action targets have been identified, and new diversified antiosteoporosis drugs have been developed. At present, the commonly used antiosteoporosis drugs in the clinic can be divided into two main categories, namely, drugs that inhibit bone absorption (such as bisphosphonates and selective oestrogen receptor modulators) and drugs that promote bone formation (such as parathyroid hormone analogues).[5-7] However, concerns about the side effects and long-term efficacy of new drugs have led to inadequate treatment of many patients with osteoporosis, prompting the need for new treatment strategies for osteoporosis. Biotherapy has become a new method for the treatment of osteoporosis in recent years. The main goal of osteoporosis biotherapy is to identify and design

specific antibody drugs or pseudoreceptors for important targets of the osteoporosis signalling pathway to inhibit or promote the signalling transmission of a certain pathway, thereby inhibiting osteoclasts or promoting osteogenesis.[8-10]

The Wnt signallingling pathway is a complex network of protein interactions. While it is most commonly associated with embryonic development and cancer, the Wnt signalling also plays a significant role in the normal physiological processes of adult animals.[11,12] The Wnt signalling transduction pathways is a group of signalling transduction pathways with multiple downstream channels triggered by the binding of the Wnt ligand protein and the membrane protein receptor. Extracellular signals are transmitted to cells through the activation of intracellular segments of cell surface receptors.[13] The Wnt signalling pathway has become an important signalling pathway of bone metabolism that affects almost all aspects of bone physiology. As an extracellular factor, Wnt binds to the frizzled membrane receptor protein and enters the nucleus to combine with T cell-specific transcription factor/lymphoid enhancing factor to form a complex polymer, which activates the transcription of downstream target genes and promotes the differentiation and proliferation of osteoblasts.[14,15] The effects of the Wnt signalling pathway on osteoclasts are mostly produced through osteoprotegerin and the receptor activator of nuclear factor κB ligand pathway. Upregulation of the Wnt signalling pathway in osteoblasts promotes the expression of osteoprotegerin, and the combination of osteoprotegerin and nuclear factor κB receptor activating factor blocks the interaction between rank and nuclear factor κB ligand, thus reducing the differentiation of osteoclast precursor cells into mature osteoclasts.[16,17] In addition to direct effects on bone tissue, components of the Wnt signalling pathway also regulate bone metabolic processes through interactions with other molecules or signalling pathways, such as bone morphogenetic proteins.[18] The Wnt signalling pathway also synergises with oestrogen signalling receptors and promotes early osteogenic differentiation and late bone matrix mineralisation.[19] In addition, the Wnt signalling pathway also synergises with the Notch signalling pathway or the Hedgehog pathway and regulates osteogenic differentiation.[20,21] At present, romosozumab, denosumab, and other newly developed drugs in the clinic participate in the regulation of osteoporosis by regulating the Wnt signalling pathway, thereby affecting the osteogenesis of bone marrow mesenchymal stem cells, the proliferation and differentiation of osteoblasts, and the production of osteoclasts.[22] Thus, this pathway plays a crucial role in osteogenesis and deserves the attention of researchers.

By gaining a deeper understanding of the specific mechanisms of Wnt signalling, researchers can more precisely modulate these pathways to optimise therapeutic methods. For example, studies on specific activators or inhibitors of the Wnt signalling pathway can help develop drugs that more effectively enhance bone formation or inhibit bone resorption. Additionally, investigating the differences in the expression and activity of Wnt signalling in different types of osteoporosis patients may reveal why some patients respond better to these drugs, thereby guiding the development of personalised treatment strategies.

Bibliometrics is a discipline in which the American bibliographer Alan Pritchard applied mathematical and statistical methods to the study of books and other communication media in 1969. Bibliometrics is a scientific method used to analyse the distribution structure, quantitative relationships, and change laws of documents on the basis of the document system and metrological characteristics of the documents via mathematical, statistical, and other metrological methods.[23] The results of bibliometric analysis can be displayed in the form of a knowledge map. A knowledge atlas is an image that shows the relationship between the development process and the structure of scientific knowledge, providing both a visual knowledge graph and a serialised knowledge pedigree. A knowledge atlas enables researchers to quickly understand the current state of research in a specific field and anticipate future areas of interest.[24-26] Bibliometrics has been widely used in various diseases and scientific research areas, including the prevention of ischaemic stroke, the study of novel coronaviruses, and the application of tranexamic acid.[27-29] However, no bibliometric analysis or summary of the relationship between osteoporosis and the Wnt signalling pathway has been reported.

Given the profound impact of Wnt signalling on skeletal health and disease, the present study employed a bibliometric approach to dissect the global research landscape of Wnt signalling in osteoporosis. Literature on the Wnt signalling pathway in the field of osteoporosis was retrieved from scientific networks spanning from 2002 to 2021. By examining the quantity and impact of academic papers, the aim of the present study was to elucidate the evolving role of the Wnt signalling pathway in osteoporosis research, focusing on the most influential studies, emerging trends, and potential gaps in the current knowledge base. This analysis is crucial for determining future directions in osteoporosis research and optimising therapeutic strategies that harness the regenerative potential of the Wnt signalling pathway.

2. Methods

2.1. Search strategy

Two authors independently screened and extracted data from the final set of included articles. The extracted bibliographic information included publication date, author, country/region, institution, journal, keywords, citation frequency, funding sources, and the type of study conducted. The retrieval method is shown in **Figure 1**. The search formula was TS=(Wnt OR "Wnt signalling") AND TS=(Osteoporosis OR Osteoporoses OR "Osteoporosis Age Related" OR "Bone Loss Age-Related" OR "Age-Related Bone Loss*" OR "Bone

