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Publication Trends in Osteoporosis Treatment from 2001 to 2020

Journal:	Journal of Orthopaedic Surgery
Manuscript ID	OSJ-22-0019
Manuscript Type:	Review Article
Keywords:	bibliometric, publication trend, osteoporosis, treatment
Abstract:	The prevalence of osteoporosis is continuing to escalate with the increasingly elderly population. The aim with this study was to investigate the profile of research articles on osteoporosis treatment published in the past two decades using bibliometric analysis. All publications about osteoporosis treatment published between 2001 and 2020 in Web of Science (WoS) index were downloaded and analyzed using bibliometric methods. In the Title search section in WoS, the documents with the keywords related to "osteoporosis treatment" were identified. The records extracted were analyzed for citation characteristics, including the distribution of publication years, languages, countries or regions, journals, articles, and authors. There were 29,738 publications, 26,085 of which were articles. There was a steady increase in the number of published articles from 2001 to 2020. The overall number of scientific publications in WoS increased 3.5-fold. The top 5 productive countries were the USA, China, Germany, England, and Japan. The University of California system was the largest contributor. The top productive journals were Osteoporosis International (1,679; 6.4%), Bone (832; 3.2%), and Journal of Bone and Mineral Research (727; 2.8%). The article that received the greatest number of citations was published in Journal of Clinical Endocrinology & Metabolism. This study provided a systematic overview of productivity and visibility of research work in osteoporosis treatment. In terms of the trend of previous years, an increasing number of literatures related to osteoporosis treatment will be published in the future. We believe that our study is a beneficial guide for clinicians and scientists about the global outputs of osteoporosis treatment.

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Publication Trends in Osteoporosis Treatment from 2001 to 2020

3 Abstract

The prevalence of osteoporosis is continuing to escalate with the increasingly elderly population. The aim with this study was to investigate the profile of research articles on osteoporosis treatment published in the past two decades using bibliometric analysis. All publications about osteoporosis treatment published between 2001 and 2020 in Web of Science (WoS) index were downloaded and analyzed using bibliometric methods. In the Title search section in WoS, the documents with the keywords related to "osteoporosis treatment" were identified. The records extracted were analyzed for citation characteristics, including the distribution of publication years, languages, countries or regions, journals, articles, and authors. There were 29,738 publications, 26,085 of which were articles. There was a steady increase in the number of published articles from 2001 to 2020. The overall number of scientific publications in WoS increased 3.5-fold. The top 5 productive countries were the USA, China, Germany, England, and Japan. The University of California system was the largest contributor. The top productive journals were Osteoporosis International (1,679; 6.4%), Bone (832; 3.2%), and Journal of Bone and Mineral Research (727; 2.8%). The article that received the greatest number of citations was published in Journal of Clinical Endocrinology & Metabolism. This study provided a systematic overview of productivity and visibility of research work in osteoporosis treatment. In terms of the trend of previous years, an increasing number of literatures related to osteoporosis treatment will be published in the future. We believe that our study is a beneficial guide for clinicians and scientists about the global outputs of osteoporosis treatment.

Keywords: bibliometric; publication trend; osteoporosis; treatment

26 Introduction

Osteoporosis is the most common bone disease in humans, representing a major public health problem. Currently, it has been estimated that more than 200 million people are suffering from osteoporosis¹. According to recent statistics from the International Osteoporosis Foundation, worldwide, 1 in 3 women over the age of 50 years and 1 in 5 men will experience osteoporotic fractures in their lifetime¹. Since life expectancy is increasing worldwide and the risk for osteoporosis increases with age, it's not surprising that osteoporosis and its dangerous effects are increasing around the world. Because of the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population.

