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The Top 50 Most Cited Articles in Cartilage Regeneration

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Abstract

The aim of this study was to identify and analyze the top 50 most cited articles in cartilage regeneration. The impact of a scientific journal can be gauged by the total number of citations it has accrued. The top 50 most cited articles involving cartilage regeneration represent the most quoted level of evidence among this new subspecialty. This study aims to identify and analyze the 50 most cited articles in cartilage regeneration. The Web of Science™ citation indexing service was utilized to determine the most frequently cited articles published after 1956 containing "cartilage regeneration" in the "topic" or "title." The 50 most cited articles were included. The number of citations, year of publication, country of article origin, article institution, journal of publication, publication format, and authorship were then calculated for each article. The span of citations ranged from 1287 to 203 citations, with a mean of 361.02 citations per article in question. The articles originated from 11 countries, with the United States contributing 34 articles, followed by Japan with 5 articles. The articles were distributed across 34 high-impact journals. *Biomaterials* was the journal with the highest number of publications (seven articles) followed by the *Journal of Orthopaedic Research* (three articles). Of the 50 articles, 2 were clinical observational studies, 47 concerned basic science, and 1 was review article. The most cited articles involving cartilage regeneration are detected in both experimental and clinical research fields. The high ratio of basic science to clinical articles reflects the infancy of this relatively new specialty and that further clinical research is required in this area.

Keywords: bibliometric; cartilage; regeneration

Introduction

The field of orthopedic surgery continues to evolve with the advent of new technology and research. Regenerative orthopedics is rapidly becoming recognized as a new subspecialty within orthopedics.

An article receives a citation when a peer references the said article. It is broadly considered that intellectual influence of an article in a given specialty can be gauged by the level of citations received by peers. The level of evidence available to clinicians can, therefore, be estimated from assessment of the top 50 most cited articles.

Bibliometric analyses have been performed previously in medical fields and other specialties within orthopedics. Authors have examined the "classic" articles in orthopedics as a whole,[1] pediatric orthopedics,[2] shoulder surgery,[3] and spinal surgery.[4] To our knowledge, this study is the first bibliometric analysis of orthopedic cartilage regeneration.

In this study, we aim to identify the most referenced articles present in this newly established field to help give us an insight into the most quoted level of evidence currently available to clinicians and scientists alike.

Methodology

The Web of Science™ citation indexing service was utilized to determine the most frequently cited articles published from 1956 to 2016 containing "cartilage regeneration" in the "topic" or "title." The U.S. National

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Library of Medicine® premier life sciences database was analyzed in this search through the Ovid® MEDLINE indexing service.

After book chapters and proceedings articles were excluded from our search, 4063 results returned. The results were arranged from highest to lowest in terms of article citations and the top 50 were then taken for further assessment.

Articles were subsequently evaluated for several characteristics including authorship, article institution, the number of calculated citations, the year of publication, the country of origin of the article, name of journal, and publication type of article.

Ethical Statement

Ethical approval was not required to conduct this bibliometric review.

Results

A total of 4063 articles returned with the mentioned inclusion criteria. The most cited article received 1287 citations, with the 50th most cited article receiving 203 citations (Table 1). There was a mean of 361.02 citations per article. The articles were published between 1991 and 2016, with the highest number of publications occurring in 2002 (Table 2).

The oldest cited article was by Longaker et al.[5] and was published in 1991. The newest article was published in 2011 and was written by Nayak et al.[6]