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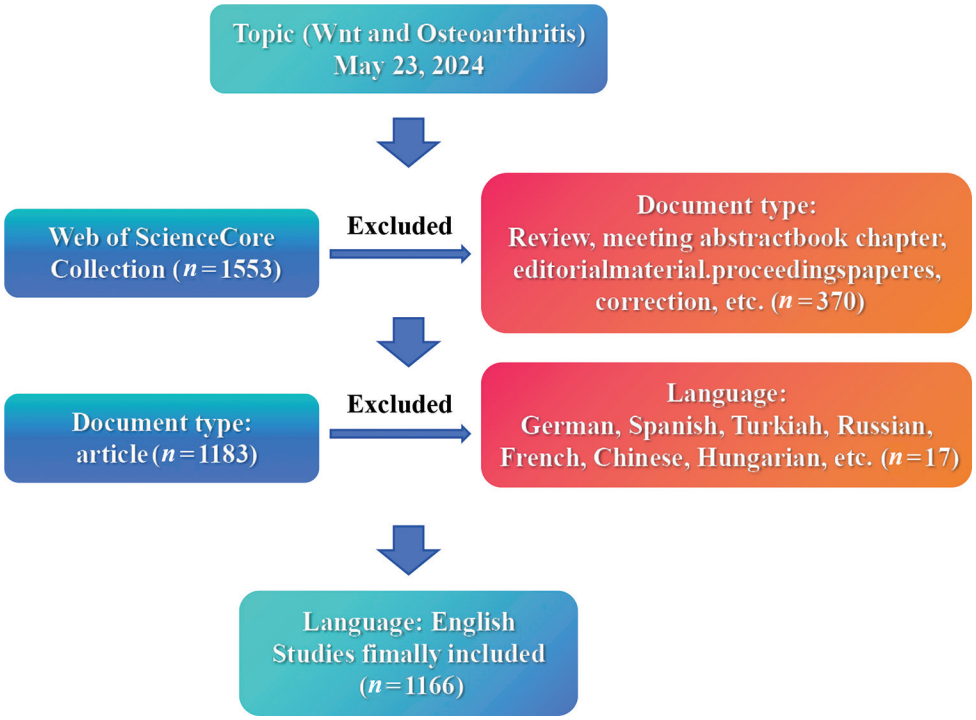

Figure 1. Inclusion criteria for paper selection

Loss* Age Related" OR "Age-Related Osteoporosis" OR "Age Related Osteoporosis" OR "Age-Related Osteoporoses" OR "Osteoporoses Age-Related" OR "Osteoporosis Post-Traumatic" OR "Osteoporosis Post Traumatic" OR "Post-Traumatic Osteoporoses" OR "Post Traumatic Osteoporosis" OR "Osteoporosis Senile" OR "Osteoporoses Senile" OR "Senile Osteoporoses" OR "Osteoporosis Involutional" OR "Senile Osteoporosis" OR "Osteoporosis Age-Related").

2.2. Data collection

Complete records and cited references from the retrieved documents were extracted for bibliometric analysis, including details such as title, publication year, author, nationality, author affiliation, published journals, abstracts, keywords, total number of publications, total number of citations, average citations per item, and H-index. Data extraction was performed independently by two authors (HYR and ZRH). In cases of disagreement, a third author (WZL) was consulted to resolve any discrepancies.

2.3. Data analysis and visualisation

In this study, VOSviewer1.6.19 (https://www.vosviewer.com/) and CiteSpace 6.2.R4 (http://cluster.cis.drexel.edu/~cchen/citespace/) were utilised to analyze collaboration among countries/regions and organisations. These tools were employed for various types of bibliometric analysis, including literature coupling analysis, co-author analysis, co-citation analysis, and keyword co-occurrence analysis.

3. Results

3.1. Global publication outputs and citations

We retrieved 1553 articles related to "Wnt and osteoporosis" from the Web of Science. After applying the exclusion criteria, 1166 articles were selected for the next stage of analysis. **Figure 2A** showed the change trend of the published amount of research literature of "Wnt signalling in osteoporosis" in recent 10 years. The results showed that there were only 3 publications in 2002, and 157 in 2021. The number of publications increased significantly on the whole, but fell slightly in 2008 and 2011, falling by 21.7% and 7.5%, respectively. At the same time, the number of citations of publications in this field also showed an upward trend (**Figure 2A**). This result demonstrated that the research of Wnt signalling in osteoporosis has attracted more and more attention at home and abroad, and the attention is gradually increasing.

3.2. Distribution of countries/regions and institutions

From 2002 to 2021, dozens of countries have published articles on the research of Wnt signalling in osteoporosis. Among them, China published the most articles among these countries, with a total of 489 articles, accounting for 31.48% of the total global articles. The second is the United States, with a total of 318 articles, accounting for 20.47% of the global total. Then came South Korea, with a total of 63 articles, accounting for 4.05% of the total number of global publications. The remaining top ten countries based on document volume are Germany (n = 60, 3.86%), Japan (n = 58, 3.73%), Italy (n = 54, 3.47%), England (n = 46, 2.96%), Canada (n = 41, 2.64%), Spain (n = 38, 2.44%), Australia (n = 34, 2.19%), as shown in **Table 1**. It is worth noting that from 2002 to 2014, the total number of publications in the United States ranked first. However, after 2015, the total number of publications in China surpassed that in the United States to become the first, which reflected the importance China attaches to research in this field (**Figure 2B**). The H-index is a metric used to assess both the quantity and impact of a researcher's academic output, reflecting their

