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Translational horizons in stem cell therapy for osteonecrosis of the femoral head: a journey from basic research to clinical practice through bibliometric insights

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Abstract

Background Osteonecrosis of the femoral head (ONFH) significantly impacts young and middle-aged adults, with steroid use implicated in many cases. Traditional treatments have limited efficacy, prompting a shift towards innovative approaches, such as stem cell therapy, offering less invasive regenerative solutions.

Methods Using bibliometric analysis from 1997 to 2023, we identified 392 articles on stem cell therapy for ONFH from the Web of Science Core Collection and analysed them using VOSviewer and CiteSpace to identify key trends and research directions.

Results From 1997 to 2023, stem cell therapy for ONFH research expanded significantly, with 392 articles evidencing global collaboration, particularly from China, the United States and South Korea. The field is characterised by 158 core authors across 26 clusters and contributions from 417 institutions in 104 research clusters, with Shanghai Jiao Tong University as a notable leader. This research is disseminated through 23 journal clusters, emphasising interdisciplinary work, with *Clinical Orthopaedics and Related Research* among the most influential journals. Key findings include the identification of the most influential papers, highlighting advances, such as use of autologous mesenchymal stem cells (MSCs) and innovative delivery mechanisms. High-frequency keyword analysis further mapped the evolution of the field, from basic mechanisms to advanced therapies, underscoring a trend towards more targeted stem cell treatments for ONFH.

Conclusion Stem cell therapy for ONFH has advanced significantly, showcasing a successful transition from basic research to clinical practice, particularly highlighted by developments in use of autologous MSCs and delivery methods. Future research will focus on refining therapies through exosome technology, targeted modulation of stress and inflammation and integration with surgical techniques, with the aim of tailored patient care and improved ONFH outcomes.

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Keywords Basic research, Bibliometric, Clinical practice, Osteonecrosis of the femoral head, Stem cell therapy

Introduction

Osteonecrosis of the femoral head (ONFH) is a debilitating condition with significant adverse effects on quality of life for young and middle-aged adults by impeding mobility and inducing severe pain. Characterised by the death of bone tissue due to inadequate blood supply, it has a multifactorial aetiology encompassing corticosteroid use [1], alcohol abuse [2], trauma [3] and genetic predisposition [4]. Based on statistics from Peking Union Medical College Hospital for the past 20 years, steroid-induced ONFH has accounted for 46.03% of all ONFH cases, highlighting its prevalence as a clinical challenge. Despite extensive research, the precise pathogenesis of ONFH remains elusive, with postulated mechanisms ranging from cellular apoptosis [5] and genetic polymorphisms [4] to intraosseous hypertension [6], immunological factors [7] and disorders of lipid metabolism [8]. This complexity underscores the pressing need for a deeper understanding and the development of more effective treatment modalities.

For patients with early-stage ONFH, clinical approaches predominantly involve core decompression (CD) and bone grafting, which, despite their therapeutic potential, are limited by significant surgical trauma and challenges in controlling the volume and shape of the harvested bone [9, 10]. As ONFH advances, leading to the collapse of the femoral head, total hip arthroplasty (THA) emerges as an effective intervention, significantly improving patients' quality of life. However, THA has a number of drawbacks, including inadequate rotational resistance and fixation that may contribute to prosthetic loosening or premature wear, thus impacting the longevity of the implant [11]. Furthermore, the finite lifespan of prosthetic joints necessitates potential revision surgeries, which is especially concerning for younger patients, adding to the economic and psychological burden [12]. These challenges highlight the critical need to develop more effective and minimally invasive treatment modalities, propelling ongoing research to explore innovative solutions for ONFH management.

In this context, stem cell therapy has emerged as a promising alternative for treating ONFH, harnessing the potential to regenerate damaged bone tissue and improve blood supply [13]. This innovative approach marks a paradigm shift in ONFH treatment, supported by extensive research into the complex pathophysiology of the condition. In 2002, a ground-breaking study at Henri Mondor Hospital in France introduced autologous bone marrow mesenchymal stem cell (MSC) transplantation alongside CD in 116 patients with early-stage ONFH, documenting significant improvements in necrotic area repair over a follow-up period of 5–11 years and setting a precedent for regenerative treatment options in ONFH management [14]. Further validation of the efficacy of this therapy was provided by a 30-year follow-up study in 2018 by the same institution, in which 48% of treated hips showed no signs of collapse. This demonstrated the long-term effectiveness of the therapy in enhancing local blood supply, reducing inflammation and increasing bone density, thus confirming the enduring success of MSC therapy in clinical settings for ONFH treatment [15]. These milestones not only underscore the effectiveness of stem cell therapy in managing ONFH but also highlight the successful translation of foundational research into clinical practice, setting a new benchmark for orthopaedic treatment strategies.

This study extends our bibliometric exploration into the dynamic realm of stem cell therapy research for ONFH, building on our previous analysis of hip-preserving treatments for early-stage ONFH. Our earlier work concluded that there is growing interest in joint-preserving surgical options for cases in the early stages, with stem cell therapy emerging as a particularly promising method for preserving hip joint function [16]. Leveraging bibliometric methods to navigate the extensive landscape of stem cell therapy research for ONFH from 1997 to 2023, this study was performed to shed light on the evolution of the field, key contributors and the emerging trends that have shaped its trajectory. By employing statistical tools to analyse scientific publications, this analysis enabled the identification of growth trends, collaborative networks and core themes within the domain of stem cell therapy for ONFH. Through a systematic review and visualisation of data from a bibliometric perspective, we not only highlight the scholarly impact and interdisciplinary collaborations driving advancements in stem cell therapy but also pave the way for future research directions. This effort underscores the potential of stem cell therapy to transform the management of ONFH, building on a foundation that recognises stem cell therapy as a forward-looking approach to preserving hip joint functionality and thus offer new hope to those affected by this challenging condition.

Materials and methods

Data sources and search strategies

In our bibliometric analysis of stem cell therapy for ONFH, the selection of the most appropriate database was critical. Initially, we chose the Web of Science (WoS) for its excellence in comprehensive early literature coverage and superior citation tracking capabilities over other databases, such as PubMed and Scopus [17]. This precise

citation tracking highlights a key advantage of WoS—the ability to provide a substantial number of citations, which is crucial for assessing the impact and academic value of the literature [18]. Further refining our data source, we focused on the WoS Core Collection, specifically selecting the Social Sciences Citation Index (SSCI) and the Science Citation Index Expanded (SCI-Expanded) to ensure a broad and authoritative analysis. The search strategy was developed based on PubMed Medical Subject Headings (MeSH) terms as follows: TS = (((Femur Head Necrosis) OR (Femur Head Necroses) OR (Osteonecrosis of the Femoral Head) OR (Head Necrosis, Femur) OR (Necrosis, Femur Head) OR (Aseptic Necrosis of Femur Head) OR (Necrosis, Aseptic, of Femur Head) OR (Necrosis, Avascular, of Femur Head) OR (Ischemic Necrosis Of Femoral Head) OR (Femoral Head, Avascular Necrosis Of) OR (Avascular Necrosis Of Femoral Head, Primary) OR (Avascular Necrosis of Femur Head)) AND ((Stem Cells) OR (Cell, Stem) OR (Cells, Stem) OR (Stem Cell) OR (Progenitor Cells) OR (Cell, Progenitor) OR (Cells, Progenitor) OR (Progenitor Cell) OR (Mother Cells) OR (Cell, Mother) OR (Cells, Mother) OR (Mother Cell) OR (Colony-Forming Unit) OR (Colony Forming Unit) OR (Colony-Forming Units) OR (Colony Forming Units))).

