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Bibliometric Analysis of Zinc and Bone

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Abstract

Background: Zinc plays a crucial role in bone health; however, there is a lack of bibliometric analysis on zinc and bone research. This study aims to fill this research gap by conducting a bibliometric analysis of the development and research focus of zinc and bone-related studies. ***Methods:*** We performed a search in the Web of Science Core Collection and selected relevant literature on zinc and bone. We then conducted statistical analysis and visualized the literature to reveal the development trends and key areas of zinc and bone research. ***Results:*** From the retrieved literature, we observed an increasing trend in zinc and bone-related research since the 1990s. China emerged as a core country in research related to zinc and bone, with Shanghai Jiao Tong University being the institution with the greatest influence in this field. Yamaguchi, M emerged as the author with the greatest influence in research related to zinc and bone. These studies mainly focused on the role of zinc in bone formation, bone density and quality, bone diseases, and bone tissue engineering. ***Conclusion:*** Research on zinc and bone is growing, and there is increasing interest in the role of zinc in bone health. Future research should focus on gaining a deeper understanding of the toxicity and safety of zinc-based biomaterials, optimizing material design to improve biocompatibility and functionality, investigating the mechanisms of bio-interactions, and expanding the application areas of zinc-based biomaterials to drive their development in clinical and biomedical settings.

Keywords: zinc, bone, bibliometric

1. Introduction

Zinc is an essential trace nutrient that plays a critical role in bone health and possesses multiple functions. Firstly, research has shown that zinc is involved in bone formation, osteoporosis, and fracture healing processes. In terms of bone formation, zinc participates in regulating the proliferation and differentiation of bone cells, which is crucial for the formation of healthy bone matrix. The presence of zinc contributes to the promotion of collagen synthesis and participates in the deposition of calcium and phosphate minerals, thereby enhancing bone strength and stability (O'Connor JP, Kanjilal D, Teitelbaum M, Lin SS & Cottrell JA, 2020). Conversely, dietary zinc deficiency impairs growth and results in bone fragility (Sadighi A, Roshan MM, Moradi A & Ostadrahimi A, 2008). Secondly, zinc's regulatory role is vital for inflammation resolution and bone tissue reconstruction during fracture healing. Studies have found that zinc supplementation significantly increases serum zinc levels and alkaline phosphatase activity, both of which are important parameters for assessing fracture healing. Increased zinc promotes the formation of granulation tissue, accelerates the healing process of fractures, and helps maintain the integrity and structural stability of bone tissue (Sadighi A, Roshan MM, Moradi A & Ostadrahimi A, 2008). Additionally, zinc deficiency is closely associated with the development of osteoporosis. Inadequate zinc

affects the function of bone cells, disrupts normal metabolic processes in bone tissue, and influences the balance of calcium, phosphate, and other elements. This may lead to osteoporosis, bone loss, and increased bone fragility. Therefore, zinc supplementation may be beneficial in the prevention and treatment of osteoporosis and maintaining bone health (Chou J, Hao J, Hatoyama H, Ben-Nissan B, Milthorpe B & Otsuka M, 2013). There is a close relationship between zinc and bone health. Zinc plays a significant role in bone formation, fracture healing, and osteoporosis by regulating bone cell function, promoting bone tissue reconstruction, and maintaining skeletal structural stability. Further in-depth research on the interaction between zinc and bone can provide new theoretical foundations and treatment strategies for the maintenance of bone health and the treatment of related diseases.

Bibliometrics is an interdisciplinary research field that employs quantitative analysis of scientific literature to reveal trends and structures in scientific research, assess the quality and impact of academic journals, authors, and research institutions, facilitate academic communication and scientific policy-making, and provide scientific evidence for research evaluation and decision-making. Currently, bibliometrics has been widely applied in the field of biomedical research. However, there is a lack of bibliometric analysis specifically focusing on zinc and bone. Therefore, the purpose of this study is to conduct a quantitative and visual analysis of annual publication output, active countries, prolific institutions, authors, and keywords related to zinc and bone, in order to understand the development trends and hot topics in the field of zinc and bone.

2. Methods

The literature was obtained from the Web of Science Core Collection. The search query was "TI=zinc and TI=bone*" and the search was conducted on June 12, 2023, to ensure the inclusion of up-to-date information. The inclusion criteria were set as follows: document types limited to articles and reviews, and language limited to English. The literature search process is illustrated in Figure 1. A total of 436 articles were initially retrieved. After applying the inclusion criteria, 65 articles that did not meet the criteria were excluded, resulting in a final inclusion of 371 articles. The retrieved records were exported in "Plain Text File" format, and basic information such as country, authors, institutions, and keywords were extracted. The data was then imported into VOSviewer and CiteSpace software. VOSviewer was used for visualization and cluster analysis of countries, institutions, and authors, while CiteSpace was used for keyword burst analysis.