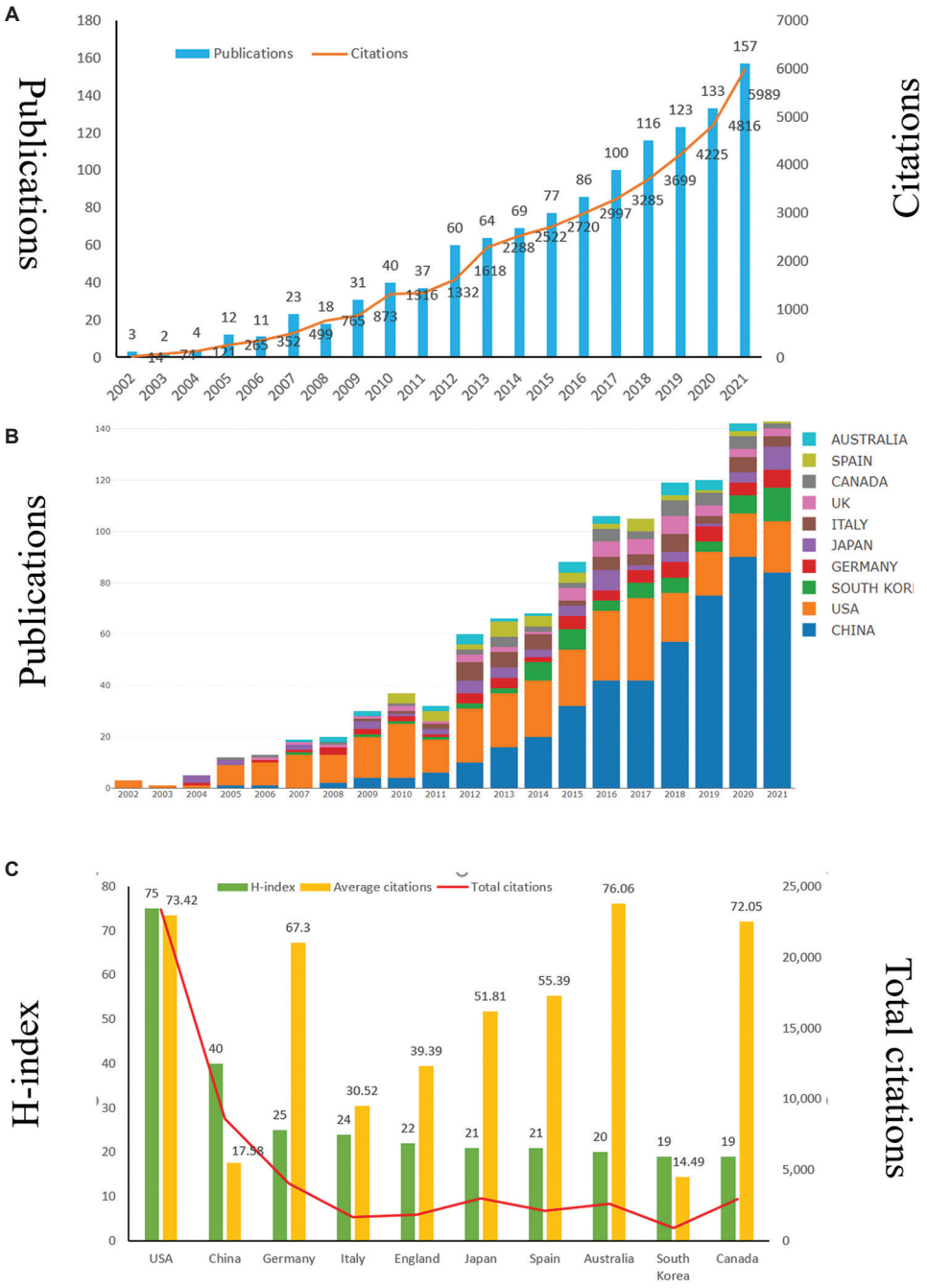

Figure 2. Global trends in publications about Wnt signalling in osteoporosis. (A) The number of publications per year over the last 20 years. (B) The annual global publication output. (C) The H-index, average citations per article, and total number of citations for the top 10 countries/regions.

Table 1. Ranking of top 10 active countries in the field of osteoporosis and Wnt signalling research

Rank	Country	Total publications	Total citations	Average citations	H-index
1	China	489	8595	17.58	40
2	USA	318	23348	73.42	75
3	South Korea	63	913	14.49	19
4	Germany	60	4038	67.3	25
5	Japan	58	3005	51.81	21
6	Italy	54	1648	30.52	24
7	England	46	1812	39.39	22
8	Canada	41	2954	72.05	19
9	Spain	38	2105	55.39	21
10	Australia	34	2586	76.06	20

productivity and the significance of their publications. The total number of citations of publications in the United States is the highest, reaching 23,348, with an average of 73.42 citations and an H index of 75. This indicated that the research results in this field in the United States are of high quality and representative (**Figure 2C**). Although China ranks first in the total number of publications, the average number of citations per publication is relatively low, at only 17.58. This may mean that research in China is more focused on emerging or cutting-edge fields, which may take longer to be accepted and cited by the international academic community. In addition, although China has a large number of publications, some studies may not be as innovative and in-depth as some developed countries. This may have resulted in a lower average citation rate. Therefore, future research should place greater emphasis on quality and originality to enhance international influence and citation rates. For scientific research, international scientific research cooperation can improve the influence of research results and stimulate academic progress, which is the key factor to promote scientific progress. **Figure 3A** showed the close cooperative relationship between the United States, China, Germany, Canada and other countries. In addition, we used Vosviewer software to analyse the collaborative visualisation network between these countries (**Figure 3B**). China had the strongest total link strength, which meant that China had a leading influence in this field. The United States, France and Belgium had the highest concentration of publications before 2015, Italy, Canada, England and Germany published articles in the next two years, and articles from China and Thailand were mainly published after 2018 (**Figure 3C**). It was more intuitive to identify the number of publications in these countries from the density map (**Figure 3D**).

Among institutions around the world, the top 10 institutions that have published articles on the research of Wnt signalling in osteoporosis were shown in **Table 2**. Shanghai Jiao Tong University ranked first with 50 articles, followed by Harvard University and Southern Medical University China, which ranked second and third with 48 and 30 articles respectively. Additionally, Harvard University has the highest total number of citations (4088), the highest average number of citations per publication (67.3), and the highest H-index (25), indicating its substantial impact on the field of osteoporosis research. The cooperation between institutions is relatively close, which is mainly divided into five institutional clusters. Each color in the five clusters indicates the close cooperation between these institutions, among which the red cluster led by Shanghai Jiao Tong University had the closest cooperation (**Figure 4A**). From the organisation distribution density map of VOSviewer published articles, we could also find that Shanghai Jiao Tong University was a leading organisation contributing to Wnt and osteoporosis-related research (**Figure 4B**).

3.3. Authors and co-cited authors

In the related fields of osteoporosis and Wnt signalling research, the top three most productive authors were Robling Alexander (n = 20), Warman Mathew (n = 16), and Gatti David (n = 15). Among them, the total number of citations of Warman