Data collection and cleaning

After searching the WoS Core Collection, we discovered the first research article on stem cell therapy for ONFH published in 1997. Given our focus on the current research trends in stem cell therapy for ONFH and the potential for review articles to skew these trends, reviews were excluded from the analysis. We set our search from 1 January 1997 to 31 December 2023, including all languages and specifically targeting research articles. Following a rigorous selection process, we ultimately

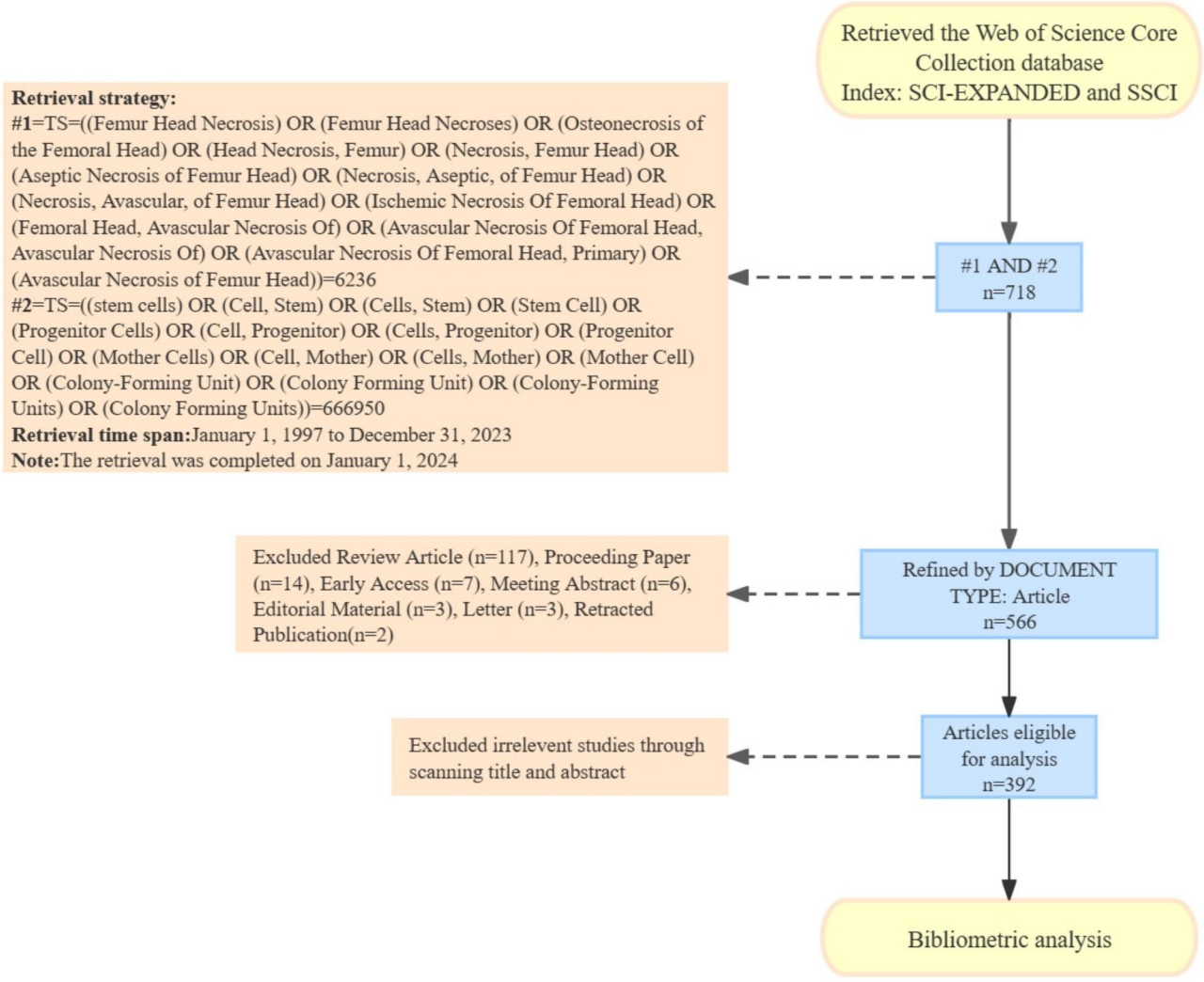

Fig. 1 The flowchart of the inclusion and exclusion process of stem cell therapy in ONFH research

included 392 research articles in the subsequent bibliometric analysis. Figure 1 illustrates our complete filtering procedure. Finally, we recorded and saved the collected raw data, including full records and cited references, for use in the subsequent bibliometric analysis.

Bibliometric analysis

Bibliometric analysis, a methodological approach using statistical tools to analyse the scientific literature, is instrumental in understanding the patterns and trends within specific research fields. This approach not only tracks publication and citation trends but also delves into the deeper knowledge structure and developmental trajectories of a study area [19]. In the context of our research, this method was applied to the field of stem cell therapy for ONFH to identify key themes, chart scientific discourse and pinpoint research gaps.

To enrich this exploration, we incorporated CiteSpace and VOSviewer as bibliometric tools. These tools have outstanding capacity to dissect and visualise the intricate patterns and relationships within dense scientific data sets particularly pertinent to stem cell therapy for ONFH. CiteSpace excels in pinpointing evolving trends, emerging hotspots and paradigm shifts within the knowledge domains of stem cell therapy, facilitated by its sophisticated co-citation networks and temporal visualisations [20]. VOSviewer complements this by mapping the vast literature landscape, elucidating the nuanced interplay between diverse research topics within ONFH treatment [21]. Using the combination of CiteSpace and VOSviewer, we aimed to obtain a nuanced, multi-dimensional view of the field. This will not only shed light on existing research contours but also guide future endeavours in stem cell therapy for ONFH, setting a benchmark for meticulous and impactful research in this area.

Results

Scholarly impact and growth trends

From 1997 to 2023, a total of 392 research articles on stem cell therapy for ONFH were authored by 2011 researchers from 417 organisations across 24 countries. These works have collectively garnered 9479 citations, averaging 24.18 citations per article. The H-index, which measures both the productivity and citation impact of the publications, is a notable 51.

The global literature on stem cell therapy for ONFH increased markedly from 1997 to 2023. Starting from a solitary publication in 1997, there have been significant increases in both the number of annual publications and contributing authors. The citation count, a measure of the influence of the research, has shown a similar upward trend, particularly after 2010, with a peak in 2022. These trends are depicted in Fig. 2, which encapsulates the growth in publication number, authorship and citation frequency over the 26-year period.

Collaboration dynamics among core authors

In our previous research, we detailed criteria for identifying core authors in a field based on publication numbers [16]. Generally, core authors are those who have authored more than half of the publications on a given topic. Applying this to the field of stem cell therapy for

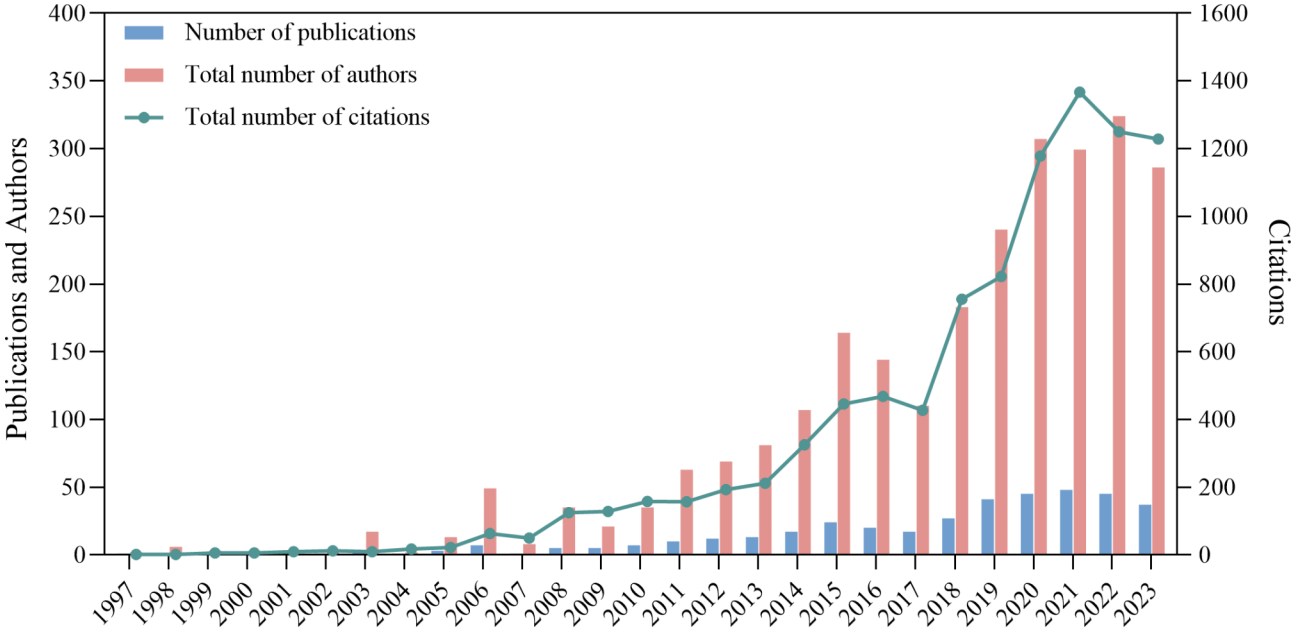

Fig. 2 Statistical chart of the total number of papers, number of authors, and citation counts for stem cell therapy for ONFH research each year from 1997 to 2023