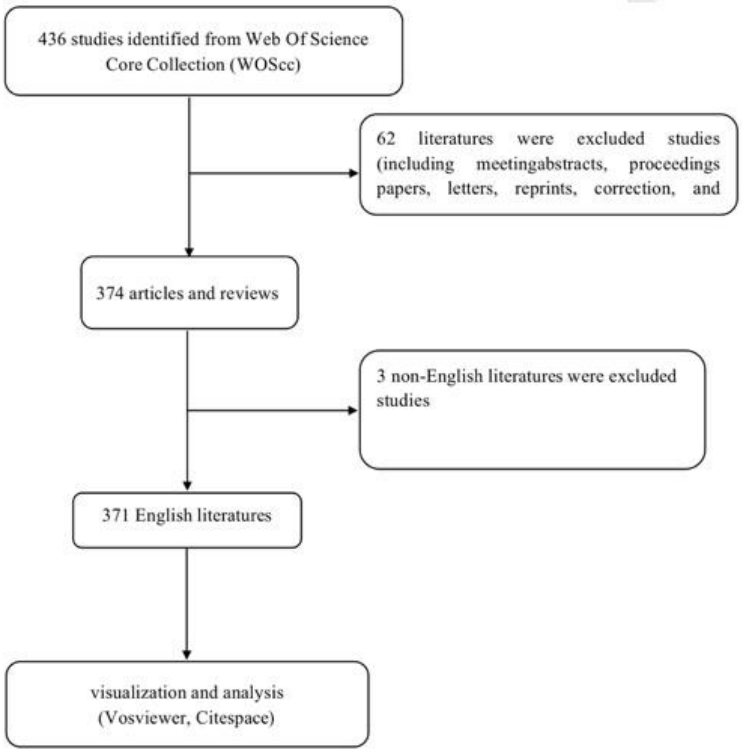


Figure 1. Literature search process

3. Results

3.1 General Statistics

A total of 371 articles were retrieved from the WOSCC database, comprising 362 articles (97.57%) and 9 reviews (0.24%). The annual publication and citation trends are shown in Figure 2. The number of publications has shown an increasing trend from 2001 to 2023. The annual publication count remained around 10 articles from 2001 to 2015, but has steadily increased since 2016. The peak publication year was 2020, with 38 articles published. It is noteworthy that the citation count has also exhibited an exponential increase. The citation count exceeded 1000 in 2020, with a peak of 1761 citations in 2022, and it is expected to continue to increase in 2023. These results indicate sustained attention to research on zinc and bone over the past two decades, and it is anticipated to continue generating continued interest in the academic community.

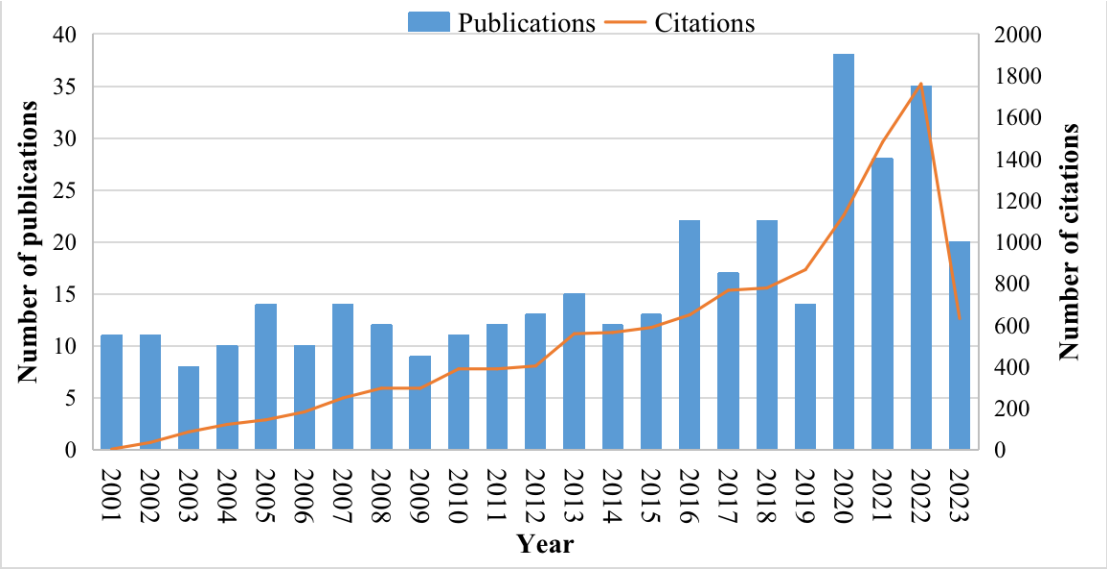


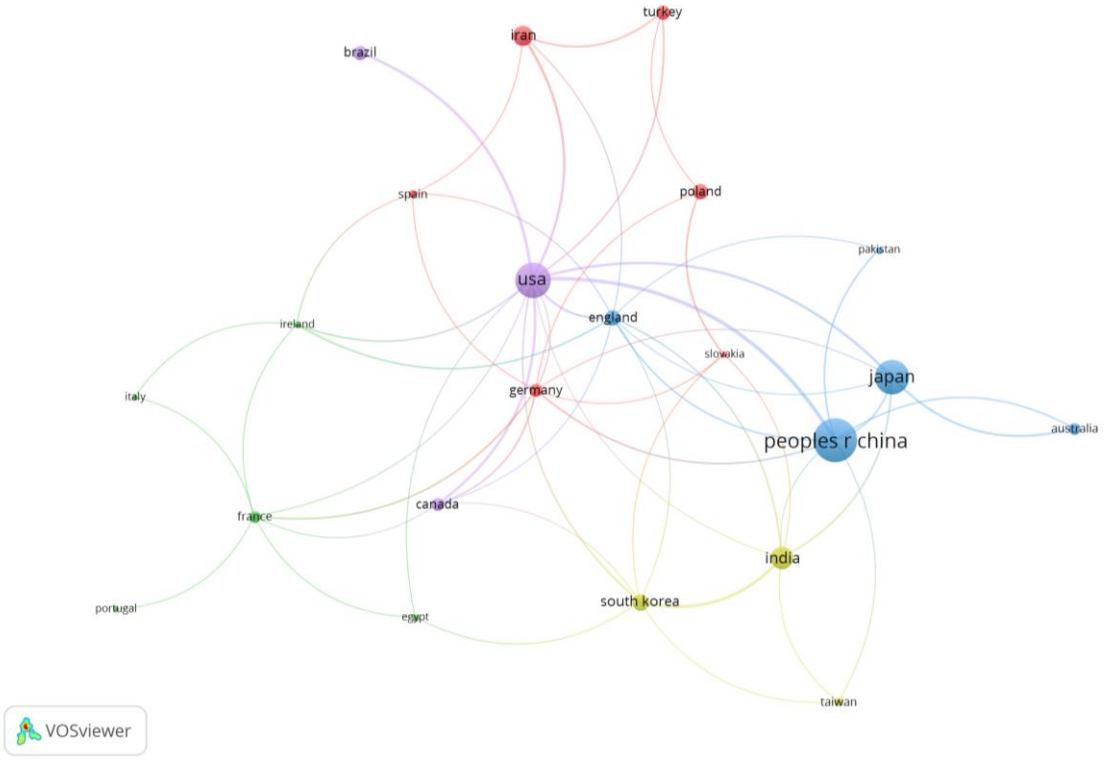
Figure 2. The annual number of publications and citations related to zinc and bone