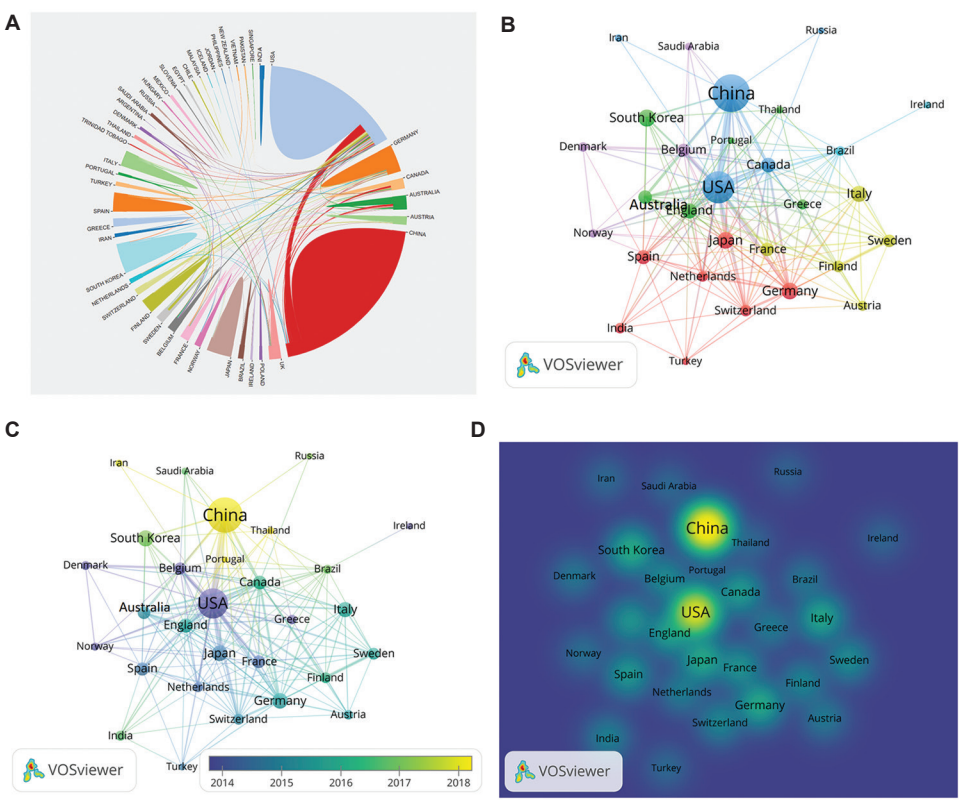

Figure 3. Overview of national publications. (A) Cooperation among different countries. (B) The collaboration network of countries. (C) Publication time of articles in each country. (D) Heat map of the number of articles published in each country. The size of the circle represented the number of publications, and the width of the line between the two circles represented the degree of cooperation.

Table 2. Ranking of top 10 active institutions in the field of osteoporosis and Wnt signalling research

Rank	Institutions	Country	Total publicatios	Total citations	Average citations	H-index
1	Shanghai Jiao Tong University	China	50	1466	29.32	17
2	Harvard University	USA	48	4088	85.17	28
3	Southern Medical University China	China	30	401	13.37	11
4	Air Force Military Medical University	China	27	1073	39.74	14
5	Amgen Inc.	USA	26	3902	150.08	20
6	Indiana University Purdue University Indianapolis	USA	23	1026	44.61	14
7	Chinese Academy of Sciences	China	22	1042	47.36	13
8	Sichuan University	China	20	302	15.1	10
9	Fudan University	China	18	634	35.22	9
10	University of Verona	Italy	18	494	27.44	10

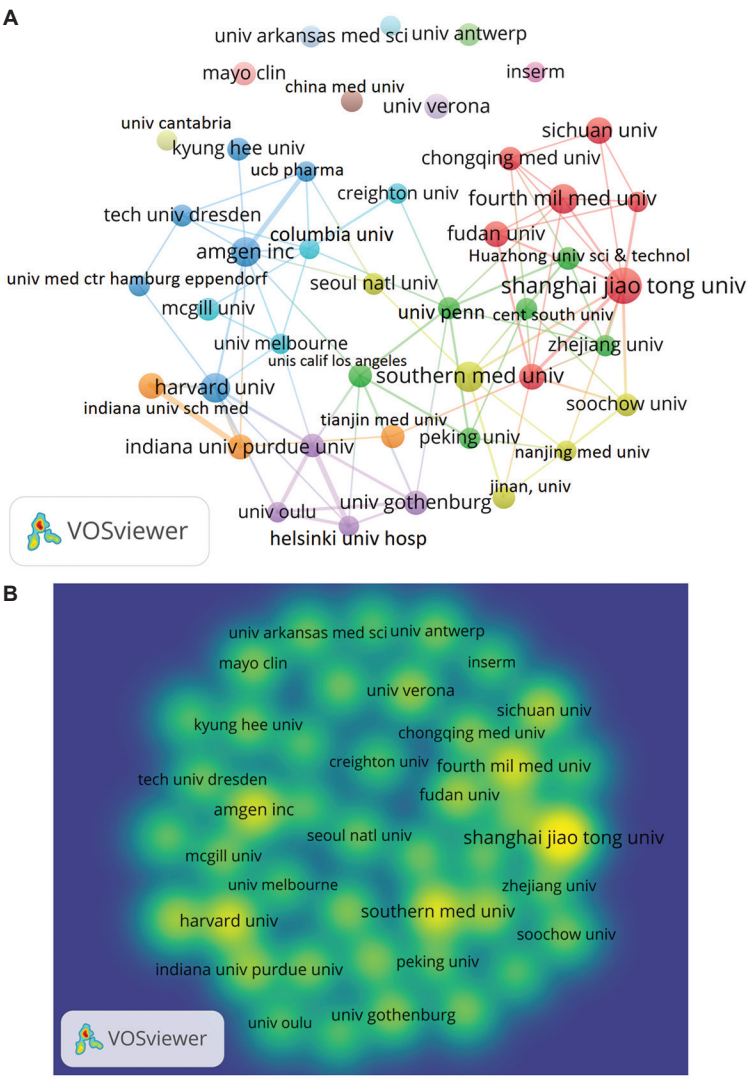

Figure 4. Visualisation map of institutions involved in Wnt signalling in osteoporosis. (A) Collaboration between institutions involved in Wnt signalling in osteoporosis. (B) Dynamics and trends of these institutions over time.

Mathew's articles was the highest (1031 citations). This showed that he made great achievements in the research of osteoporosis and Wnt signalling, and his publications had great academic value. From the perspective of cooperation, the current research was dominated by academic groups, among which Gatti David, Rossini Maurizio, idolazzi Luca and viapoana ombretta had the closest cooperation relationship (**Figure 5A**). When the works of two authors are cited by a third author in the same document, a co-citation relationship is established between the two authors. Baron R was the most cited author, followed by Li XD and balemen W. Therefore, we could see that Robling Alexander and Baron R played a key role in this field (**Figure 5B**).