Fig. 3 Comprehensive mapping of core authors, institutions, and global collaboration in ONFH stem cell therapy research. (**A**) Co-authorship analysis of 158 core authors. (**B**) Co-authorship analysis of 417 institutions. (**C**) Geographic distribution and country cooperation

Table 1 Top 10 most productive authors

Rank	Author	Country	Affiliation	Publications	TC	AC
1	Zhang, C. Q.	China	Shanghai Jiao Tong University Affiliated Sixth People's Hospital	16	563	35.2
2	Zhang, J.	China	The First Affiliated Hospital of Chongqing Medical University	13	161	12.4
3	Peng, W. X.	China	The Affiliated Hospital of Guizhou Medical University	11	157	14.3
4	Gao, Y. S.	China	Shanghai Jiao Tong University Affiliated Sixth People's Hospital	11	236	21.5
5	Feng, Y.	China	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	10	388	38.8
6	Yang, S. H.	China	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	10	394	39.4
7	He, W.	China	The Third Affiliated Hospital of Guangzhou University of Chinese Medicine	10	200	20.0
8	Kang, P. D.	China	West China Hospital, Sichuan University	10	157	15.7
9	Tong, P. J.	China	The First Affiliated Hospital of Zhejiang Chinese Medicine University	10	162	16.2
10	Li, T.	China	The Affiliated Hospital of Qingdao University	9	147	16.3

AC, average citations; TC, total citations

ONFH, we designated authors with three or more publications as core authors, and identified 158 individuals in this area. We developed a collaboration network from 158 authors, forming 26 clusters (Fig. 3A). Notably, Cluster 1, led by Professor Feng Yong from Huazhong University of Science and Technology, collaborated closely with Cluster 3, directed by Professor Zhang Changqing from Shanghai Jiao Tong University. Other key clusters include Cluster 2 under Professor Wang Yisheng from Zhengzhou University, Cluster 4 by Professor Zhao Dewei of Dalian University and Clusters 5–8 led by Professors Chen Tingmei, He Wei, Zhang Jian and Wang Kunzheng, respectively. Among these, at least two clusters have established intercluster collaborations. The extent

Table 2 Top 10 most productive institutions

Rank	Institution	Country	Publications	TC	AC
1	Shanghai Jiao Tong University	China	38	1046	27.5
2	Huazhong University of Science and Technology	China	24	723	30.1
3	Xi'an Jiaotong University	China	20	338	16.9
4	Zhengzhou University	China	18	511	28.4
5	Sichuan University	China	16	199	12.4
6	Wuhan University	China	14	317	22.6
7	Shandong University	China	14	238	17.0
8	Guizhou Medical University	China	12	169	14.1
9	Zhejiang Chinese Medical University	China	12	162	13.5
10	Qingdao University	China	11	46	4.2

Table 3 Top 10 most productive countries

Rank	Country	Continent	Publications	AC	TLS
1	China	Asia	309	19.7	15
2	USA	North America	26	36.3	15
3	South Korea	Asia	13	34.4	2
4	France	Europe	9	101.0	5
5	Japan	Asia	9	37.8	2
6	Italy	Europe	8	26.1	4
7	Spain	Europe	8	9.1	3
8	China Taiwan	Asia	8	28.0	1
9	Germany	Europe	6	27.0	3
10	UK	Europe	5	12.0	2

TLS, total link strength

of individual contributions within these clusters can be further appreciated by consulting Table 1, which lists the top 10 productive authors in this field, underscoring their centrality and influence in the research network.

Core institutions and collaborative networks

The study encompassed 417 institutions, each presented as nodes in Fig. 3B, to illustrate the widespread institutional engagement in this research domain. Each node is colour-coded to represent one of the 104 research clusters and node size indicating the institution's publication count. The various colours of the nodes indicate different research clusters, with each colour grouping institutions that share a similar research focus. Thicker lines between nodes illustrate more frequent collaborations, highlighting the intensity of research exchanges. In particular, the primary cluster, which includes Sichuan and Shandong Universities, shows strong connectivity, indicative of a shared research direction. Complementing this, the data in Table 2 highlight the top 10 most productive institutions, with Shanghai Jiao Tong University leading in terms of publication volume, followed by other influential institutions that contribute to the network's density and diversity of research collaboration in ONFH stem cell therapy.

Global collaboration and productivity

The distribution of scholarly output in stem cell therapy for ONFH reflects a significant international scope, with 392 papers authored by a collaborative network spanning 24 countries. Table 3 ranks the top 10 nations in ONFH stem cell therapy research, with China leading at 309 publications followed by the United States and South Korea with 26 and 13 papers, respectively. France, Italy, Spain, Germany, the United Kingdom, Japan and China Taiwan also make notable contributions, with France garnering the highest average number of citations. The detailed network interactions among these countries, indicating the frequency and strength of their research collaborations, are visually captured in Fig. 3C. The map showcases China's dominant role in publication volume while highlighting the significant collaborative ties between China and South Korea, as well as the collective European research endeavours.

Journal clusters and citations

Journal cluster analysis unveiled a network of 23 clusters that capture the collaborative essence and expansive reach of stem cell therapy research for ONFH (Fig. 4A). Figure 4B elaborates on the intricate journal interactions, indicating that publications in molecular/biology/immunology often reference studies from the sports/rehabilitation/sport and molecular/biology/genetics fields,