Nevertheless, to the best of our knowledge, the recent research status and future research trends of osteoporosis treatment have not been well studied. In the context of the high profile of osteoporosis treatment, it is particularly meaningful to understand the global status quo of the field and predict future research trends. Bibliometrics is the statistical analysis of scientific publications such as articles and books². With the wide availability of bibliometric analytical software, there is a rapid proliferation of bibliometric studies on various medical topics in recent years³. For example, bibliometric analyses have been utilized to profile the trend of research on various diseases or interventions⁴. The importance of bibliometric studies has been increasing thanks to the need for summarizing the research topics that particularly have a high number of publications⁵. By providing a summary of the literature, bibliometric studies help researchers to gain time in terms of literature review⁶. In addition, it enables researchers to have new ideas by demonstrating past and current trends⁷. Recently, parallel to the increase in the prevalence of osteoporosis and the increase in the development of the countries, there has been an important increase in the number of publications and citations

about osteoporosis treatment. However, few studies have specifically explored the

52 bibliometric profile of osteoporosis treatment research.

53 The current study used bibliometric analysis to study the profile of research articles on

osteoporosis treatment published in the past two decades (2001–2020) and to identify

55 promising research direction in the future of osteoporosis treatment.

57 Material and Methods

This study was exempted from review of institutional review board since it did not involveany human subjects. There were no ethical questions about the data.

60 Literature Search

The literature review was performed using the "osteoporosis treatment" key word in the Title search section. All publications on osteoporosis treatment with this search method were downloaded from the Web of Science (WoS) database using bibliometric methods. The WoS is recognized as the most suitable online database for bibliometric analysis^{8, 9}. The database included SCIE, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED. Terms used during the search were: Theme=((osteoporosis treatment) OR (treatment, osteoporosis) OR (treatment for osteoporosis) OR (osteoporosis management) OR (osteoporosis medication)). The search was conducted on Nov 2, 2021. Document retrieval and export should be completed within 1 day to avoid bias caused by continuous database update. The publication period was limited to 20 years, 2001-2020. Original and review articles were selected for further analyses because they accounted for the majority of document types that also included complete research ideas and results¹⁰. The exclusion criteria were as follows: editorials, letters, errata, meeting abstracts, conference papers, and duplicate printings. No language restriction was imposed in the search strategy. In our bibliometric analysis, there was no need

to check for duplicate documents as all data are retrieved from one database. We also counted the number of published papers according to the following medication classes: bisphosphonate, denosumab, selective estrogen receptor modulators (SERM), and teriparatide. Multiple naming of different drugs within one paper was classified into each medication class. **Data Extraction** All literature retrieval and data extraction were completed independently by two authors with familiar literature retrieval background. When they disagree, the differences are fully discussed until they reach an agreement. The records extracted were analyzed for citation characteristics, including the distribution of publication years, languages, institutions, countries or regions, journals, impact factor (as determined by its 2020 average published by Journal Citation Reports), articles, growth rate, and authors. Growth rate was calculated using the following equation: Growth Rate = [(Frequency of Current Year-frequency of Last)]Year)/(Frequency of Last Year)]*100¹¹. In addition, total citations, average citations per item, and h-index (Hirsch index) were extracted from the WoS citation report. The h-index is an author-level metric that attempts to measure both the productivity and citation impact of the publications of a scientist or scholar; an author has index h if his or her number of papers have at least h citations¹². And thus, the h-index reflects both the number of publications and the number of citations per publication. Particularly, h-index can be extended to describe publications of a country, a journal, or an organization¹³.

94 Statistical analysis

The data downloaded from the WoS were analyzed quantitatively and qualitatively by Microsoft Excel 2016 (Microsoft Corp, Redmond, WA). We performed a quantitative description of time distribution, country of origin, institution, number of studies by author, and frequency of citation by country through the bibliometric approach. Linear regression analyses were performed to estimate the number of publications in the following years.