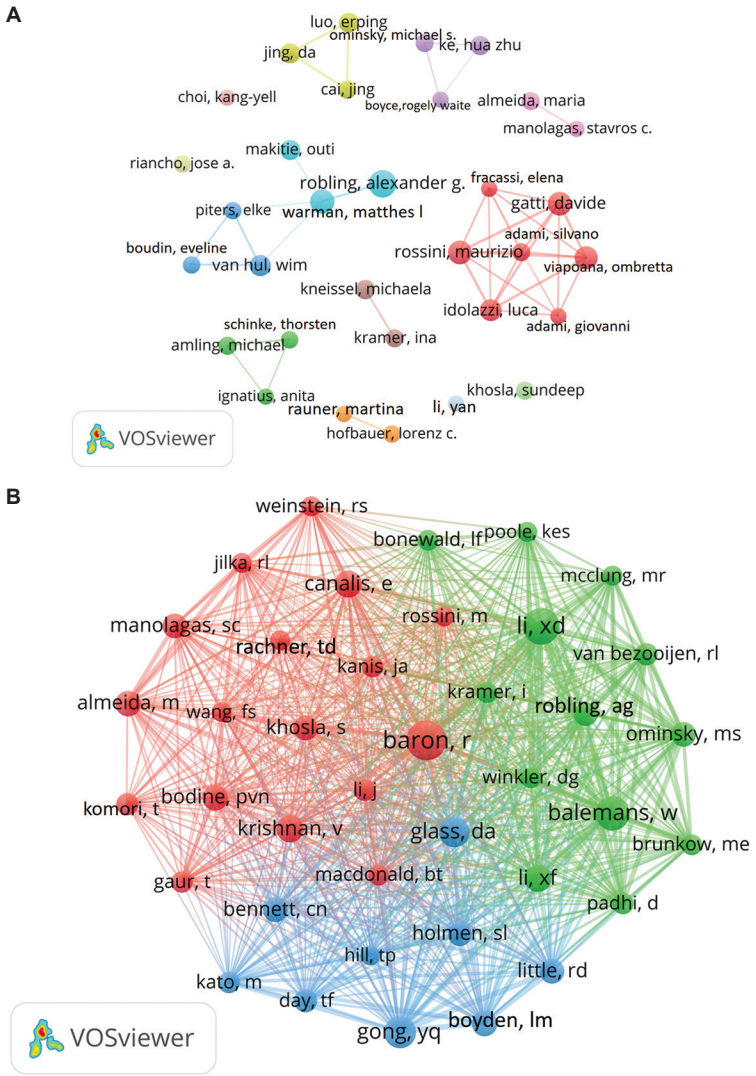

Figure 5. Visualisation of active authors analysis. (A) Network visualisation analysis of author collaboration. (B) Network visualisation map of co-cited authors of the articles.

3.4. Journals and co-cited journals

Different periodicals include different publishing fields. Therefore, we analysed the periodical distribution of publications related to osteoporosis and Wnt signalling. **Table 3** summarises the top ten most active journals that published articles related to osteoporosis and Wnt signalling. The top three journals were Bone (n = 89), *Journal of Bone and Mineral Research* (n = 79) and PLoS One (n = 38). Among the top 10 journals, most of them belonged to the JCR division in Q1 and Q2, indicating that the quality of these articles was also very good. The influence of a journal is also assessed by its co-citation frequency, indicating its importance and relevance within a specific research area. Therefore, we performed co-cited analysis by VOSviewer software, which indicated that the relationship between Journal of Bone and Mineral Research and Bone was the closest (**Figure 6**). In this field, journals with a large number of publications also had high centrality (**Figure 6**).

Additionally, the dual-map overlay of journals was created using Citespace software to analyze the distribution of relationships among different journals. There were two citation paths in this picture. The green path showed that the research published in the journals of "dentistry, pharmacology, surgery" and "medicine, medical clinical, neurology, sports, ophthalmology" tended to be cited, mainly in "molecular, biology, genetics". The orange colored path showed that the research published in the journals of "molecular, biology and immunology" also tended to cite journals mainly in the field of "molecular, biology and genetics" (**Figure 7**). It could be seen that journals in the field of "molecular, biology and genetics" published the most articles on osteoporosis and Wnt signalling in the past decade. We can expect that future breakthroughs in this field will be published there.

3.5. Co-cited references

Co-cited references is one of the core indicators of bibliometrics. Co-cited references refers to that two documents appear together in the reference catalogue of the third cited document. Furthermore, the two documents establish a co-citation relationship. Analysing the

Table 3. Ranking of top 10 productive and co-cited journals in the field of osteoporosis and Wnt signalling research

Rank	Journal	Articles Counts	Country	JCR	IF	Co-cited Journal	Cocitation	JCR	IF
1	*Bone*	89	USA	Q1	4.398	*Journal of Bone and Mineral Research*	4345	Q1	6.741
2	*Journal of Bone and Mineral Research*	79	USA	Q1	6.741	*Bone*	2582	Q1	4.398
3	*PLoS One*	38	USA	Q2	3.240	*Journal of Biological Chemistry*	2132	–	5.157
4	*Calcified Tissue International*	30	USA	Q2	4.333	*Osteoporosis International*	967	Q2	4.507
5	*Biochemical and Biophysical Research Communications*	24	USA	Q2	3.575	*Cell*	953	Q1	41.58
6	*Osteoporosis International*	24	England	Q2	4.507	*Proceedings of the National Academy of Sciences of the United States of America*	904	Q1	11.20
7	*Scientific Reports*	21	England	Q1	4.379	*Journal of Clinical Endocrinology Metabolism*	853	Q1	5.958
8	*International Journal of Molecular Sciences*	18	USA	Q2	5.923	*PLoS One*	832	Q2	3.240
9	*Journal of Clinical Endocrinology Metabolism*	17	USA	Q1	5.958	*Nature*	784	Q1	49.96
10	*Journal of Biological Chemistry*	16	USA	–	5.157	*Endocrinology*	760	Q2	4.736