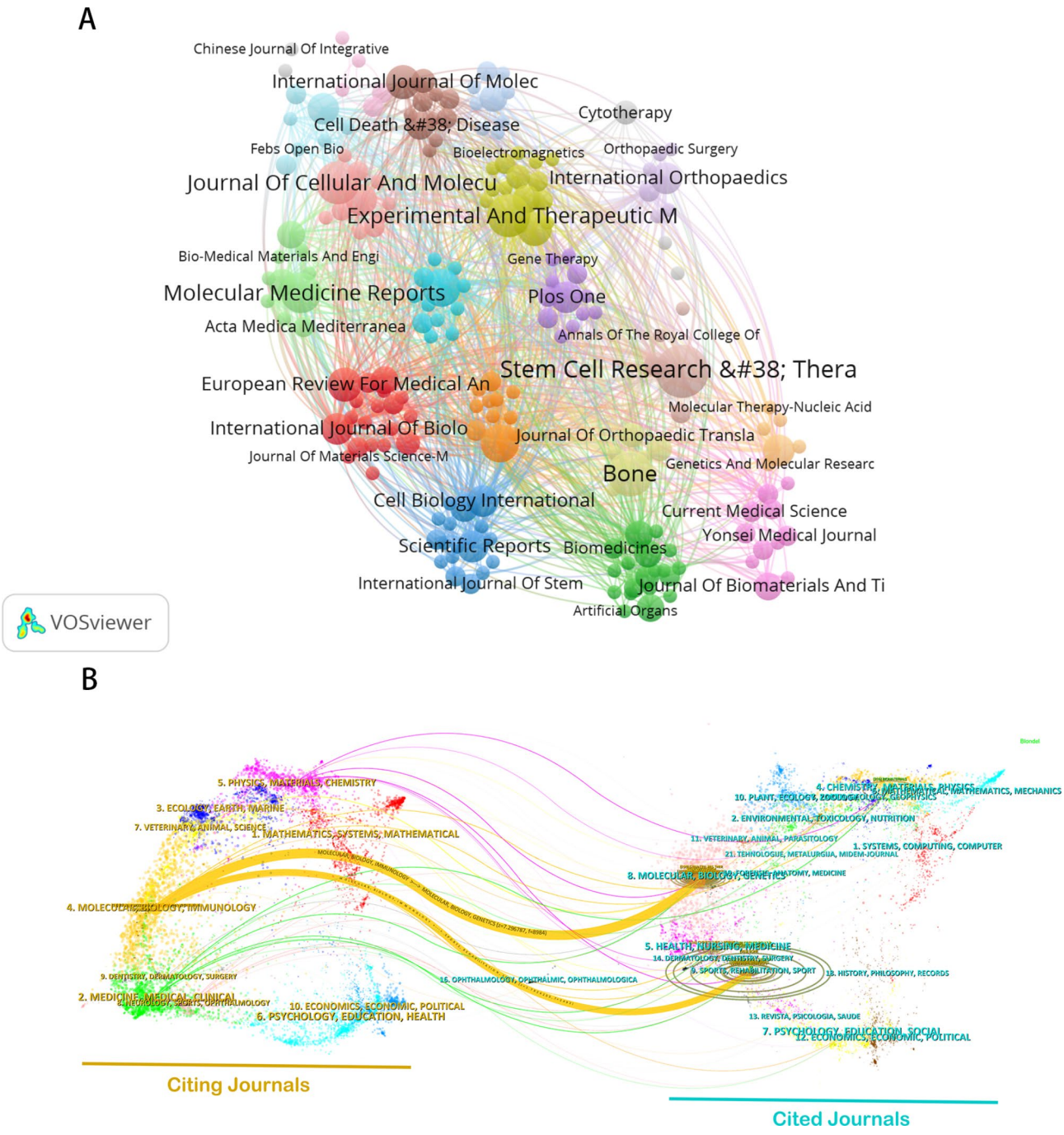

Fig. 4 Journal landscape in ONFH stem cell therapy research network clusters and dual-map overlays. (**A**) Network map of journal cluster. (**B**) The dual-map overlay of journals

underscoring a rich interdisciplinary dialogue. Notably, the top three most cited journals are *Clinical Orthopaedics and Related Research*, *Journal of Bone and Joint Surgery-American Volume* and *Bone*. Table 4 lists the top 10 contributing journals, with *Stem Cell Research Therapy* at the top with 14 publications and a Q1-ranked impact factor of 7.5. *Bone* also showed substantial influence with 10 publications. Taken together, Fig. 4A and B, along with Table 4, highlight the key journals driving stem cell therapy research for ONFH and underscore the global collaboration, with significant input from the United Kingdom, United States and Greece, thus delineating the publishing dynamics and knowledge dissemination in the field.

Table 4 Top 10 related popular journals

Rank	Journals	Publications	AC	IF-2022	JCR	Country
1	*Stem Cell Research Therapy*	14	23.9	7.5	Q1	UK
2	*Bone*	10	73.9	4.1	Q2	USA
3	*Experimental and Therapeutic Medicine*	9	12.0	2.7	Q4	Greece
4	*Journal of Cellular and Molecular Medicine*	9	18.1	5.3	Q2	UK
5	*Molecular Medicine Reports*	8	16.5	3.4	Q3	Greece
6	*Stem Cells International*	7	7.1	4.3	Q2	USA
7	*Clinical Orthopaedics and Related Research*	7	98.4	4.3	Q1	USA
8	*Journal of Orthopaedic Surgery and Research*	6	7.7	2.6	Q2	UK
9	*European Review for Medical and Pharmacological Sciences*	6	9.6	3.3	Q2	Italy
10	*International Journal of Molecular Medicine*	6	16.7	5.4	Q2	USA

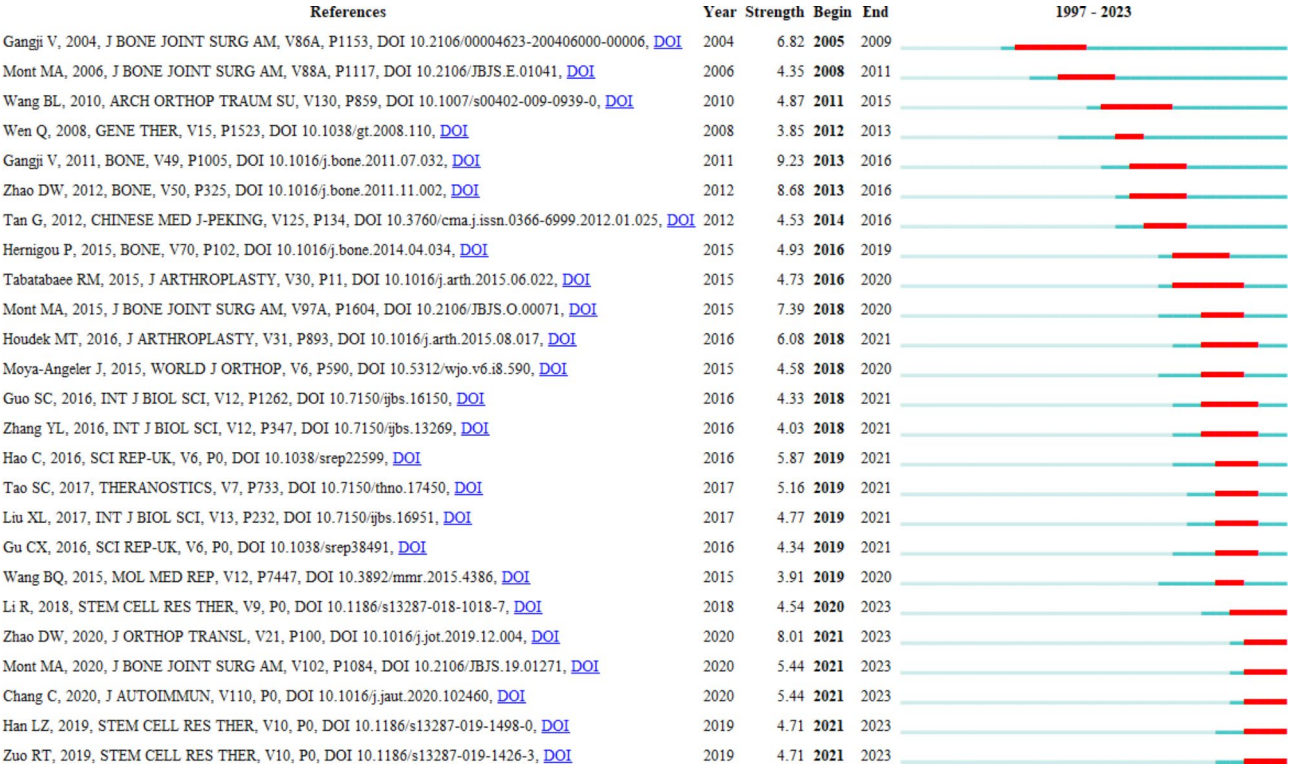

Fig. 5 Top 25 references with the strongest citation bursts in stem cell therapy for ONFH research

Most influential papers

In our study, we identified the top 25 papers with the strongest citation bursts representing a sudden surge in citations for these references within the field, highlighting their significance and impact during specific periods (Fig. 5). Gangji et al.'s studies on using bone marrow cell implantation for osteonecrosis treatment marked significant milestones, receiving the highest citation bursts pre- and post-2010 [22]. Their paper introduced a groundbreaking approach, leading citations before 2010, while their 2011 follow-up, confirming long-term benefits, again peaked in citations after 2010 [23]. These bursts underscore their pivotal role in advancing regenerative orthopedic therapies. *Journal of Bone and Joint Surgery-American Volume* was the leading journal by publication volume, reflecting its central role in the dissemination of research in the field. The accompanying bar graph illustrates the citation peaks, reflecting the impact and relevance of these studies over time. Table 5 shows the top 10 most cited research papers, showcasing the application of autologous MSCs [23, 24], the use of beta-tricalcium phosphate [25] and cell-infiltratable hydrogels for improving delivery [26]. It also sheds light on the strategic approach of combining CD with bone marrow grafting [14, 27], the significant regulatory role of non-coding RNAs in osteogenesis [28] and the necessity of counteracting the adverse effects of glucocorticosteroids (GCs) on bone marrow mesenchymal stromal cells (BMSCs) [29, 30]. Furthermore, induced pluripotent stem cell-derived MSC exosomes (iPS-MSC-Exos) have