Wilcoxon Signed Rank test was used to determine any significant differences between the groups in terms of continuous variables. SPSS (version 22.0, SPSS Inc., Chicago, IL) was used for statistical analysis. Statistical analysis was performed by an independent statistician blinded to group allocations. Significance was reported at the 95% confidence level (p < p0.05). Results Search results and studies included The literature review retrieved 29,738 publications on osteoporosis treatment published between 2001 and 2020. Of all these publications, 21,556 (72.5%) were articles, 4,529 (15.2%) were reviews, 764 (2.6%) were proceedings papers, 45 (0.2%) were book chapters, and 55 (0.2%) were other (retracted publications, and early access) (Fig. 1). Bibliometric analyses were performed on 26085 (articles and review articles) out of 29,738 publications. 24604 (94.3%) were identified from SCIE, 1350 (5.2%) were identified from ESCI and 1263 (4.8%) were identified from SSCI and 917 (3.5%) were identified from others. Twenty-seven languages of publication were identified in the 26085 articles retrieved. The three predominant languages were English (n = 24751; 94.9%), German (n = 608; 2.3%) and Spanish (n = 193; 0.7%). All other languages including French, Turkish, Russian, Portuguese, Polish, Czech, Italian, Japanese, Korean, Hungarian and Chinese amounted to less than 2%. **Development of publications** 640 articles were published in 2001, increasing to 2222 in 2020. The mean number of articles published over the period is 1304.3 per year. Fig. 2A indicates that the number of articles increased steadily during the 20-year period. The overall number of scientific publications in

WoS increased 3.5-fold. The largest growth in publications since 2001 was between 2004 and

2005, from 717 to 910 publications, an annual growth rate of 26.9%. The year 2020 (2222 papers) was the peak of the number of literatures. Of the 26085 articles, 17084 (65.5%) were published in the last decade, compared with 9001 (34.5%) in the decade prior. The average growth rate of the literature related to osteoporosis treatment was 6.65% over the last 20 years. Using the cumulative number of publications, we calculated the linear adjustment and found y = 80.7586x - 161061 with $r^2 = 0.974$ (Fig. 2B). It is predicted that the number of publications will reach 2475 by 2025 according to the curve model. Distribution of the countries and active authors Authors from a total of 133 countries or regions contributed to the 26085 published articles. The distribution of the top productive world countries is demonstrated in Table 1. The USA has the largest number of publications. The top productive countries were the USA, China, Germany, England, and Japan. The top three countries accounted for 49.5% of all articles. Publications from the USA had the highest h-index (234, citations per article =49.87), followed by those from the England (h-index= 144; citations per article = 53.98) and those from Canada (h-index = 120; citations per article = 53.78). The top active 5 authors who had the highest number of publications on this issue were Reginster JY (259), Cooper C (220), Kanis JA (210), Eastell R (154), and Lewiecki EM (142).**Highly contributive institutions** The top active 5 universities that had the highest number of publications on this issue were University of California System (906, 3.5%), Harvard university (676, 2.6%), Institut National de la Santé et de la Recherché Medicale (521, 2.0%), University of Sheffield (486, 1.8%), and University of California San Francisco (447, 1.7%). Thus, although there is no doubt that USA currently has the most powerful impact on the field with respect to both

150	productivity and contribution, European institutions also play an outstanding role. Institutions
151	from Asia, South America, and Africa were not among the top 10. Table 2 shows the 10
152	organizations that have contributed the most in the field of osteoporosis treatment.
153	Active research areas and active journals
154	Based on the JCR categories, the publication output data was distributed into subject
155	categories. Quite logically the most frequent category was by far Endocrinology Metabolism
156	(6834, 26.2%) followed by Pharmacology Pharmacy (2521, 9.7%), Orthopedics (2428, 9.3%),
157	Medicine General Internal (2139, 8.2%), and Medicine Research Experimental (1738, 6.7%).
158	The top 10 journals that had the highest number of publications about osteoporosis treatment
159	and the total number of citations are listed in Table 3. Osteoporosis International (IF: 4.507)
160	was the highest-ranking journal. The top 3 journals that had the highest number of
161	publications were Osteoporosis International (1,679; 6.4%), Bone (832, 3.2%), and Journal of
162	Bone and Mineral Research (727; 2.8%), accounting for 12.4% of all published literature
163	relating to the field. The New England Journal of Medicine, which had the highest 2020
164	impact factor (91.245) among all of these journals, published 36 articles.
165	Citation analysis
166	Table 4 shows the top-cited 10 articles that were analyzed bibliometrically according to the
167	total number of citations in the 2001 to 2020 period. The last column of Table 4 shows the
168	average number of citations of the articles per year. The highest number of citations of a
169	single article belonged to Holick MF of the Boston University (4728 citations), which was
170	published in Journal of Clinical Endocrinology & Metabolism. According to our analysis of
171	the WoS database, all highly cited articles (151) related to osteoporosis treatment had been
172	cited 46916 times since 2001 (46671 times without self-citations). The cited frequency per
173	paper was 310.7 times.
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	 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173