3.2 Country/Region Analysis

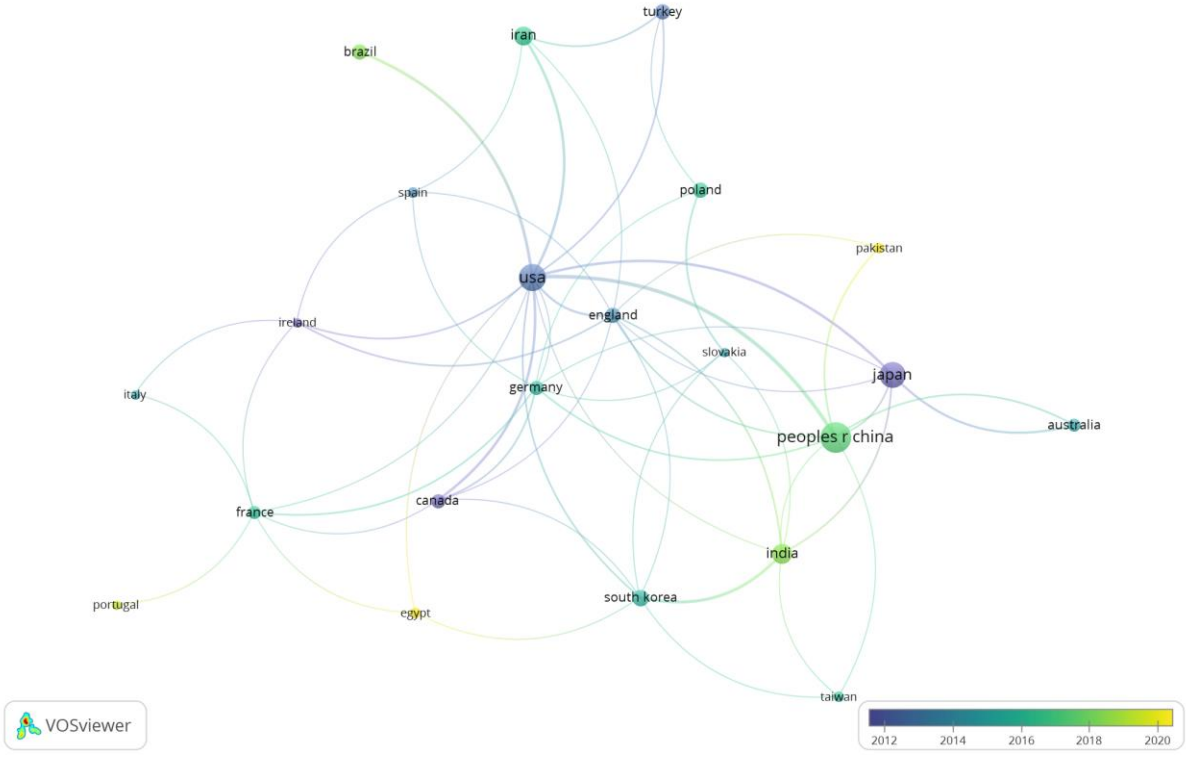
A total of 55 countries/regions have contributed to research in the field of zinc and bone. Table 1 presents the top ten productive countries, with China ranking first with 82 publications, followed by the United States (59 publications), and Japan (55 publications) in the third position. In terms of citations, the top three countries are the United States (4867 citations), China (2472 citations), and Japan (1701 citations). Figure 3A displays the country collaboration network, while Figure 3B shows the overlay map. As depicted in Figure 3A, China has the highest proportion of publications and exhibits the strongest collaboration with the United States. Figure 3B reveals that Japan and the United States have an earlier average publication time compared to China. The concentration of Chinese publications in recent years might explain the lower citation count compared to the United States. Consequently, China emerges as a core country in research related to zinc and bone.

Table 1. The top ten productive countries

Rank	Country	Documents	Citations
1	China	82	2472
2	USA	59	4867
3	Japan	55	1701
4	India	30	690
5	Iran	25	490
6	South Korea	20	583
7	England	17	523
8	Poland	17	388
9	Brazil	15	234
10	Turkey	15	221