Table 5 Top 10 most cited research papers

Rank	Title	First author	First author address	Journal	Main contents	TC	Year	TC per year
1	Treatment of osteonecrosis with autologous bone marrow grafting[14]	Hernigou, P.	Hôpital Henri Mondor	*Clin Orthop Relat Res*	CD with autologous bone marrow for ONFH before collapse can improve outcomes using stem cells to regenerate bone, reducing hip replacements.	406	2002	18.5
2	Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells[24]	Zhao, D. W.	Dalian University of Technology	*Bone*	Autologous BMSC therapy for early-stage ONFH delays collapse and improves hip function over CD alone, reducing lesions safely.	236	2012	19.7
3	Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: Five year follow-up of a prospective controlled study[23]	Gangji, V.	Erasme Hospital, Université Libre de Bruxelles	*Bone*	Implanting autologous BMSCs in early-stage ONFH reduces pain and slows progression, outperforming CD.	204	2011	15.7
4	Decrease in the mesenchymal stem-cell pool in the proximal femur in corticosteroid-induced osteonecrosis[29]	Hernigou, P.	Hôpital Henri Mondor	*J Bone Joint Surg Br*	GCs reduce fibroblast colonies, impairing bone marrow cell activity and reducing stem cell counts vital for bone health.	177	1999	7.1
5	Exosomes Secreted from Human-Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Prevent Osteonecrosis of the Femoral Head by Promoting Angiogenesis[31]	Liu, X. L.	Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University	*Int J Biol Sci*	iPS-MSC-Exos transplantation boosts angiogenesis and prevents bone loss in ONFH by activating PI3K/Akt in endothelial cells.	173	2017	24.7
6	Dynamic and Cell-Infiltratable Hydrogels as Injectable Carrier of Therapeutic Cells and Drugs for Treating Challenging Bone Defects[26]	Feng, Q.	Fujian Normal University	*ACS Cent Sci*	Injectable gelatine hydrogels for treatment of steroid-induced ONFH allow easy delivery of stem cells and drugs, enhancing repair and drug delivery, and supporting minimally invasive therapy.	151	2019	30.2
7	Steroid-induced adipogenesis in a pluripotential cell line from bone marrow[30]	Cui, Q.	University of Virginia School of Medicine	*J Bone Joint Surg Am*	Dexamethasone drives BMSCs to become fat cells, not bone cells, linking steroid use to osteonecrosis and highlighting the need to tackle bone marrow fat for its prevention.	140	1997	5.2
8	Tissue-engineered approach for the treatment of steroid-induced osteonecrosis of the femoral head: transplantation of autologous mesenchymal stem cells cultured with beta-tricalcium phosphate ceramics and free vascularized fibula[25]	Kawate, K.	Nara Medical University	*Artif Organs*	Autologous MSCs with beta-tricalcium phosphate and fibula grafts showed early bone regeneration in steroid-induced ONFH treatment, promising despite limitations in severe cases.	129	2006	7.2
9	Cell therapy of hip osteonecrosis with autologous bone marrow grafting[27]	Hernigou, P.	Hôpital Henri Mondor	*Indian J Orthop*	CD and autologous bone marrow grafting in early-stage ONFH boost stem cell numbers for bone remodelling and collapse prevention, showing best results in non-collapsed hips and potential in advanced stages.	124	2009	8.3
10	Long non-coding RNA HOTAIR inhibits miR-17-5p to regulate osteogenic differentiation and proliferation in nontraumatic osteonecrosis of femoral head[28]	Wei, B. F.	Linyi People's Hospital	*PLoS One*	HOTAIR and miR-17-5p interaction influences MSC osteogenesis, indicating stem cell therapy targeting miR-17-5p/SMAD7 could address non-traumatic ONFH.	116	2017	16.6

been shown to promote angiogenesis and prevent bone loss in ONFH [31]. Taken together, these elements underscore a marked evolution towards more targeted and efficacious treatments for ONFH, as depicted in Fig. 5, and the summarised research findings in Table 5 provide a multi-faceted perspective of the research impact and clinical progress in this domain.

High-frequency keyword visualisation

To analyse trends in stem cell therapy for ONFH, we applied Price's law to 1436 keywords from 392 articles, classifying those appearing eight or more times as high-frequency terms [16, 32]. This approach yielded 97 key terms, forming the basis for the visualisations in Figs. 1, 2, 3 and 4 illustrating the main research themes and trends.

The keyword density map in Fig. 6A segments the research into four clusters. Cluster 1 (red) explores the fundamental mechanisms at the cellular level, including critical processes, such as differentiation, signalling pathways and the impact of GCs on bone biology. Cluster 2 (green) addresses therapeutic applications and bone regeneration, with a focus on MSCs and CD. Cluster 3 (blue) examines the genetics and cellular behaviour influencing osteogenesis and regeneration. Finally, cluster 4 (yellow) ties in systemic factors, such as GC usage with the pathogenesis of ONFH. This collection of terms reflects the comprehensive approach to understanding and advancing stem cell therapies in the context of ONFH. Figure 6B tracks the shift from foundational understanding towards therapeutic interventions, such as CD, and exploration of the roles of osteogenic differentiation and gene expression. This evolution points towards a refinement in treatments and the pivotal role of stem cells in tissue regeneration. Figure 6 C charts nearly three decades of research progression from basic concepts to the sophisticated study of the critical roles of MSCs and bone marrow. This underlines an integrated approach to understanding and treating ONFH, with significant focus on stem cell sources and targeted treatment areas. Finally, the citation burst analysis shown in Fig. 6D revealed temporal peaks in research interest in key topics, marking transitions in research focus from early regenerative strategies to recent interest in disease aetiology, cellular mechanisms and advanced therapeutic approaches. Taken together, these figures depict a research landscape that has matured to address the complexities of ONFH through foundational science and clinical innovations.

These figures present the detailed structure and development of the research landscape on stem cell therapy for ONFH, from densely researched concepts to temporal trends and bursts of scholarly activity.

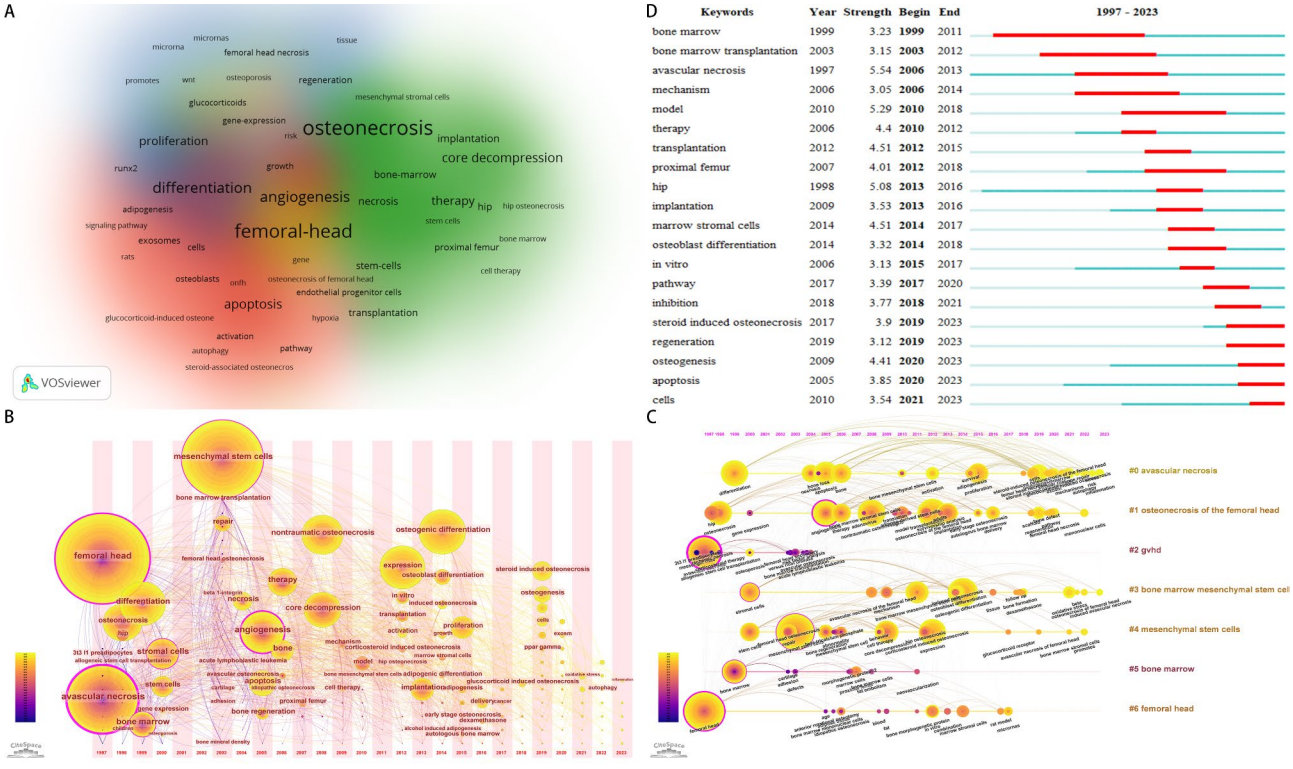

Fig. 6 Comprehensive analysis of high-frequency keywords in stem cell therapy for ONFH research from 1997 to 2023. (**A**) Visualization of high-frequency keyword density map. (**B**) High-frequency keyword timezone visualization map (**C**) High-frequency keyword timeline visualization map (**D**) Top 25 keywords with the strongest citation bursts