175	
176	Drug classes
177	In terms of drug classes, the anti-osteoporosis medication most frequently researched were
178	bisphophonate (9997), followed by SERM (3801), denosumab (2820), and teriparatide (2051).
179	The increase in number of publications on each drug was consistent and stable in general, but
180	the number of publications related to SERM has fluctuated slightly over the past 20 years.
181	Figure 3 shows that the relative supremacy of the bisphosphonate and SERM has declined
182	over the recent 5 years. On the contrary, increasing trends are observed for denosumab and
183	teriparatide during the last two decades (Fig. 3). The increase in publications on denosumab
184	jumped significantly between 2016–2017 (growth rate = 26%). There was a statistically
185	significant difference in the rate of increase of all publications on denosumab and teriparatide
186	compared to all publications on osteoporosis treatment over the study period ($p=0.001$ and
187	p=0.019, respectively). All articles related to currently licensed romosozumab were
188	published between 2014 and 2020.
189	

190 Discussion

Bibliometrics is increasingly used to assess the quantity and quality of scientific research output in many research fields worldwide. Very little information on publication trends has so far been published in the osteoporosis treatment field. In this bibliometric study, we present the results of publication on the topic of osteoporosis treatment published between 2001 and 2020. We analyzed countries, institutions, journals, and authors that have made high contributions to this field and have discovered the direction of rapid development that may become future trends to attract scholars, which will provide convenience and shortcuts for later research.

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Bibliometric studies have progressed in many scientific fields, including cardiovascular disease¹⁴, respiratory medicine¹⁵, gastrointestinal diseases¹⁶, diabetes¹⁷, and ophthalmic studies¹⁸. In recent years, a large volume of literature has become available to practitioners prescribing anti-osteoporosis medication. According to our study, over the past 20 years, the number of articles about osteoporosis treatment has shown an increasing trend in general. This may be due to the rapid increase in the number of patients with osteoporosis with the aging of the population, and the continuous penetration of the concept of "fracture prevention" has prompted an increasing number of physicians, surgeons and patients to have an interest in osteoporosis treatment. This in turn stimulates the research and development of alternate therapies by academic institutes as well as pharmaceutical companies for establishing novel osteoporosis treatment strategies with high potency and low complication compared to conventional modalities. Given the situation of ageing populations in most developing countries, the number of patients with osteoporosis is expected to increase in the coming years¹⁹. We predict that the trend in the next 5 years or even 10 years will have an even more significant growth. The increase in the number of high-quality research studies can be an indicator of rapid improvement in the country's level of education, service delivery, and shift from a production-based economy to a knowledge-based economy²⁰. The USA is by far the most productive country and is responsible for the greatest of number of citations, suggesting that there were both quality and quantity in their publications regarding osteoporosis treatment research. This is mainly attributed to the USA having the most advanced medical research level and the strongest economic strength around the world. China also has had many publications regarding osteoporosis treatment in the recent years. China ranked second in total number of articles, but seventh in citation frequency and tenth in h-index. This suggested that the quality of articles from China still required improvements.

