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REVIEW

From Mechanobiology to Mechanical Repair Strategies: A Bibliometric Analysis of Biomechanical Studies of Intervertebral Discs

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Abstract: Neck pain and low back pain are major challenges in public health, and intervertebral disc (IVD) biomechanics is an important multidisciplinary field. To date, no bibliometric literature review of the relevant literature has been performed, so we explored the emerging trends, landmark studies, and major contributors to IVD biomechanics research. We searched the Web of Science core collection (1900–2022) using keywords mainly composed of "biomechanics" and "intervertebral disc" to conduct a bibliometric analysis of original papers and their references, focusing on citations, authors, journals, and countries/regions. A co-citation analysis and clustering of the references were also completed. A total of 3189 records met the inclusion criteria. In the co-citation network, cluster #0, labeled as "annulus fibrosus tissue engineering", and cluster #1, labeled as "micromechanical environment", were the biggest clusters. References by MacLean et al and Holzapfel et al were positioned exactly between them and had high betweenness centrality. There existed a research topic evolution between mechanobiology and mechanical repair strategies of IVDs, and the latter had been identified as an emerging trend in IVD biomechanics. Numerous landmark studies had contributed to several fields, including mechanical testing of normal and pathological IVDs, mechanical evaluation of new repair strategies and development of finite element model. Adams MA was the author most cited by IVD biomechanics papers. *Spine*, the *European Spine Journal*, and the *Journal of Biomechanics* were the three journals where the most original articles and their references have been published. The United States has contributed most to the literature (n = 1277 papers); however, the research output of China is increasing. In conclusion, the present study suggests that IVD repair is an emerging trend in IVD biomechanics.
Keywords: emerging trend, co-citation, CiteSpace, annulus fibrosus

Introduction

Neck pain and low back pain are major challenges in public health, with prevalence rates of nearly 3.6% and 7.0% and affecting 288.7 million and 570 million people worldwide, respectively.[1,2] Specifically, low back pain is the primary contributor to years lived with disability among all diseases.[2] Diseases of the intervertebral discs (IVDs), such as degeneration, are important causes of pain, and >400 million people are diagnosed with symptomatic disc degeneration worldwide each year.[3]

Normal IVDs are kidney-bean shaped structure lying between adjacent vertebral bodies. The height and diameter of them are approximately 7–10 mm and 4 cm respectively.[4] In each IVD, there is a jelly-like core, the nucleus pulposus (NP), surrounded by a tire-like structure called the annulus fibrosus (AF), both of which are sandwiched by the cartilage end plates (CEPs).[5] Mechanical function is the major component of IVD physiology. Due to well-designed architecture and interaction of their three main components, IVDs can provide support and flexibility to the spine, allowing it to bend, twist, distribute compression and absorb shock.

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The tissues of IVDs are mainly composed of water, proteoglycans, and collagen. The relative content of them is different between NP, AF and CEPs, resulting in distinctive mechanical properties. The NP has the highest proteoglycan content which accounts for roughly 50% of the dry weight, leading to a high water content (75–90%) and a predominantly hydrostatic behavior.[6] The negatively charged proteoglycans provides an osmotic potential,[7] which is then converted into hydrostatic pressure through hydration. Intradiscal pressure provides the tissue with high compressive properties by supporting the CEPs and tensioning the AF. Normal human NP has an effective aggregate modulus of 1.0 MPa in confined compression.[8] Intradiscal pressure presents a diurnal change according to the fluctuating loading of IVDs. Resting intradiscal pressure is roughly 0.1–0.24 MPa at night and increases to 0.3–1.1 MPa when standing or sitting, and to 2.3 MPa when lifting a 20-kg weight in a flexed position.[9,10]

AF is a complex structure made up of 15–25 highly organized concentric layers,[11] which are composed of alternatingly aligned oblique collagen fibers oriented at ±25–45° to the horizontal plane and interspersed with proteoglycans.[5] Due to its high collagen content which is approximately 50–70% of the dry weight,[12] the AF has a superior tension-bearing capacity. According to the direction of loading, the average tensile modulus of AF is approximately 0.2–183 MPa.[5] The concentric layers of AF are interconnected through a network of smaller fibers, which provides superior capacity to resist the shear by intra-lamellar skewing.[13] Multi-scale architecture also provides prominent mechanical anisotropy and nonlinearity to AF. From the outer to the inner annulus, there is a decrease in the ratio of collagens I to II and in collagen fiber angle. The spatial variations in structure and composition lead to its anisotropy.[14] Crimp of the collagen fibers in AF provides the nonlinearity.[15] When the fibers are stretched, the fibers progressively straighten with minimal resistance and the tensile stress–strain curve is nonlinear. After the fiber has been straight, it starts taking load and the stress–strain curve become linear. Nonlinearity is important to permit both disc motion and stability.