Discussion

Stem cell therapy for ONFH has attracted increasing attention

The journey of stem cell therapy research for ONFH from 1997 to 2023 highlights an unwavering commitment to tackling a critical health challenge. This began with a ground-breaking 1997 study on the impact of steroids on MSC differentiation, setting a robust foundation for the field by illuminating the pathophysiological roots of steroid-induced osteonecrosis and suggesting avenues for therapeutic interventions [30]. The significant increases in research interest and publications post-2013 can be traced back to Nobel Laureate Randy Schekman's assertion about the unparalleled advantages of stem cells in disease treatment, positing that stem cell technology could, in theory, cure all diseases. This statement catalysed a renewed focus within the orthopaedic community on the distinct benefits of stem cell therapy for ONFH, leading to increased research output and application in clinical settings. The collaboration of thousands of researchers and organisations globally has been instrumental in advancing this field, as evidenced by the growing body of impactful studies, underscored by a noteworthy H-index and citation count. This evolution indicates the promise of stem cell therapy to provide innovative treatments for ONFH, building upon the early foundations and interdisciplinary efforts.

ONFH stem cell therapy research forms a global network dominated by China and enriched by international partnerships

Creating collaboration maps among authors, institutions and global research efforts in stem cell therapy for ONFH allows visualisation of the academic network and its dynamics. These maps offer insights into key contributors, collaboration patterns and knowledge dissemination, facilitating more efficient and targeted research partnerships.

The field of ONFH stem cell therapy research involves a tightly-knit global network, where authors, institutions and countries are interlinked to drive scientific progress. Chinese authors and institutions lead in ONFH stem cell therapy research, forming key clusters in the global network. The concentration of top authors and institutions within China, such as those from Shanghai Jiao Tong University and Huazhong University of Science and Technology, points to a national infrastructure with robust support for ONFH research. Shanghai Jiao Tong University, represented by Professor Zhang Changqing's team, is particularly prominent in this field. Their research investigates various stem cells, such as bone marrow mononuclear cells [33], endothelial progenitor cells [34] and MSCs from adipose tissue and synovial fluid [35, 36]. They also study the complex molecular mechanisms and signalling pathways involved in disease and treatment. Their focus lies in understanding how these cells contribute to vascularisation [31, 33, 34, 37], bone regeneration [33, 36–38] and tissue repair [36, 39], particularly in preventing and reversing ONFH [31, 35, 40–44]. Furthermore, Professor Zhang's research involves the development of new therapeutic strategies, including small molecules [36, 38, 41, 43–47], gene therapy [39] and stem cell-derived exosomes [31, 35] to enhance regenerative outcomes. He also explores environmental [34, 41, 45, 46] and pharmacological [40, 43] factors influencing ONFH, with the aim of developing preventive measures. Through studies on molecular pathways, such as HIF-1α [39], Akt [45] and TLR4/NF-κB [38], Professor Zhang and his team pioneer advances in stem cell efficacy and targeted treatments for ONFH, showcasing Shanghai Jiao Tong University's leadership in combating ONFH.

Globally, China leads in ONFH research, with significant contributions from the United States, South Korea and Europe, indicating diverse international involvement. The United States and South Korea, behind China in publications and France's high citation level, highlight a research world where both quality and quantity matter. The collaboration network highlights China as a central and prolific player in global ONFH stem cell therapy research. Collaboration in stem cell therapy for ONFH, notably between China, South Korea and Europe, forms specialised research clusters but also prompts questions on the global applicability of the findings, given regional genetic and environmental differences. The dominance of Chinese research in ONFH stem cell therapy emphasises the importance of collaborative frameworks to incorporate diverse clinical insights and patient experiences globally, ensuring research findings are universally applicable. The integration of authors, institutions and countries in the narrative shows that advancing ONFH stem cell therapy relies on fostering cross-border collaborations, valuing individual expertise and leveraging collective institutional strength. Recognising strategic alliances among countries is crucial to pushing boundaries and translating knowledge into accessible treatments.

In conclusion, while the data reflect a certain concentration of research in China, the real power of the scientific endeavour lies in the interconnectivity and mutual reinforcement of authors, institutions and countries. By nurturing this tripartite synergy, the field can move towards a more integrated and globally informed research agenda.

Top journals drive progress in stem cell therapy for ONFH

The synergy between top journals and their highly cited papers drives progress in ONFH stem cell therapy. Certain journals are prominent as preferred platforms for high-impact research, showcasing their reach, reputation

and ability to attract pioneering work in the field. Examining the top-cited papers in Table 5 reveals that many are from the most prolific journals listed in Table 4. This significant overlap suggests that these journals not only disseminate research widely but also shape the research agenda by publishing seminal studies in the field. For example, *Bone* and *Clinical Orthopaedics and Related Research* lead in not only publication volume but also in pivotal studies with significant citations [14, 23, 24]. This underscores their dual role as disseminators and shapers of influential research narratives. As core publications in the field, high-quality research can be submitted to these journals and those interested in top-notch studies in ONFH stem cell therapy can find valuable resources within them.

The seminal work by Gangji et al. [22, 23], marked by significant citation bursts, has been pivotal in directing ONFH research, particularly emphasising the role of MSCs. These pivotal papers, along with other highly cited studies, affirm the consensus of the scientific community on the central role of MSCs in the development of treatments for ONFH. The citation bursts not only validate the quality of the studies but also highlight their timeliness and signal strategic advances in treatment approaches, such as integrating CD with bone marrow grafting [14, 27]. The focus on MSCs [23–25, 28, 30], beta-tricalcium phosphate [25] and cell-infiltratable hydrogels [26] in these top-cited papers highlights innovative frontiers in the field, where materials science significantly enhances biomedical methods. Moreover, the high-impact literature demonstrates the evolution of the field through multidisciplinary approaches, integrating molecular biology techniques, such as the regulatory role of non-coding RNAs [28] and exosomes [31] in osteogenesis and angiogenesis into surgical strategies. This fusion of surgical innovation with advanced biomaterials and molecular insights addresses the complex challenges of ONFH, paving the way for more targeted and multifaceted treatment strategies based on these foundational studies. Further, the integration of research on GC-induced osteoporosis within these papers highlights a critical concern in ONFH treatment i.e., the mitigation of adverse effects from common medications [29]. The citation of such studies reflects awareness within the field of the need to balance therapeutic efficacy with the management of potential side effects.

In essence, the dialogue between highly cited papers and their journals reflects a dynamic scientific narrative. It highlights the role of journals in advancing research by featuring ground-breaking studies, emphasising the importance of strategic publication choices and journals as gatekeepers of scientific quality and innovation. Maintaining this high standard of research dissemination is crucial for advancing stem cell therapies for ONFH.

Stem cell therapy for ONFH evolved from basic research to clinical practice and beyond into combination therapies

Research on stem cell therapy for ONFH has evolved significantly from 1997 to 2023, with each stage building upon previous discoveries and offering valuable insights for future studies (Fig. 7).