The results of this study may be helpful for all those involved in worldwide osteoporosis treatment research. Fellows and researchers choosing an institution for advanced work may be interested in such an analysis. Governments and policy makers can also ascertain the most effective countries and institutions in the world in this field, and this analysis may assist them to apprehend and predict the dynamic directions of osteoporosis research and to target resources so that further developments can be encouraged, supported and monitored. According to our study, Osteoporosis International, Bone, and Journal of Bone and Mineral Research are the top three productive journals on osteoporosis treatment, indicating that there will be more studies on this topic to be published on these journals. Given its reliable content, we can expect future breakthroughs in this field to be published there, and authors interested in osteoporosis treatment should pay more attention to these journals. We believe that our study can help clinicians and researchers better understand osteoporosis research worldwide and be useful, for example, in choosing appropriate journals for publication and collaborations. Journals can determine where they stand in relation to other journals in publishing articles related to osteoporosis treatment. Impact factors have been extensively used to evaluate the quality of a journal²¹. In our study, we presented the top ten journals with the highest number of articles and their impact factors, but further analysis and discussion are required. Journals with high impact factors occasionally publish low-quality articles, and doubts about the importance of impact factors may remain²². A large volume of literature has concurrently become available to practitioners prescribing various anti-osteoporosis medications. However, the quality of this literature varies substantially, making it challenging for clinicians attempting to utilize the best available evidence. A bibliometric analysis is one of the methods used to quantitatively examine a research field. Describing the utilization and scope of the most influential anti-osteoporosis medication literature is useful in explaining the current research landscape and helps to direct

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 future research relevant to the community for osteoporosis treatment. According to the present study, bisphosphonate was the most studied drug for osteoporosis treatment. However, fewer papers have been published on bisphosphonates over the last years. This is not surprising as bisphosphonates had been a hot research topic between 2010 and 2015. The plateauing and subsequent decline in the use of bisphosphonates is noted from 2015 to 2020, which follows reports of safety concerns in popular media despite consensus reports documenting their safety in the scientific literature²³. On the contrary, many of the publications related to denosumab have shaped the current research and clinical landscape. Several factors may have contributed to the switch from traditional bisphosphonates to denosumab in the outpatient management of osteoporosis. Hadji et al²⁴ recently described that the 2-year persistence of denosumab was 39.8%, which was 1.5-2 times higher than that for bisphosphonates, and that risk of discontinuation was significantly lower for denosumab than for bisphosphonates. Patient preference to 6-monthly denosumab injections versus daily oral tablets or quarterly bisphosphonates was not surprising in relation to the more acceptable route of administration (subcutaneously) and the less frequent dosing regimen of the 6-monthly treatment option. This study presents data related to currently licensed anti-osteoporosis medications, and newer drugs are constantly under development. During the study period, romosozumab received regulatory approval for the treatment of severe osteoporosis. Concurrently, many of the studies related to currently licensed romosozumab show superiority compared with older classes of anti-osteoporosis medications²⁵. There are some limitations to this study. First, we only utilize WoS to formulate our literature search, not the Medline or Embase database, and therefore it is plausible some studies about osteoporosis treatment not included in this search engine were excluded. Although relatively objective and comprehensive, our conclusions may not be generalizable. However, it appears that no perfect medical database exists, and WoS represents the largest bibliometric database