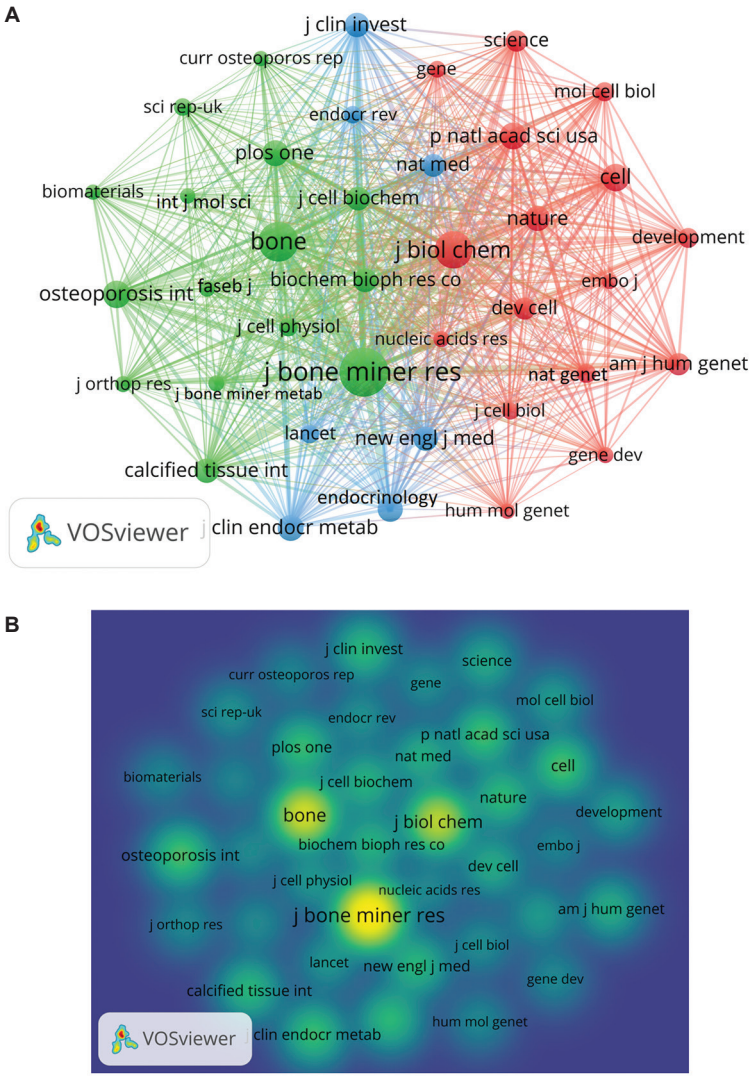

Figure 6. Cocitation analysis of journals. (A) Network visualisation analysis of Cocitation. (B) Density visualisation map of cocitation.

co-citation relationships within a document's spatial data set can be viewed as conducting a co-citation analysis of the documents.[30] Therefore, we used CiteSpace software to construct the cocitation correlation and clustering network diagram (**Figure 8A** and **B**). **Table 4** showed the top 10 references with the highest citation frequency. Among them, the article entitled "Wnt signalling in bone homeostasis and disease: from human mutations to treatments" published by Baron R on *Nature Medicine* in 2013 (95 citations in total) has been cited the most. The main content was to introduce the importance of Wnt signalling transduction to bone, and review the current research understanding of the mechanism of Wnt signal regulation of bone homeostasis. The second was Padhi D's article published in the *Journal of Bone and Mineral Research* in 2011, which mainly introduced that sclerosing protein monoclonal antibody AMG 785 was a generally well tolerated and effective bone anabolic agent. Ranked third was the article published by McClung MR in the *New England*

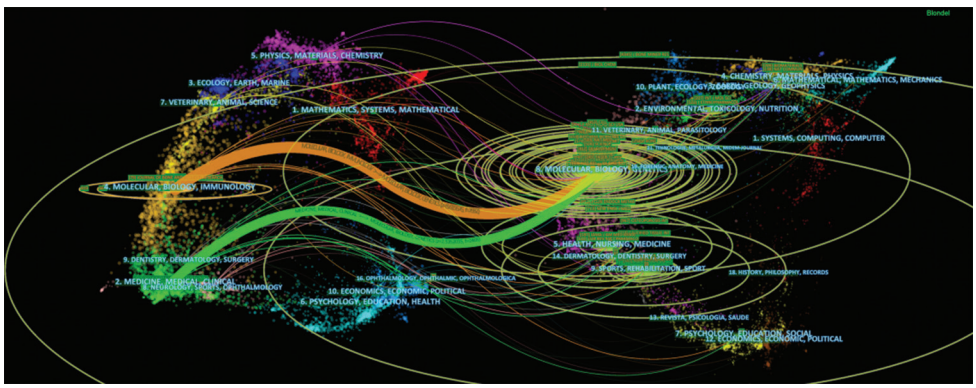

Figure 7. The dual-map overlay of articles focusing on Wnt signalling and osteoporosis research illustrates the citation relationships, with the citing journals on the left, the cited journals on the right, and the lines representing the paths of citation. The positions of the starting and ending points of these curves told us how an article was based on the previous work, because the cited graph and the cited graph were divided into multiple subject areas, and each position on the map belonged to one of them.

Figure 8. Co-citation analysis of references. (A) Network visualisation analysis of co-cited references. (B) Cluster analysis of co-cited references.

Journal of Medicine, which mainly introduced that among postmenopausal women with low bone mass, the sclerosing protein monoclonal antibody romosozumab was associated with increased bone mineral density and bone formation, as well as decreased bone resorption. As shown in **Figure 8B**, 22 clusters were generated according to the subject of the field. Each cluster highlighted a period of high citation, research fields and core literature groups, showing a distinct degree of professional or subject concentration. Among the 22 clusters, the largest cluster (#9) was related to association study, followed by cluster #2 (loading) and cluster #5 (sclerostin).

In order to better discover and locate hot topics that suddenly heat up in a certain field, outbreak detection is a very effective tool. In this study, we analysed the top 10 references with a surge in citations. We mainly focused on the literature that broke out after 2015 to better understand the current research trends (**Figure 9**). Among them, the article published by Baron R on Nature Medicine in 2013 had the highest outbreak intensity, and it also maintained a certain outbreak intensity after 2015. The references ranking second and third in outbreak intensity have no intensity after 2007, probably because there were new research results for our reference. The article published by Cosmo F in the *New England Journal of Medicine* in 2016 had maintained the outbreak intensity until 2021. The main content of the article was that among postmenopausal women with osteoporosis, the risk of osteoporosis after using romosozumab was significantly reduced. The clinical trial results of this article laid a certain foundation for romosozumab to become the world's first approved monoclonal antibody drug for the treatment of postmenopausal osteoporosis.