Table 1. Number of Citations Received per Author in Top 50 Most Cited Articles

1. Hollister[10]	1287	26. Moutos et al.[32]	304
2. Mackay et al.[11]	755	27. Saris et al.[33]	288
3. Wakitani et al.[12]	698	28. Kragl et al.[34]	285
4. Hutmacher[13]	683	29. Dezawa et al.[35]	285
5. Kisiday et al.[14]	593	30. Darling and Athanasiou[36]	283
6. Yoo et al.[15]	549	31. Mikos et al.[37]	279
7. Bruder et al.[7]	542	32. Rose and Oreffo[38]	271
8. Bruder et al.[8]	524	33. Freyman et al.[39]	271
9. Mo[16]	505	34. Yang et al.[40]	253
10. Bruder et al.[9]	492	35. Tuli et al.[41]	250
11. Murphy et al.[17]	445	36. Alhadlaq and Mao[42]	245
12. Wakitani et al.[18]	436	37. Nayak et al.[6]	238
13. Peng et al.[19]	423	38. Lacroix and Prendergast[43]	232
14. Erickson et al.[20]	405	39. Almany and Seliktar[44]	226
15. Kadiyala et al.[21]	383	40. Glowacki and Mizuno[45]	223
16. Kim et al.[22]	374	41. Angele et al.[46]	216
17. Vunjak-Novakovic et al.[23]	367	42. Nakagawa et al.[47]	214
18. Li et al.[24]	366	43. Karande et al.[48]	207
19. Cima et al.[25]	365	44. Shah et al.[49]	216
20. Albrecht et al.[26]	325	45. Reddi[50]	206
21. Temenoff and Mikos[27]	322	46. Carter et al.[51]	206
22. Caplan et al.[28]	311	47. Thein-Han and Misra[52]	205
23. Yoshimura et al.[29]	305	48. Lee et al.[53]	204
24. Minasi et al.[30]	303	49. Oliveira et al.[54]	204
25. Haines-Butterick et al.[31]	289	50. Longaker et al.[5]	203

Table 2. Number of Top Cited Articles Published per Named Year

Publication year	No. of top cited articles published
2002	7
1998	6
2005	5
2006	4
2000	3
2001	3
2003	3
2004	3
2007	3
1991	2
1997	2
2008	2
2009	2
2010	2
1994	1
1995	1
2011	1

The top 50 articles originated from 11 countries, with the United States contributing 34 articles, followed by Japan with 5 articles (Table 3).

The top three institutions responsible for the top cited articles all came from the United States, with Case Western Reserve University (6), Harvard University (6), and Osiris Therapeutics Inc. (4) topping the list (Table 4).

The top 50 cited articles were published in 34 high impact journals with *Biomaterials* (7), *Journal of Orthopaedic Research* (3), and *Tissue Engineering* (3) topping the list (Table 5).

Of the 50 articles, 2 were clinical observational studies, 46 concerned basic science, and 1 was a review article. Of the 46 basic science articles, 19 concerned the principle of tissue engineering, whereas the remaining 28 concerned cellular biology.

A total of 17 authors published two or more of the top cited articles with Bruder et al.[7–9] involved as coauthor in four of the top cited articles (Table 6).

Table 3. Number of Top Cited Articles Published per Country of Origin

Country of origin	No. of top cited journals
United States	34
Japan	5
Singapore	3
Italy	2
England	1
Germany	1
Israel	1
The Netherlands	1
Portugal	1
Republic of Ireland	1

Table 4. Institution with Two or More of the Top Cited Articles

Institution	Number of top cited articles
Case Western Reserve University	6
Harvard University	6
Osiris Therapeutics Inc.	6
Brigham Women's Hospital	3
Massachusetts Institute of Technology	3
National University of Singapore	3
Rice University	3
Columbia University	2
Duke University	2
Osaka Minami National Hospital	2
Tufts University	2
University of California San Francisco	2
University of Washington	2

Discussion

The top 50 most cited articles in cartilage regeneration represent the most quoted level of evidence in this field. Trends into clinical research can be graphically and visually represented through the number of citations received per annum. An article gaining increasing citation counts per year reflects an increasing trend in a specific topic. Although bibliometric studies do not represent scientific quality, an increasing trend in a subject can be considered an estimate of the standard of clinical work being undertaken worldwide.

This is of particular relevance to newly established subspecialties, whereby a transition process from established basic science articles to clinical observational studies is required.

The most cited article in our search was authored by Hollister[10] in the year 2005 and received 1287 citations. The article studied "Porous Scaffold Design for Tissue Engineering."

The authors identify in their progress article the paradigm shift from using synthetic implants and tissue grafts to an engineering approach that utilizes degradable porous scaffolds integrated with biological cells for tissue regeneration.[10] Here the advent of tissue engineering modalities, specifically computational topology design (CTD) and solid free-form fabrication (SFF), is discussed.[10] Integration of CTD and SFF results in scaffolds with improved mechanical properties that are required for bone tissue engineering because of the greater requirement for stiffness and strength.[10] The authors postulate that these "Designer" scaffolds may lead to improved bone and cartilage regeneration, probably because of high interconnected porosity.[10] The benefits of interconnected porosity are postulated to include improved cell seeding and channels to guide cell migration.[10]

Table 5. Journals with Two or More of the Most Cited Articles

Journal	No. of top cited articles
Biomaterials	7
Journal of Orthopaedic Research	3
Tissue Engineering	3
Biochemical and Biophysical Research Communications	2
Clinical Orthopaedics and Related Research	2
Journal of Bone and Joint Surgery, American Volume	2
Nature Materials	2