274	currently available ^{5, 26} . Second, bibliometric data are changing over time, there may have
275	different conclusion with the time passes by. So this study should be updated in the future.
276	Another significant limitation is the search terms that were used, which may not have
277	identified all the publications related to the subject of the study completely.
278	In conclusion, there has been a consistent increase in the volume of published articles on
279	osteoporosis treatment by the scientific community over the 20-year period. This study
280	identified which journals in this field published more articles about osteoporosis treatment
281	and which articles in these journals received more citations. Publication trends in
282	osteoporosis treatment are useful to monitor publication output per country or continent, to
283	monitor research interests in drug classes, and to see applications of new methods to the field.
284	We believe that our study provides a systematic analysis of osteoporosis treatment and could
285	be a beneficial guide for clinicians and scientists.
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287 288	Declaration of conflicting interests
	Declaration of conflicting interests The author(s) declared no potential conflicts of interest with respect to the research,
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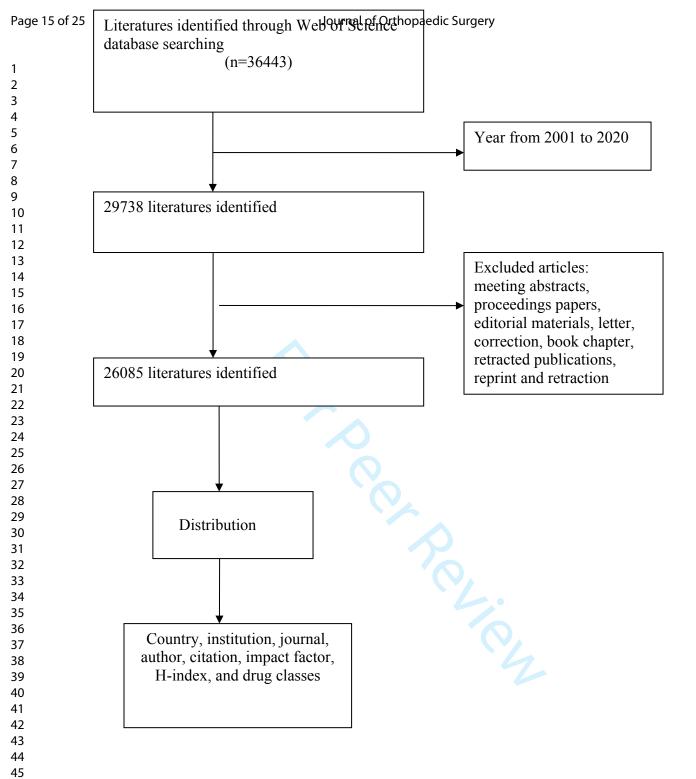


Figure 1. Flow chart of literature filtering included in this study

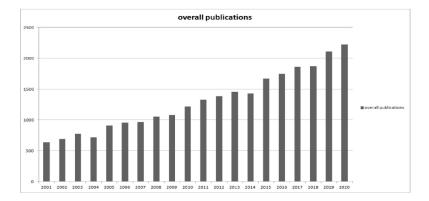
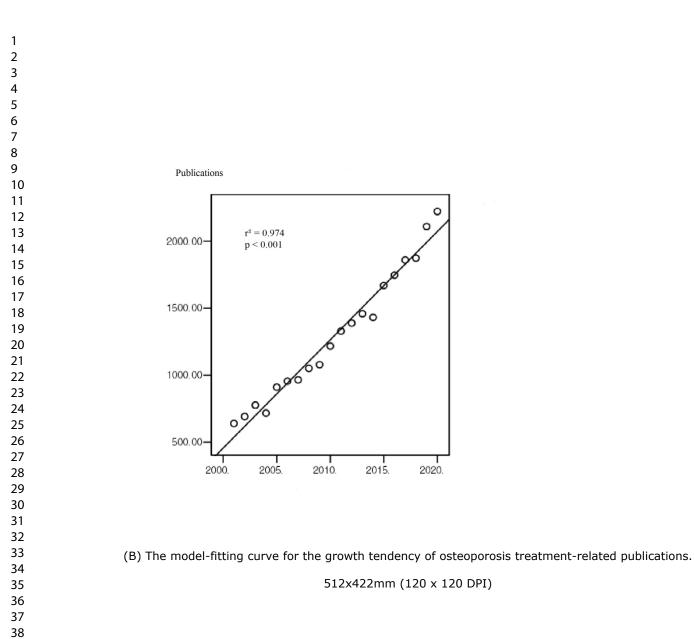


Figure 2. (A) Distribution of yearly publications on osteoporosis treatment from 2001 to 2020