3.6. Analysis of keywords

Use VOSviewer to cluster and visualise high-frequency keywords to understand the research topic more comprehensively. Among all the keywords included, osteoporosis is the most frequently mentioned keyword, followed by osteogenes, Wnt, and osteoblasts (**Figure 10A**). Then, we use VOSviewer to divide the color of keywords according to the average year of publication. As shown in **Figure 10B**, yellow keywords indicate that they appear

Table 4. Ranking of top 10 co-cited references in the field of osteoporosis and Wnt signalling research

Rank	Author	Citations	Title	Journal	Year
1	Baron R	95	WNT signalling in bone homeostasis and disease: from human mutations to treatments	*Nat Med*	2013
2	Padhi D	50	Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody	*J Bone Miner Res*	2011
3	McClung MR	42	Romosozumab in postmenopausal women with low bone mineral density	*N Engl J Med*	2014
4	Estrada K	38	Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture	*Nat Genet*	2012
5	Krishnan V	37	Regulation of bone mass by Wnt signalling	*J Clin Invest*	2006
6	Li XD	37	Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength	*J Bone Miner Res*	2008
7	Cosman F	36	Romosozumab treatment in postmenopausal women with osteoporosis	*N Engl J Med*	2016
8	Modder UI	32	Relation of age, gender, and bone mass to circulating sclerostin levels in women and men	*J Bone Miner Res*	2011
9	Kato M	30	Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in Lrp5, a Wnt coreceptor	*J Cell Biol*	2002
10	Ominsky MS	–	Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength	*J Bone Miner Res*	2010

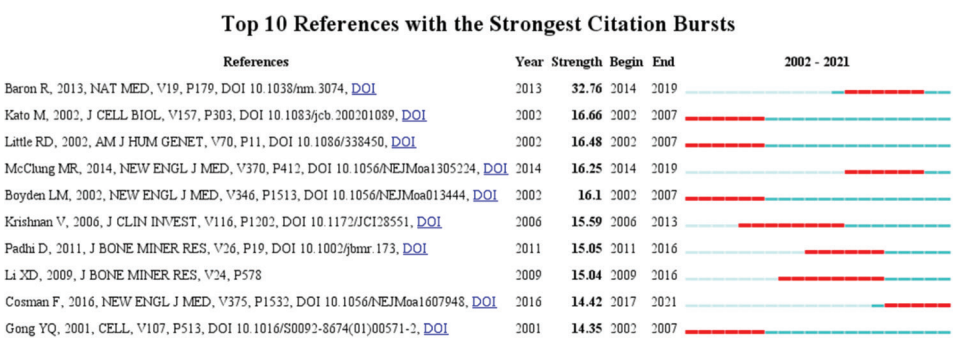

Figure 9. Representative references among the top ten with the strongest citation bursts

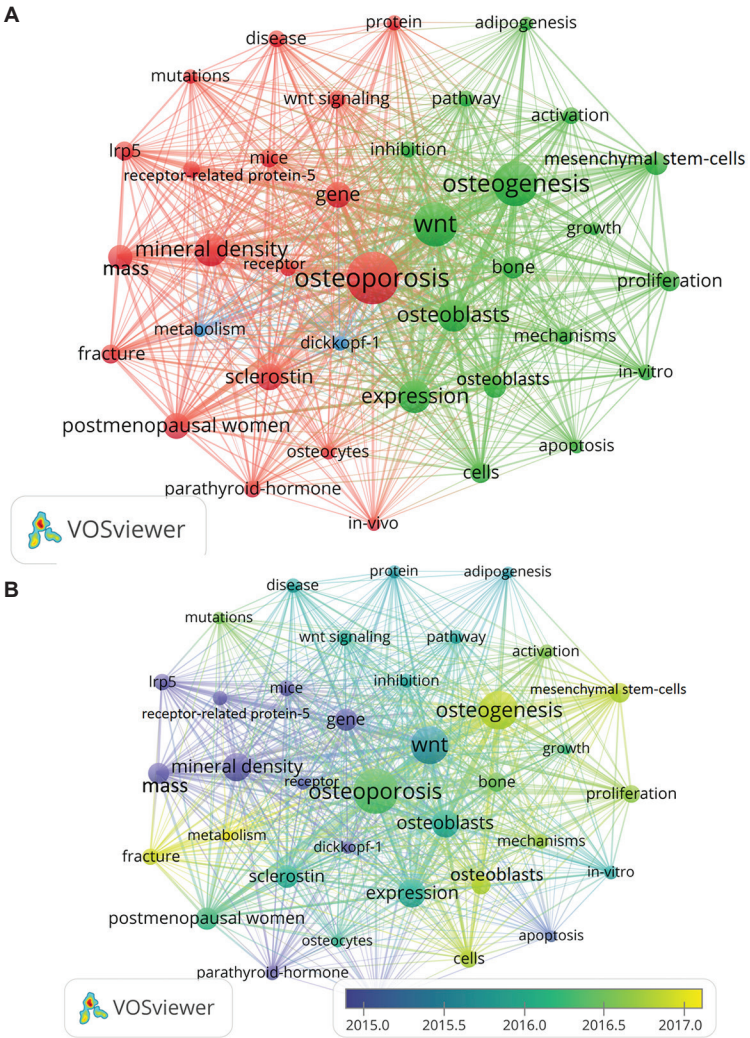

Figure 10. Visualisation of keyword analysis. (A) The network map of keywords. (B) Evolution of keyword frequency. The thickness of links represents the frequency of occurrence, and the color of nodes represents the clustering classification.

later than blue keywords. In the early days, "gene", "mineral density" and "mass" were the main topics. Recent trends show that the terms "osteogenesis", "metabolism", "structure" and "osteoblasts" are becoming more and more popular.

4. Discussion

Osteoporosis is a metabolic disorder characterised by a decrease in bone mass and strength, resulting in weakened bone structure and a higher susceptibility to fractures. Our statistical and quantitative analysis found that from 2001 to 2021, the research on osteoporosis and Wnt signalling pathway has made significant progress, and more and more researchers are entering this research field. Although the research on osteoporosis and Wnt signalling pathway is extensive, the analysis of its research status and trend is not clear. In this study, we conducted an in-depth analysis, exploration, and exposition of the current research status, development trends, and current research hotspots related to osteoporosis and the Wnt signalling pathway. At the same time, our research will help researchers understand the current situation of osteoporosis research more comprehensively, so as to guide the future research direction.

4.1. General information

In the past two decades, the number of research articles on osteoporosis and Wnt signalling pathway has been increasing every year. In addition, it is expected that the annual output of publications will increase rapidly in the next decade, which shows that this research field has broad prospects. China has published the most relevant articles among these countries, with a total of 489 articles, accounting for 31.48% of the total global publications. The second is the United States, with a total of 318 articles, accounting for 20.47% of the global total, which further shows that China and the United States have invested a lot of work and energy in this field. The United States, China, Germany, Canada and other countries have established close cooperative relations. The analysis of the coauthors of countries and institutions shows that international cooperation is becoming a trend in this field. Regarding research institutions, Shanghai Jiao Tong University has the highest number of publications, while Harvard University ranks first in terms of total citations.