Table 6. Authors with Two or More of the Top Cited Articles

Author	Number of top cited articles
Bruder, S	4
Caplan, A	4
Goldberg, V	3
Kadiyala, S	3
Wakitani, S	3
Barry, F	2
Fink, D	2
Freed, L	2
Guilak, F	2
Johnstone, B	2
Langer, R	2
Mao, JJ	2
Mikos, A	2
Mooney, D	2
Murphy, J	2
Vunjak-Novakovic, G	2
Yoo, J	2

The authors do stipulate in this article that the optimal material for regeneration has yet to be identified.[10] Further, Hollister discusses the need to investigate tissue interfacing from multiple material interfacing.[10] Further *in vivo* trials are required to help answer these questions.

This article was followed by "Chondrogenic Differentiation of Cultured Human Mesenchymal Stem Cells from Marrow" authored by Mackay et al.[11] in the year 1998. This article received 755 citations.

Although Hollister primarily discusses what the composite requirements of the tissue scaffold, Mackay et al. deal with the differentiation and maintenance of biofactors.[11] Here, human mesenchymal stem cells (MSCs) were induced to express the morphology of chondrocytes: the required biofactor for articular cartilage regeneration.[11] Differentiation of MSCs was undertaken through exposure to a medium of 100 nM dexamethasone as well as 10 ng/mL transforming growth factor beta(3).[11] Within a fortnight of exposure to the aforementioned medium, the involved cells secreted an extracellular matrix typical of chondrogenic activity (type II collagen, aggrecan, and anionic proteoglycans).[11]

The authors go on to postulate that this improved understanding of chondrogenic differentiation will

further aim to help define the mechanisms responsible for maintenance and regeneration of cartilage tissue.[11]

The third most cited article was undertaken in 1995 by Wakitani et al.[12] The authors here studied "Myogenic Cells Derived from Rat Bone-Marrow Mesenchymal Stem Cells Exposed to 5-Azacytidine." This article predates the study by McKay et al. by 3 years. Again the differentiation of MSCs is discussed. In contrast to the study performed by McKay, Wakitani et al. discuss the differentiation of rat MSCs on exposure to 5-azacytidine.[12] This compound had previously been shown to convert cells of the rat embryonic fibroblastic cell line into myoblasts, adipocytes, and chondrocytes.[12] This study again identified the ability of animal MSCs to differentiate *in vitro* into myogenic and adipocytic phenotypes.[12] Wakitani et al. suggest that MSCs in the bone marrow may be a pertinent biofactor for regenerative purposes.[12]

The top three cited articles were published in *Nature Materials*, *Tissue Engineering*, and *Muscle & Nerve*, respectively.

The emergence of regenerative orthopedics as a new subspecialty is represented by the publication year of the top cited articles. All of the top cited articles were published after the year 1990 with the majority being published recently in the noughties with the most publications occurring in the year 2002.

We can see from our research that the bulk of regenerative orthopedic research is being undertaken in the United States, with 34 of the top 50 articles originating in the United States. Of the contributing institutions, Case Western University contributed 6 of the top 50 articles and Harvard University contributed 6 articles.

Third level universities dominate the top contributing institutions. Osiris Therapeutics Inc. is also involved as a main contributor with four top cited articles to its name.

Our search returned a considerable number of articles, 4036 in total, reflecting the largest interest in the subject; of the 50 most cited articles, the ratio of basic science articles to clinical observational articles was large, 47:3. The top cited articles were primarily basic science based with a predisposition toward cellular biology followed by tissue engineering. It can be seen from basic science data that the overall majority of the work undertaken by the science community at present was to

(a) investigate the outcome of enhanced tissue scaffolding to regenerate articular cartilage and
(b) investigate the usage of MSCs to help regenerate articular cartilage.

Overall, there are several limitations to this study. As already described, bibliometric studies do not analyze scientific quality, merely the popularity. Bias in favor of English written articles, and self-citation as well as citation omission of competitors may influence the top results.

All in all, the research currently being undertaken can potentially sculpt a pathway for observational clinical data to be performed.

Conclusion

The high ratio of basic science to clinical data reflects the need for further clinical observational trials to be performed in the area of regenerative orthopedics.

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Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CTD = computational topology design
MSCs = mesenchymal stem cells
SFF = solid free-form fabrication