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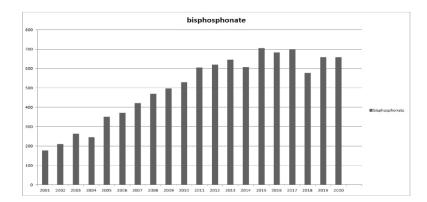
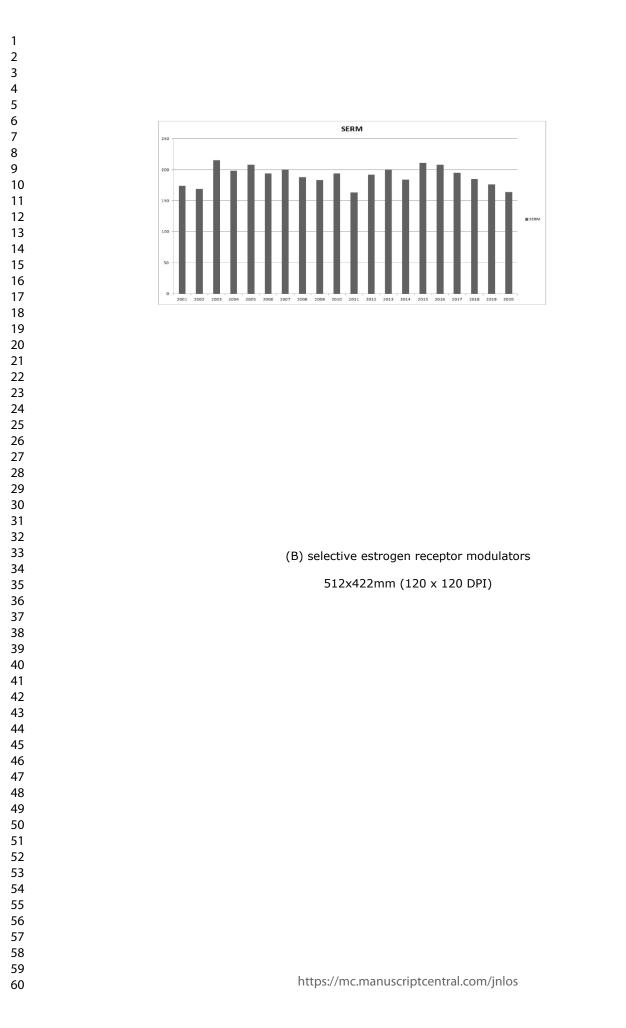
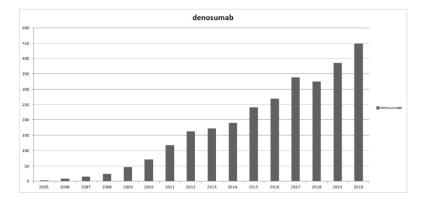


Figure 3. Distribution of yearly publications on each anti-osteoporosis medication (A) bisphosphonate

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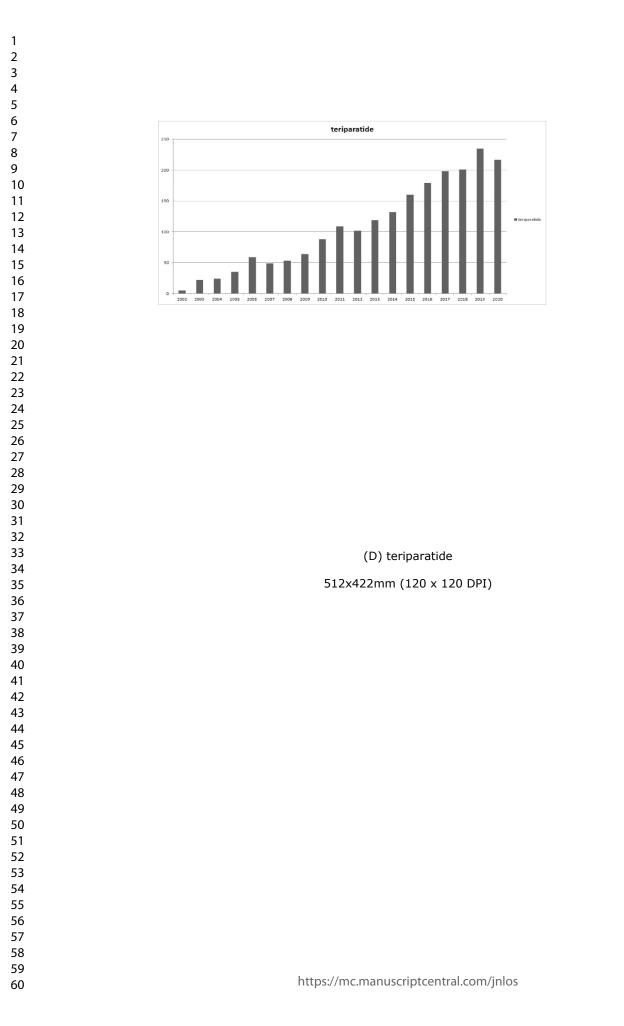
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(C) denosumab