By analysing the most influential authors, scholars can better understand existing collaborative networks and discover

potential partners both domestically and internationally.[31] The most prolific author is Robling Alexander from the United States, who has published 20 articles in total. His main research is that Wnt pathway related therapies are developed for the treatment of bone diseases.[32] His latest research shows that Notum is an inhibitor of osteocyte activity to inhibit cortical bone formation, and may participate in a variety of signal pathways that are important for bone homeostasis.[33] In addition, the author was cited most frequently by Roland Baron from the United States. His article entitled "Wnt signalling in bone homeostasis and disease: from human mutations to treatments" published on *Nature Medicine* was cited most frequently. He emphasised the importance of Wnt signalling to bones in the general population.[34] Besides the United States, Chinese scholar Li has also achieved significant academic accomplishments. However, the quality and impact of articles published in China still lag behind those from the United States. Despite the numerous research results published by Chinese scholars in this field, only one of the top 10 highly cited articles is from China. The innovation and depth of research is likely to be the main reason for the differences between China and the United States in this field. It is hoped that in subsequent studies, Chinese researchers will provide heavyweight research results in this field.

From the perspective of journal analysis, Bone, *Journal of Bone and Mineral Research* and *PLoS One* have published the most articles in the world. Although China is the largest publishing country among the top 10 journals, there are no Chinese journals, indicating that China should strengthen the development of several international journals in this field to attract more scientific publications and disseminate academic ideas.

4.2. The hotspots and frontiers

Research hotspots refer to topics that researchers highly value and discuss, and keywords can briefly describe the main content and themes of the literature, reflecting the core ideas and key points of the paper. Therefore, through keyword co-occurrence, research hotspots in this field can be analysed. Keyword analysis results show that osteoporosis, osteogenes, Wnt and osteoblasts are the keyword clustering centers. In the early days, "gene", "mineral density" and "mass" were the main topics. Recent trends show that "osteogenesis", "metabolism", "structure" and "osteoblasts" have become hotspots. A new metabolic therapy for osteoporosis is developed for Wnt signal transduction. The current treatment of osteoporosis includes the use of drugs that inhibit bone resorption and promote bone formation. Drugs that inhibit bone resorption include selective estrogen receptor modulator, bisphosphonates, Denosumab, etc.

The shift towards "osteogenesis" emphasises a growing interest in the molecular and cellular mechanisms that promote bone formation. This is particularly pertinent as new therapeutic targets within the Wnt signalling pathway, known to regulate osteoblast activity, are discovered and explored. Such insights are crucial for developing treatments that not only prevent bone loss but also enhance bone formation, especially in osteoporotic patients. Similarly, the focus on "metabolism" underlines the recognition of osteoporosis as a metabolic bone disease influenced by systemic metabolic conditions. This encompasses not just the biochemical processes occurring within bone cells but also the interactions with other metabolic systems such as glucose and lipid metabolism, which have been found to impact bone density and quality. The emphasis on "structure" reflects advances in imaging technologies and computational modeling that have improved our understanding of bone architecture. These advancements provide insights into the micro-architectural changes in bone that precede overt osteoporosis, offering potential early diagnostic and intervention points. Finally, the continuous relevance of "osteoblasts" within the research indicates ongoing interest in the cell types directly responsible for bone formation. The development of new biomaterials and bioengineering approaches for enhancing osteoblast function and survival in hostile osteoporotic environments highlights a promising area of translational research. Together, these trends not only illustrate a broadening of the research landscape but also point towards a multidisciplinary approach that integrates genetics, cell biology, materials science, and clinical medicine to tackle osteoporosis. Such a holistic approach is crucial for developing effective prevention strategies, diagnostic tools, and therapeutic interventions that address the complexities of the disease.

On the other hand, osteogenic enhancers such as Teriparatide use the opposite mechanism to increase bone turnover.[35-37] The research on different types of osteoporosis and the relationship between osteoporosis and adipose tissue content are the frontiers at present. It preliminarily reveals the hotspots and trends, provides reference content for research topics, and is conducive to the continuity and direction of research project design.

Of course, this study presents certain limitations: this study only included literature from the Web of Science Core Collection and failed to include excellent research results from other databases. At the same time, the assessments of bibliometrics were limited to published academic papers, but failed to include reports or other scientific research results in written form. Last but not least, the data from 2022–2024 related to Wnt signalling and osteoporosis were not included in this manuscript for the following reasons. First, the researches related to Wnt signalling and osteoporosis sprang up from 2002, and the data included in bibliometrics articles were integers for the entire five years. Therefore, we chose the twenty years of data from January 1, 2002 to December 31, 2021 in this study. Second, we chose the data from January 1, 2002 to December 31, 2021 because the research findings from the past 3 years (2022–2024) are still emerging and have not yet gained widespread acceptance in the field. By focusing on data up to 2021, we aimed to ensure that our review is based on well-established and widely recognised research outcomes. To sum up, the important role of Wnt signalling in bone homeostasis and disease, as well as the new osteoporosis therapy through drug targeting Wnt signalling. Although the recent progress has been applied in clinical practice, there are still problems

to be overcome in clinical practice. It is hopeful to continue to expand the research in this field and further understand the benefits of Wnt signalling transduction for patients.

5. Conclusions

This study provides a detailed overview of global research trends on osteoporosis and the Wnt signalling pathway from 2002 to 2021 through bibliometric analysis, and preliminarily explores the current research status, hotspots, and future development directions. We recommend that future research delve deeper into the cellular and molecular mechanisms of the Wnt signalling pathway, develop new clinical drugs targeting this pathway, and consider the therapeutic responses of different populations. Additionally, promoting interdisciplinary collaboration, international data sharing, and adjusting public health strategies based on the latest scientific advancements are crucial for advancing scientific research and clinical applications in this field. Through these specific insights and research directions, this study not only summarises existing achievements but also provides guidance for future research and practice, demonstrating its profound scientific and practical significance.

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Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Conceptualization: All authors; *Formal analysis:* All authors; *Writing-original draft:* All authors; *Writing-review & editing:* All authors. All authors read and approved the final version of the manuscript.

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