1997–2003: basic research and mechanistic understanding

In the late 1990s, foundational research into ONFH significantly advanced our understanding of its pathophysiology, focusing on GCs, MSCs, differentiation and transplantation. GCs were identified as a critical factor in promoting adipogenic differentiation of MSCs, skewing them away from osteogenic pathways and thus contributing to ONFH [30, 48]. This period underscored the pivotal role of MSCs in regenerative medicine, with their potential for multilineage differentiation being explored as both a therapeutic opportunity and a mechanism underlying the disease. The differentiation of MSCs into adipocytes or osteoblasts became central to understanding the development of ONFH and revealing how external factors, such as GCs, could alter bone integrity. Meanwhile, stem cell transplantation highlighted the dual aspects of the therapeutic potential of MSCs and the risks of ONFH post-transplantation due to high-dose GC therapy [49, 50]. This era of research laid the groundwork for future therapeutic strategies, emphasising the complexity of ONFH and the importance of targeting cellular mechanisms for effective treatment.

2004–2010: bridging regenerative medicine and surgical innovation

Between 2004 and 2010, the field of ONFH research was defined by a dynamic and multidisciplinary approach, with stem cell therapy at the forefront. Researchers examined the potential of MSCs for bone regeneration, exploring not just their natural differentiation abilities but also the enhanced potential through genetic modifications. Central to this period was the emphasis on angiogenesis, a critical factor for enhancing blood flow to necrotic bone areas, which was explored through the implantation of autologous bone marrow mononuclear cells and the application of growth factors to stimulate the formation of new blood vessels [51]. Gene therapy became a pioneering approach, enhancing regenerative treatments for bone and vascular growth by modifying MSCs with genes encoding proteins, such as bone morphogenetic protein (BMP) and vascular endothelial growth factor (VEGF) [52]. Concurrently, surgical techniques, particularly CD, were refined and often used in tandem with stem cell therapies, marking a significant advance in treatment strategies combining mechanical interventions with biological healing processes [53].

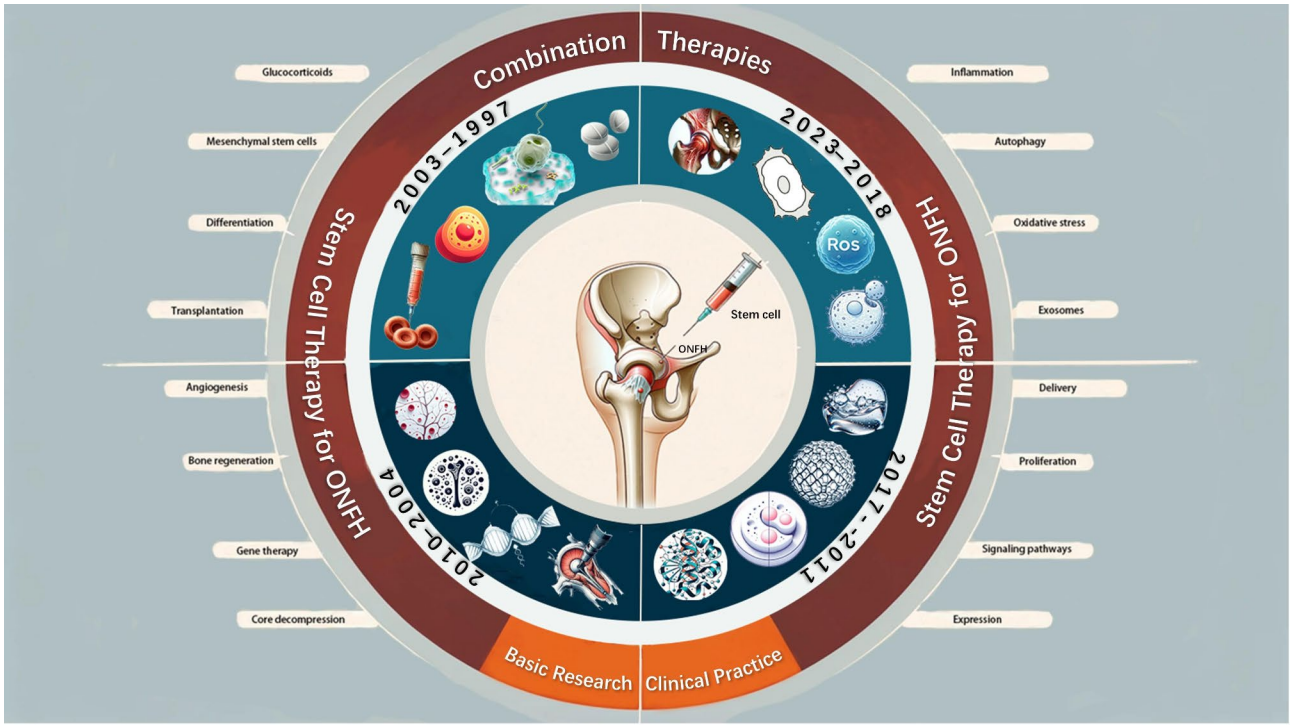

Fig. 7 Evolution of stem cell therapy for ONFH from 1997 to 2023 from basic research to clinical practice and beyond into combination therapies: (1) 1997–2003: Glucocorticoids, Mesenchymal Stem Cells, Differentiation, Transplantation; (2) 2004–2010: Angiogenesis, Bone Regeneration, Gene Therapy, Core Decompression; (3) 2011–2017: Expression, Signaling Pathways, Proliferation, Delivery; (4) 2018–2023: Exosomes, Oxidative Stress, Autophagy, Inflammation

The research efforts in this period have contributed significantly to the understanding and treatment of ONFH, highlighting the complexity of the disease and the need for a comprehensive approach combining cellular therapy, genetic engineering and surgical intervention. The insights gained and the methodologies developed over these years have laid a solid foundation for future studies, with the aim of developing still more effective and personalised treatment strategies for ONFH, ultimately improving patient outcomes and quality of life.

2011–2017: Cellular mechanisms and expression

From 2011 to 2017, stem cell therapy for ONFH shifted towards a deeper understanding of cellular mechanisms, moving past gene therapy to focus on the roles of cellular expression and signalling in enhancing the regenerative functions of MSCs. This period aimed to leverage protein expression and signalling pathways to improve osteogenesis and angiogenesis, and thus enhance the strategies for bone tissue regeneration.

The exploration of cellular expression during this period examined into the intricate roles of proteins, such as calcitonin gene-related peptide (CGRP) and hepatocyte growth factor (HGF), which were shown to significantly influence the behaviour of MSCs and their efficacy in tissue repair [54, 55]. Moreover, the focus extended to the expression of microRNAs (miRNAs), such as miR-17-5p and miR-27a, which were found to play significant roles in modulating osteoblastic differentiation and cell proliferation by targeting key signalling molecules and pathways [56, 57]. This era also underscored the importance of signalling pathways, with research illuminating how pathways, such as Wnt/β-catenin and PI3K/Akt, could be manipulated to drive MSCs towards desired regenerative outcomes, highlighting a shift towards a more nuanced understanding of cellular mechanisms [58, 59]. Enhancement of cell proliferation emerged as a critical area, with studies aiming not only to increase the number of stem cells available for tissue repair but also to ensure that these cells could survive, proliferate and differentiate effectively in the harsh microenvironment of the necrotic femoral head [56, 60]. This objective led to the development of preconditioning strategies and the use of supportive cytokines and growth factors that prepare stem cells for optimal performance after transplantation. Advances in delivery techniques underscored this era, with a shift towards more sophisticated methods that not only ensured the precise localisation of stem cells to the necrotic areas but also their sustained function and integration into the host tissue. From biomaterial scaffolds mimicking the bone extracellular matrix to targeted delivery systems utilising nanoparticles and hydrogels,

this period was characterised by a concerted effort to bridge the gap between in vitro success and in vivo applicability [61, 62].

The research from 2011 to 2017 in the treatment of ONFH through stem cell therapy reflected a multidimensional approach, moving beyond gene expression to encompass a broader spectrum of cellular behaviours and interactions. This holistic exploration of the expression of critical proteins, the modulation of signalling pathways, strategies to bolster cell proliferation and innovations in delivery mechanisms together propelled the field towards more effective, reliable and tailored therapeutic options for ONFH, setting a foundation for future breakthroughs in regenerative medicine.