(**A**) Cooperation networks across countries



(**B**) Overlay Visualization of countries

Figure 3. Co-authorship analysis of countries

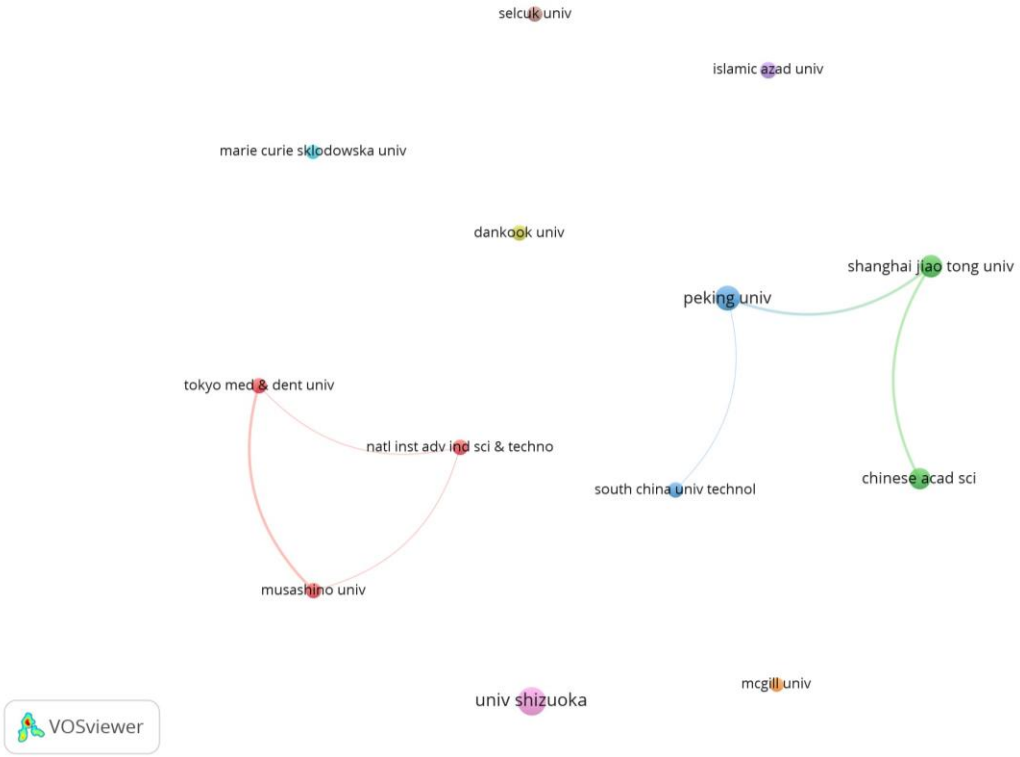
3.3 Institution Analysis

A total of 614 institutions have contributed to research in the field of zinc and bone. Table 2 presents the top ten

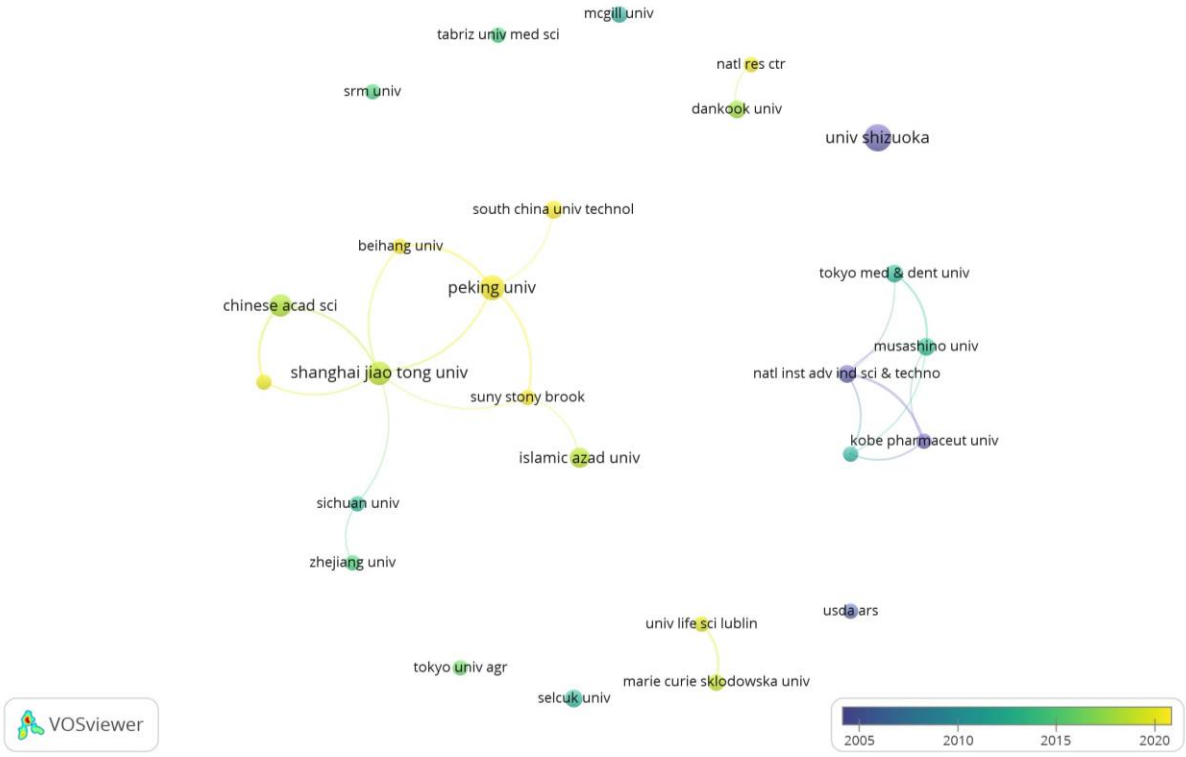
productive institutions, with University Shizuoka ranking first with 16 publications, followed by Peking University (13 publications), and Shanghai Jiao Tong University (11 publications) in the third position. In terms of citations, Shanghai Jiao Tong University ranks first with 742 citations, followed by the National Institute of Advanced Industrial Science and Technology (540 citations) in the second position, and the Chinese Academy of Sciences (511 citations) in the third position. Figure 4A displays the institution collaboration network, while Figure 4B shows the overlay map. As depicted in Figure 4A, institutions from the same country/region tend to collaborate closely, with fewer instances of cross-national collaborations. Figure 4B reveals that University Shizuoka from Japan has an earlier average publication time, while larger institutions from China have a relatively later average publication time. Although Peking University ranks second in terms of publication count, it does not appear in the top three in terms of citations, possibly due to its later average publication time. On the other hand, Shanghai Jiao Tong University, despite ranking third in terms of publication count and having a later average publication time compared to University Shizuoka, holds the highest citation count. Therefore, Shanghai Jiao Tong University emerges as the institution with the greatest influence in research related to zinc and bone.