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Table 1. Distribution	of publications ir	n the top 10 countries
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Rank	Country	Number of	Percentage	Total	Average	h-index
		publications	of total (%)	citations	citations	
1	USA	7504	28.8	374187	49.87	234
2	China	3389	12.9	58952	17.4	83
3	Germany	2030	7.8	66171	32.6	109
4	England	2023	7.7	109354	53.98	144
5	Japan	1809	6.9	41133	22.74	84
6	Italy	1627	6.2	63095	38.78	106
7	Canada	1451	5.6	78192	53.78	120
8	France	1187	4.6	62554	52.7	120
9	Australia	1066	4.0	55716	52.27	104
10	Spain	986	3.8	31731	32.18	86

Review

Rank	Institute	Number of publications	Percentage of total (%)	Total citations	h-index
1	University of California System	906	3.5	70755	123
2	Harvard university	676	2.6	53613	105
3Institut National de la Santé et de la Recherché Medicale		521	2.0	33397	95
4	University of Sheffield	486	1.8	37167	94
5	University of California San Francisco	447	1.7	41796	93
6	US Department of Veterans Affairs	408	1.6	24522	81
7	Veterans Health Administration	397	1.5	24364	81
8	Assistance publique- Hopitaux de Paris	385	1.5	22370	77
9	Columbia University	385	1.5	28440	86
10	University of Toronto	376	1.4	18741	68

Table 2. Top 10 institutions contributing to publications on osteoporosis treatment

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Rank	Journal	Number of publications	Percentage of total (%)	Number of citations	Impact factor
1	Osteoporosis International	1679	6.4	65039	4.507
2	Bone	832	3.2	34061	4.147
3	Journal of Bone and Mineral Research	727	2.8	50427	6.741
4	Calcified Tissue International	362	1.4	10948	3.86
5	Journal of Bone and Mineral Metabolism	331	1.3	6185	2.626
6	Journal of Clinical Endocrinology and Metabolism	312	1.2	31344	5.958
7	Archives of Osteoporosis	281	1.1	3836	2.017
8	PLOS ONE	238	0.9	5042	3.240
9	Journal of Clinical Densitometry	216	0.8	4133	2.617
10	Current Osteoporosis Reports	207	0.8	3512	4.69

Table 4. Top 10 most cited articles from 2001 to 2020.

Rank	Title	Year	Journal	Total citations	Average
1	Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline	2011	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	4728	429.82
2	Clinician's Guide to Prevention and Treatment of Osteoporosis	2014	OSTEOPOROSIS INT ERNATIONAL	1424	178
3	Osteoporosis: now and the future	2011	LANCET	1298	118
4	WNT signaling in bone homeostasis and disease: from human mutations to treatments	2013	NATURE MEDICINE	1109	123.22
5	Osteoporosis in the European Union: medical management, epidemiology and economic burden	2013	ARCHIVES OF OSTEOPOROSIS	941	104.56
6	Lack of Exercise Is a Major Cause of Chronic Diseases	2012	COMPREHENSIVE PHYSIOLOGY	927	92.7
7	European guidance for the diagnosis and management of osteoporosis in postmenopausal women	2013	OSTEOPOROSIS INT ERNATIONAL	852	94.67
8	Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases	2015	SCANDINAVIAN JOURNAL OF MEDICINE & SCIENCE IN SPORTS	801	114.43
9	Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture	2012	NATURE GENETICS	766	76.6
10	The Achilles' heel of senescent cells: from transcriptome to senolytic drugs	2015	AGING CELL	736	105.14