2018–2023: integrative approaches and precision medicine

From 2018 to 2023, significant advances in stem cell therapy for ONFH focused on understanding the disease and improving treatments. Research during this period emphasised exosome therapy, oxidative stress reduction, autophagy modulation and inflammation control, forming a holistic approach to combat ONFH.

Exosomes as vehicles for intercellular communication have emerged as a novel therapeutic modality in ONFH treatment. These small extracellular vesicles, derived from MSCs, carry bioactive molecules, such as miRNAs, proteins and lipids, which can modulate key processes involved in bone regeneration and repair [63, 64]. The studies highlighted in this period demonstrate the potential of exosomes to enhance osteogenesis, angiogenesis and mitigate apoptosis in osteoblasts, thereby addressing critical aspects of ONFH pathology [65, 66]. The ability of exosomes to encapsulate and deliver therapeutic agents directly to the necrotic zones offers a promising cell-free approach for ONFH treatment, reducing the risks associated with direct stem cell transplantation [65]. Oxidative stress plays a pivotal role in the pathogenesis of ONFH, contributing to cellular damage and necrosis. Research focusing on the protective effects of antioxidants, such as polydatin and betaine, against oxidative stress in BMSCs underscored the therapeutic potential of targeting oxidative pathways [46, 67]. These studies showed that mitigating oxidative stress not only protects BMSCs from glucocorticoid-induced damage but also promotes their osteogenic differentiation, highlighting the importance of antioxidant therapy in enhancing the efficacy of stem cell treatments for ONFH. Autophagy, a cellular process involved in the degradation and recycling of cytoplasmic components, has been recognised for its role in maintaining cell viability under conditions of stress. The modulation of autophagy in endothelial progenitor cells and BMSCs has shown promise in protecting against dexamethasone-induced avascular necrosis and promoting bone regeneration [68, 69]. The activation of pathways, such as the AMPK-mTOR signalling pathway, by agents, such as pravastatin, illustrates the therapeutic potential of enhancing autophagy as a means of improving the survival and function of transplanted stem cells in the necrotic femoral head [68]. Inflammation control in ONFH is a double-edged sword, as research identified its dual role in both exacerbating the disease and offering a potential therapeutic target. The role of cytokines, such as TNF-α, in modulating MSC differentiation and the impact of chronic obesity-induced inflammation on ONFH progression emphasise the need for targeted anti-inflammatory therapies [70, 71]. Strategies aimed at resolving inflammation, either through the modulation of macrophage activity or the use of anti-inflammatory compounds, such as calycosin, offer a path towards mitigating the inflammatory aspects of ONFH pathology [38, 72].

In conclusion, the period 2018–2023 showcased remarkable progress in ONFH treatment, emphasising stem cell capabilities and precision medicine. By combining tailored therapies based on individual genetic profiles and disease characteristics, such as exosome therapy, oxidative stress reduction, autophagy modulation and inflammation control, this approach has led to more personalised and effective strategies, targeting the cellular and molecular underpinnings of the disease to improve patient outcomes.

Future recommendations and directions

The research trajectory from 1997 to 2023 in stem cell therapy for ONFH has paved the way for a more nuanced understanding of the condition and opened avenues for the development of innovative treatments. Building on this rich foundation, future research directions should aim to further refine and integrate these therapeutic strategies to maximise efficacy and personalise care for patients with ONFH.

Enhanced characterisation and utilisation of exosomes

Given their potential as carriers of therapeutic agents, future studies should focus on the comprehensive characterisation of exosomes derived from MSCs from different sources. Research should explore the optimisation of exosome isolation, loading and delivery techniques to enhance their regenerative capabilities specifically for ONFH. Moreover, investigating the roles of specific miRNAs and proteins carried by exosomes in bone regeneration could lead to the development of more targeted therapies.

Advanced modulation of oxidative stress and autophagy

Recognising the crucial roles of oxidative stress and autophagy in the pathophysiology of ONFH, future efforts should focus on the development of novel

antioxidants and autophagy modulators. These studies should aim to elucidate the intricate balance between eliminating harmful oxidative stress and preserving beneficial autophagic processes, potentially through drug repurposing or novel drug discovery.

Precision anti-inflammatory therapies

Inflammation plays a dual role in ONFH, representing both a therapeutic target and a pathological factor. Future research should aim to develop more precise anti-inflammatory strategies that can selectively modulate the inflammatory response without hindering bone healing and regeneration. This could involve targeting specific cytokines, signalling pathways or immune cells implicated in the inflammatory process of ONFH.

Integration of stem cell therapy with surgical techniques

As surgical interventions continue to play a role in ONFH treatment, integrating stem cell therapy with these techniques represents a promising approach. Future studies should explore the synergistic effects of stem cell therapy combined with surgical innovations, such as CD, focusing on the timing, dosage and type of stem cells used to optimise outcomes.

Personalised and precision medicine approaches

Building on advances in genomics and proteomics, future directions should emphasise personalised medicine in ONFH treatment. This includes tailoring stem cell therapy based on individual genetic profiles, disease characteristics and specific pathophysiological mechanisms. Developing biomarkers for early detection and monitoring of progression and responses to therapy could significantly enhance the precision of treatment strategies.

Regulatory frameworks and clinical trials

Translating these innovative therapies from bench to bedside will require the establishment of robust regulatory frameworks and well-designed, multicentre clinical trials. Future research should also address the ethical, legal and social implications of advanced stem cell therapies.

By focusing on these recommendations, future research in stem cell therapy for ONFH can continue to evolve towards more effective, reliable and personalised treatments, ultimately aiming to improve the quality of life of patients suffering from this debilitating condition.

Strengths and limitations

Building on our group's prior review of the complex challenges and promising outcomes of stem cell therapy for ONFH [13], our latest research makes a unique contribution by employing bibliometric analysis and visual analytics. This innovative approach provides a comprehensive overview of the research landscape, identifying trends and highlighting gaps. Our study not only advances our understanding but also sets a new benchmark for future research in stem cell therapy for ONFH, paving the way for more informed and targeted investigations.

Despite the innovative approach, it is important to acknowledge certain limitations of this study. Our data were sourced exclusively from the WoS Core Collection, potentially omitting relevant studies from other databases and leading to gaps in our data set. In addition, our analysis, based primarily on publication volume, may not accurately capture the true influence of researchers and institutions in the field, possibly overlooking those with fewer but significant contributions. Moreover, recent breakthroughs in stem cell therapy for ONFH published after our search date would not have been included, potentially missing emerging advances in the field.

Conclusions

Advances in stem cell therapy for ONFH from 1997 to 2023 have been significantly propelled by contributions from leading researchers and institutions, with Professor Zhang Changqing from Shanghai Jiao Tong University at the forefront, pioneering key studies in the field. This era of research, marked by notable collaboration across countries, including China, the United States and South Korea, has led to important developments in treatment strategies, particularly emphasising the roles of autologous MSCs and advanced delivery systems. The collective efforts of 158 core authors have culminated in 392 publications, showcasing a concentrated push towards the development of innovative therapies. High-impact journals, such as *Clinical Orthopaedics and Related Research*, *Journal of Bone and Joint Surgery-American Volume* and *Bone*, have been instrumental in disseminating these findings. This body of work underscores a dynamic and evolving research landscape, where the publication of high-quality studies in prestigious journals has accelerated the pace of discovery and enhanced the potential for the development of clinical applications, setting a promising path for the future of ONFH treatment.

Future research in stem cell therapy for ONFH aims to refine treatments through advanced exosome utilisation, targeted modulation of oxidative stress and inflammation and integration with surgical techniques. Emphasising personalised medicine, studies will focus on optimising delivery mechanisms, developing precision therapies based on genetic insights and tailoring interventions to individual patient profiles. The progression towards the development of effective, personalised treatments will be supported by robust clinical trials and regulatory frameworks, setting a new standard for improving outcomes in ONFH care.

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Author contributions
TYW and YXZ designed the study, collected and analyzed the data, and wrote the manuscript. TL and WPS developed the concept, discussed the ideas. All the authors critically reviewed the manuscript. All the authors read and approved the final manuscript.

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Data availability
The data collected and analyzed in the article are from WOS, an open access database of scholarly articles, and are properly adopted and collected.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable since the manuscript is entirely original; the tables and figures presented are original for this article and have neither been published nor are currently under consideration for publication by any other journal.

Competing interests
The authors have declared that no competing interest exists.

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