Biomechanics also play an important role in the pathogenesis and therapeutics of many disc disorders. In terms of pathology, altered biomechanics can directly affect IVD cell anabolism and catabolism. Furthermore, a degraded extracellular matrix can influence the biomechanical behavior of IVDs, such as by reducing the intradiscal pressure and the ability to retain water under compressive forces.[16] As a result, the mechanical characterization of IVDs can help to elucidate mechanisms of IVD disorders and understand how the material properties of IVDs are influenced by these disorders. Using this knowledge, novel biomaterials can then be designed and clinically implemented.

IVD biomechanics is a rapidly developing and important interdisciplinary discipline of spinal surgery. While many biomechanical and mechanobiological behaviors of native IVDs and tissue engineering scaffolds have been recorded by in vitro and in vivo studies, IVD biomechanics is still an active domain. However, a comprehensive understanding of IVD biomechanics remains an important gap in the literature. The present study aims to explore the emerging trends, landmark studies, and major contributors of IVD biomechanics over several decades using bibliometric analysis, a widely used quantitative method to understand the knowledge structure of a specific domain.[17–19] In particular, citation count is widely used as a metric by bibliometric studies to determine the impact of a portion of peer-reviewed papers.[20] However, the overall citation count of a study is not indicative of its impact on a specific domain. Many citations of papers in IVD biomechanics have been contributed by papers in other subfields of orthopedics or clinical neurology, and highly cited papers of IVD biomechanics may not have actually had the level of impact on the field that their citation count suggests. Therefore, we also pay close attention to citations contributed by IVD biomechanical studies to find out the foundation supporting this field, which is an important feature of the present study.

Materials and Methods

Data Collection

The present study performs a bibliometric analysis and review of IVD biomechanical literatures included in Web of Science core collection, which is one of the largest and most reputable global citation databases, as well as a widely used database for bibliometric analysis.[17–19] The search strategy and flowchart of literature selection are shown in Table 1 and Figure 1, respectively. This study only included records of which documents are original research articles, review articles, early access papers, or proceedings papers. As a result, book chapters, meeting abstracts, editorial materials, letters corrections, and books were eliminated from consideration. Furthermore, papers not published in the English language were excluded. The process of searching and exporting papers was completed by two researchers independently to reduce errors.

Table 1 Search Strategy Used to Identify Original Papers of IVD Biomechanics in the Web of Science Core Collection

Category	Search Field	Search String
Intervertebral discs	TI	((disc OR disk) AND (intervertebral OR lumbar OR cervical OR thoracic OR degenerat* OR herniat*)) OR ("annulus fibrosus" OR "nucleus pulposus" OR endplate)
	OR	
	AK	((disc OR disk) AND (intervertebral OR lumbar OR cervical OR thoracic OR degenerat* OR herniat*)) OR ("annulus fibrosus" OR "nucleus pulposus" OR endplate)
	OR	
	KP	((disc OR disk) AND (intervertebral OR lumbar OR cervical OR thoracic OR degenerat* OR herniat*)) OR ("annulus fibrosus" OR "nucleus pulposus" OR endplate)
AND		
Biomechanics	TI	(biomechanic* or mechanic* or finite element)
	OR	
	AK	(biomechanic* or mechanic* or finite element)
	OR	
	KP	(biomechanic* or mechanic* or finite element)

Note: Asterisk *is a search wildcard of Web of Science representing any group of characters.
Abbreviations: TI, title; AK, author keyword; KP, keyword plus.

Data Analysis

All records included were imported into CiteSpace, which is a popular bibliometric software program designed by Chen et al using the Java language,[21] to perform a citation analysis.

The major contributors of IVD biomechanics were determined by research output and citation counts of authors, journals, and countries. Research outputs were available in the Web of Science. Citation counts of contributors in corresponding time slices were computed by CiteSpace.

Specifically, we established a co-citation network and performed clustering of the references. Based on the co-citation analysis, the landmark work, evolution of research topics, and emerging trends in IVD biomechanics were identified. The CiteSpace parameters of the co-citation network used by this study were as follows: timespan, January 2000–December 2022; time slice, 1 year; references selected criteria in each time slice, the top 50 most-cited references; and algorithm of the link strength between nodes, cosine.