Table 2. The top ten productive institutions

Rank	Institution	Documents	Citations
1	University Shizuoka	16	341
2	Peking University	13	490
3	Shanghai Jiao Tong University	11	742
4	Chinese Azad Sci	10	511
5	Islamic Azad University	7	159
6	Musashino University	6	132
7	Tokyoo Med & Dent University	6	203
8	Nati Inst Adv Ind Sci & Technol	6	540
9	Selcuk University	6	77
10	Dankook University	6	67



(**A**) Cooperation networks across institutions



(**B**) Overlay Visualization of institutions

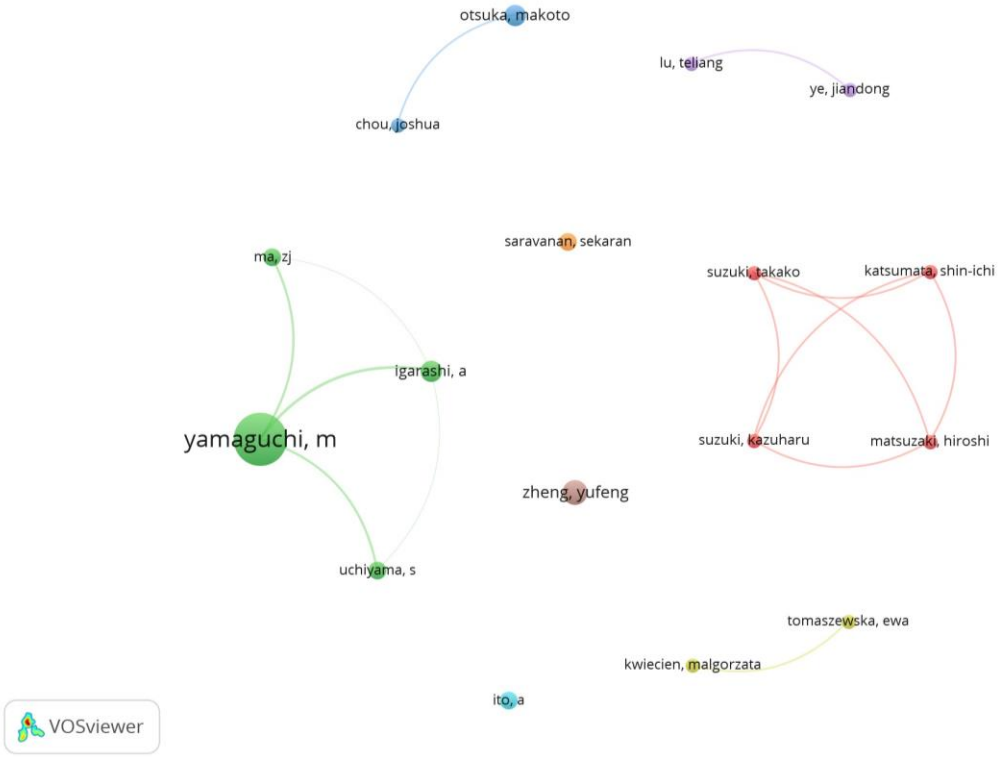
Figure 4. Co-authorship analysis of institutions

3.4 Author Analysis

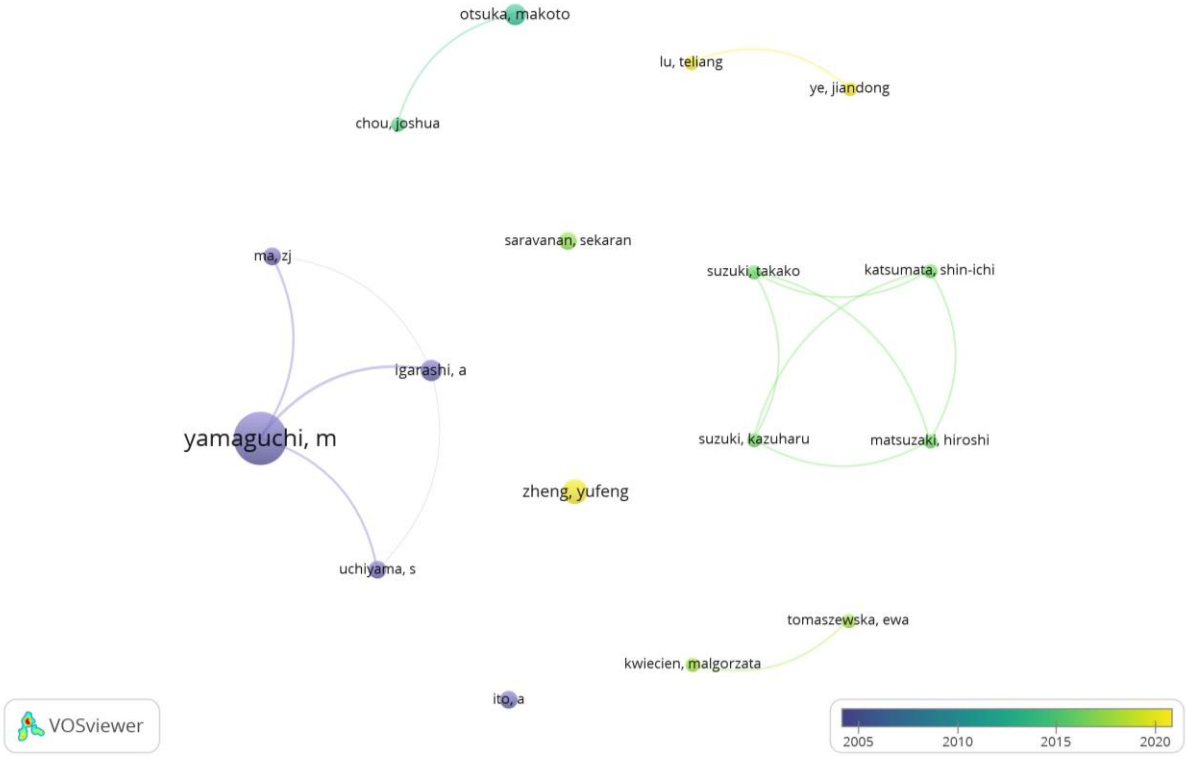
A total of 2000 authors have contributed to research in the field of zinc and bone. Table 3 presents the top ten productive authors, with Yamaguchi, M ranking first with 15 publications, followed by Zheng, Yufeng (7 publications), and Otsuka, Makoto (6 publications) in the third position. In terms of citations, Ito, A ranks first with 515 citations, followed by Zheng, Yufeng (413 citations) in the second position, and Saravanan, Sekaran (345 citations) in the third position. Figure 5A displays the author co-citation network, while Figure 5B shows the overlay map. As depicted in Figure 5A, authors from the same country/region tend to collaborate closely, with fewer instances of cross-national collaborations. Figure 5B reveals that Yamaguchi, M has an earlier average publication time, while authors from China have a relatively later average publication time. Interestingly, although Zheng, Yufeng has a later average publication time, both their citation count and publication count rank second. Therefore, Yamaguchi, M emerges as the author with the greatest influence in research related to zinc and bone.

Table 3. The top ten productive authors

Rank	Author	Documents	Citations
1	Yamaguchi, M	15	331
2	Zheng, Yufeng	7	413
3	Otsuka, Makoto	6	132
4	Igarashi, A	6	110
5	Ito, A	5	515
6	Saravanan, Sekaran	5	345
7	Ma, Zj	5	135
8	Uchiyama, S	5	103
9	Chou, Joshua	4	86
10	Kwiecien, Malgorzata	4	59



(**A**) Cooperation networks across authors



(**B**) Overlay Visualization of authors

Figure 5. Co-authorship analysis of authors

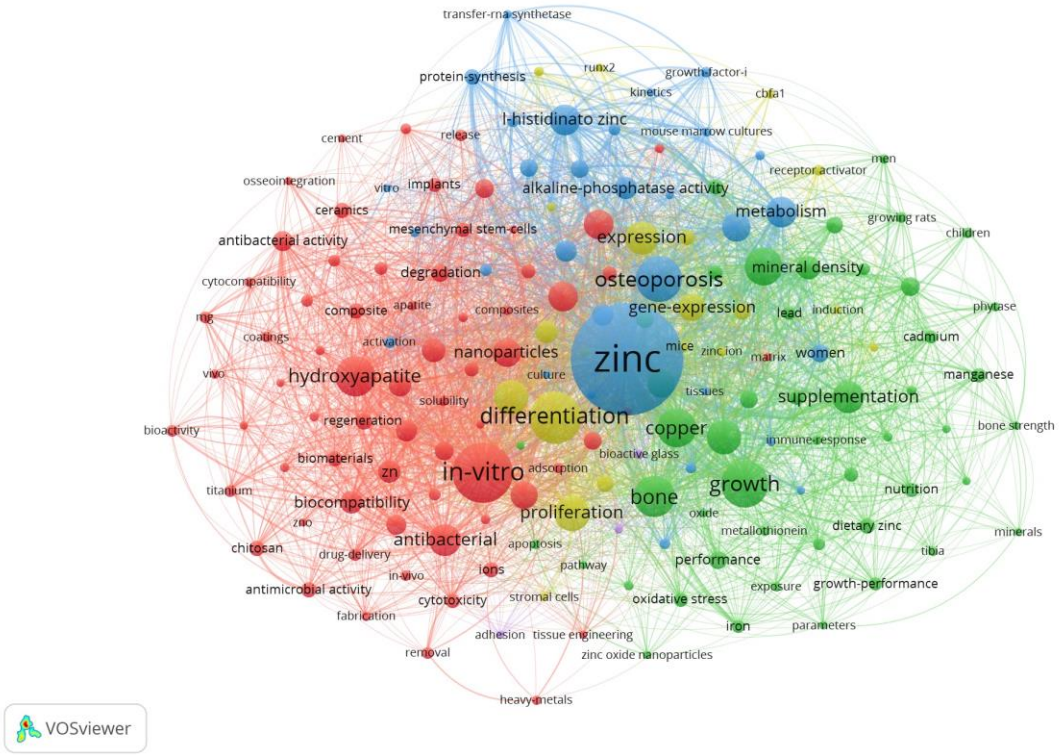
3.5 Keyword Analysis

A total of 2071 keywords are associated with research in the field of zinc and bone. Table 4 presents the keywords with a frequency greater than 20. The top five keywords are Zinc (120), in-vitro (57), differentiation

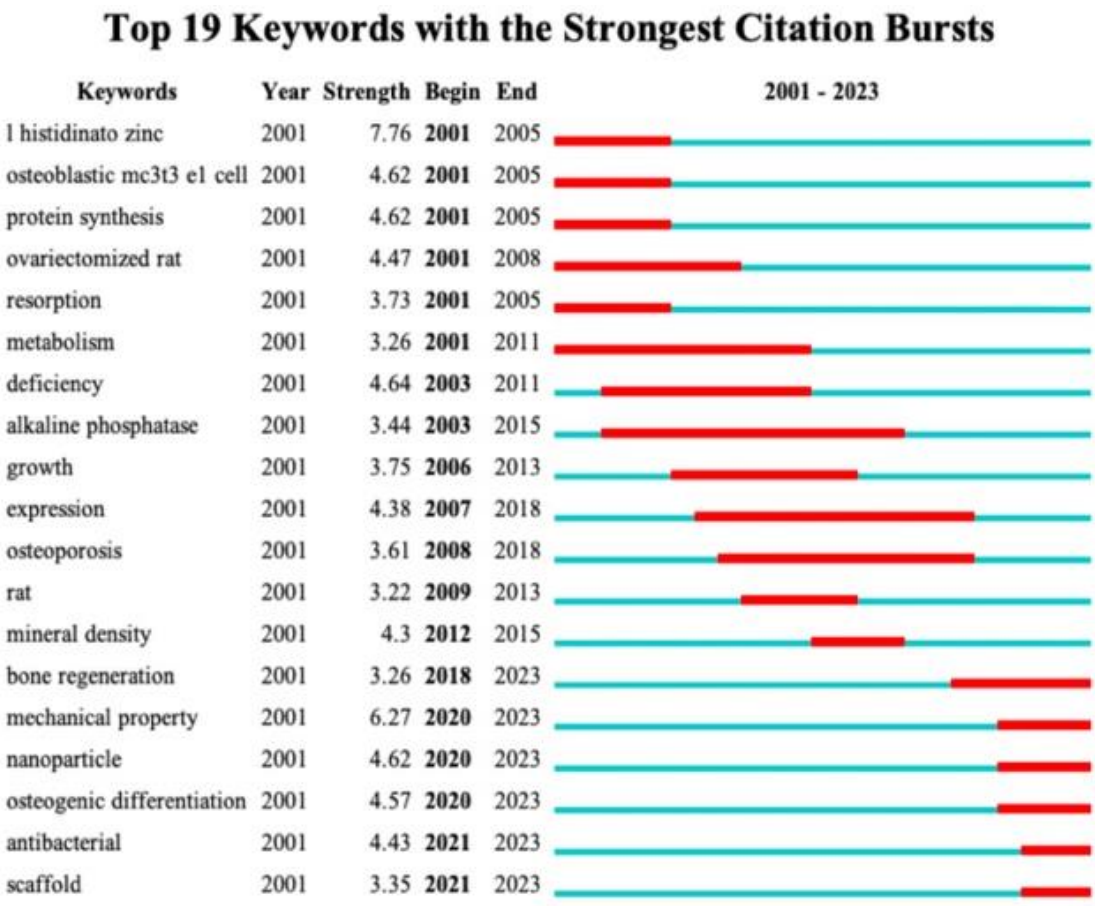
(47), growth (40), and osteoporosis (42). Figure 6A and Figure 6B display the co-occurrence network and the overlay map of keywords, respectively. Figure 6A illustrates the co-occurrence analysis of keywords, which can be divided into five clusters represented by different colors (red, yellow, blue, purple, and green). Figure 6B depicts the temporal distribution of keywords, providing insights into more recent keywords. Therefore, nanoparticles, antibacterial, and osteogenesis are the latest research hotspots.

Table 4. The top 22 **occurrence** keywords

Rank	keywords	**occurrence**	Rank	keywords	**occurrence**
1	zinc	120	12	cells	28
2	in-vitro	57	13	expression	27
3	differentiation	47	14	antibacterial	26
4	growth	42	15	supplementation	26
5	osteoporosis	40	16	l-histidinato zinc	25
6	bone	36	17	metabolism	25
7	hydroxyapatite	34	18	magnesium	24
8	copper	33	19	mechanical-properties	24
9	deficiency	32	20	resorption	22
10	proliferation	29	21	nanoparticles	22
11	calcium	28	22	osteogenesis	21



(A) Cooperation networks across keywords



(**B**) Distribution of keywords

Figure 6. Co-authorship analysis of keywords

4. Discussion

To the best of our knowledge, this is the first literature-based bibliometric analysis conducted on zinc and bone research. Our study identified trends and hotspots in zinc and bone-related research. The results indicate a growing trend in the number of publications and citations concerning zinc and bone from 2001 to 2023. Particularly, there has been a continuous increase in the annual publication count since 2016, reaching its peak in 2020. These findings suggest sustained interest and vigorous development in the field of zinc and bone research. We found that China is the most productive country in zinc and bone research, although its citation count ranks second behind the United States. This may be attributed to China's concentration of publications in recent years. University Shizuoka emerged as the most productive institution, while Shanghai Jiao Tong University had the highest citation count. This highlights the strong academic influence of Shanghai Jiao Tong University in the field of zinc and bone research. However, there is room for improvement in terms of international and inter-institutional collaborations and communication. Furthermore, Yamaguchi, M is identified as the author with the greatest impact in the field of zinc and bone research. It is worth noting that these findings are subject to the limitations of the database used and the specific search criteria applied. Further studies and collaborations are warranted to deepen our understanding of the research landscape in the zinc and bone domain and to facilitate knowledge exchange and scientific advancements in this field.

4.1 Hotspots and Frontiers

4.1.1 Zinc, Nanoparticles, and Bone

Research on zinc and bone using nanotechnology is a hot topic in bone tissue engineering. Zinc oxide nanoparticles (ZnO-NPs) are common zinc-containing metal oxide nanoparticles that exhibit low toxicity and possess desirable biological functions, including antibacterial, anticancer, and osteogenic properties (Li YH, Yang Y, Qing YA, et al, 2020). A study developed hydroxyapatite and zinc-doped hydroxyapatite nanoparticles as carriers for ciprofloxacin delivery systems, demonstrating high local dosage. These nanoparticles exhibited excellent antibacterial activity and achieved controlled release of ciprofloxacin, with the presence of zinc increasing the drug release percentage (Venkatasubbu GD, Ramasamy S, Ramakrishnan V & Kumar J, 2011).

The application of zinc in bone through nanotechnology and the introduction of antibacterial materials have enhanced the antibacterial properties of hydroxyapatite nanoparticles and improved the proliferation capacity of bone marrow stem cells, displaying favorable characteristics for bone tissue engineering (Maleki-Ghaleh H, Siadati MH, Fallah A, et al, 2021). By developing dual-ion releasing nanoparticles containing zinc and iron, these nanoparticles can promote the differentiation of mesenchymal stem cells into osteogenic cells and induce blood vessel formation, exhibiting optimized properties for bone tissue engineering (Kim YJ, Lee J, Im GB, et al, 2021). Through controlled release mechanisms, these nanoparticles can modulate gene expression and secretion factors in stem cells, improve cellular activity, and enhance the osteogenic potential of stem cells, providing a promising platform for future biomedical applications. However, zinc oxide nanoparticles may have potential harmful effects, even at low doses, as they can increase levels of reactive oxygen species and trigger inflammatory responses (Heng BC, Zhao XX, Tan EC, et al, 2011). Zinc-based biomaterials, including biodegradable metals, nanoparticles, and coatings for medical implants that release zinc ions, may lead to increased systemic and serum zinc concentrations (Qu XH, Yang HT, Yu ZF, et al, 2020). Therefore, future research should focus on gaining a deeper understanding of the toxicity and safety of zinc-based biomaterials, optimizing material design to improve biocompatibility and functionality, investigating the mechanisms of bio-interactions, and expanding the application areas of zinc-based biomaterials to drive their development in clinical and biomedical settings.

4.1.2 Antibacterial, Zinc, and Bone

In the context of applications related to bone, the use of antimicrobial zinc is an emerging research field. Zinc exhibits potent antimicrobial properties, making it potentially valuable in the prevention and treatment of infections associated with bone implants or fractures. Incorporating zinc into bone graft materials or coatings can inhibit bacterial growth, reduce the risk of infection, and promote bone healing. A study utilized a co-precipitation method to prepare zinc-doped hydroxyapatite, creating an antimicrobial artificial bone material for postoperative joint procedures to inhibit bacterial infection or proliferation, ultimately preventing the occurrence of osteomyelitis. Experimental results demonstrated that zinc-hydroxyapatite coatings exhibited good biocompatibility and antimicrobial capabilities (Yang YC, Chen CC, Wang JB, Wang YC & Lin FH, 2017). Future research needs to further explore the optimal dosage, delivery methods of zinc, and its long-term effects on promoting antimicrobial activity and improving bone health.

4.1.3 Osteogenesis, Zinc, and Bone

Zinc plays a crucial role in the process of osteogenesis, participating in the formation and maintenance of bone tissue and exerting regulatory effects on the function and metabolism of bone cells. Zinc promotes the proliferation and differentiation of osteoblasts, regulates the synthesis and mineralization of the bone matrix, and contributes to bone remodeling and repair processes (Abrisham SM, Yaghmaei M, Abbas FM, Sharifi D & Abrisham SMJ, 2010). Adequate zinc intake and metabolism are essential for maintaining skeletal health and normal growth of bone density. Zinc-modified titanium materials exhibit excellent biocompatibility and, by releasing appropriate concentrations of zinc ions, promote angiogenesis and bone regeneration, which are of great significance for bone reconstruction around implants. Proper concentrations of zinc ions can induce the proliferation and osteogenic differentiation of endothelial cells and regulate the behavior of osteoblasts by activating the MAPK/ERK signaling pathway (Zhu WQ, Li K, Su S, Chen W, Liu Y & Qiu J, 2022). Zinc is closely associated with osteogenesis. Introducing zinc oxide nanoparticles (ZnO-NPs) into magnesium phosphate cement (MPCs) enhances its osteogenic capability. Studies have found that ZnO-NP-enhanced MPCs exhibit characteristics such as prolonged setting time, reduced exothermic temperature, and increased compressive strength. Furthermore, co-culturing ZnO-NPs with murine bone marrow mesenchymal stem cells (mBMSCs) promotes the differentiation, proliferation, and mineralization capacity of mBMSCs and significantly increases the expression of osteogenic-related genes and proteins (Wang XM, Shi F, Zhao DC & Yan YG, 2022). These findings suggest that ZnO-NP-enhanced MPCs possess the ability to promote osteogenesis and mineralization. These studies provide new insights into the mechanisms of osteogenesis and angiogenesis on zinc-modified titanium surfaces and lay the groundwork for promoting the application of zinc-modified titanium surfaces in the field of orthopedics. However, both zinc excess and deficiency can have detrimental effects on skeletal health. Therefore, maintaining proper zinc balance is crucial for promoting skeletal health and preventing bone-related diseases.

5. Conclusion

Based on the bibliometric analysis, the following conclusions can be drawn: There is a growing body of research on the relationship between zinc and bone, indicating increasing interest in the role of zinc in bone health. The research primarily focuses on the effects of zinc on bone formation, bone density and quality, and bone diseases. Most studies suggest that adequate zinc intake has positive effects on promoting osteoblast proliferation, bone matrix synthesis, and improving bone density and strength. Zinc exerts its influence on bone health through

mechanisms such as participating in signaling pathways of bone cells, activating osteogenic-related proteins, and regulating bone turnover. Future research can further investigate the mechanisms of action of zinc on bone and explore the potential applications of zinc supplementation strategies in bone health and the treatment of bone diseases.

6. Limitations

There are several limitations to the bibliometric research on zinc and bone. Firstly, the reliability of the studies is subject to the limitations of the selected databases in terms of scope and accuracy, which may result in the exclusion of some relevant literature from the analysis. Secondly, the literature selection process may involve subjective biases, leading to the oversight or exclusion of certain relevant studies, which can impact the comprehensiveness of the results. Additionally, differences in data quality and regional language bias across different studies can affect the consistency and generalizability of the findings. Lastly, the inherent limitations of bibliometric methods, such as the inability to access raw data directly and the lack of detailed information, also restrict the depth and accuracy of the research. Therefore, when interpreting and applying the results of bibliometric studies on zinc and bone, it is important to carefully consider these limitations and conduct comprehensive analysis and judgment by integrating other research methods and evidence.

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