In a bibliometric analysis, if two references (cited articles) are cited by a third article (citing article), then these two references have a co-citation relationship.[22] Based on this principle, we formed a co-citation network of references of IVD biomechanics. In the network, nodes represented references and a connection between them represented a co-citation relationship. Furthermore, a clustering analysis was performed in which the co-citation network was decomposed into many heterogeneous clusters. References within the same cluster were considered tightly connected, while those between different clusters were considered to be less connected.[23] Labels of co-citation clusters were extracted from the titles of citing articles by the log-likelihood ratio (LLR) test algorithm.[24] By observing the time range of co-citation clusters and corresponding labels, the evolution of research topics in IVD biomechanics over time could be mapped.

Emerging trends of IVD biomechanics were determined by detecting citation bursts, which indicated that some references were associated with a sharp increase in citations. Evidently, these references have attracted more attention from other researchers than those without citation bursts. If a cluster contains a lot of nodes with citation bursts, then the cluster is more likely to capture an emerging trend.

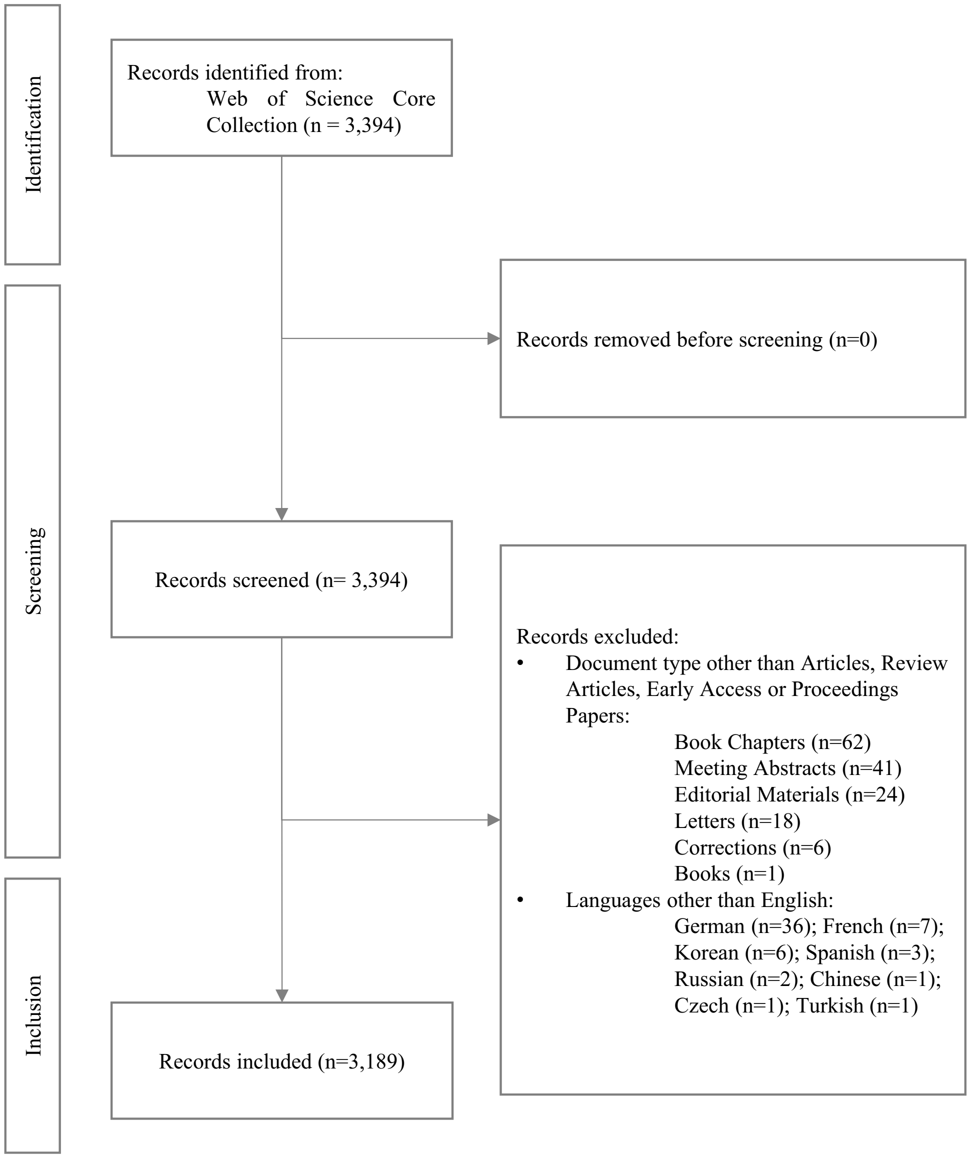

Figure 1 Flowchart of literature selection in this study.

Results

Papers of IVD Biomechanics

Overview of Publications

A total of 3189 publications were included. A paper published in 1946 ultimately did not correlate with the topic of this study; thus, the oldest paper in IVD biomechanics included herein was published by Brown et al in 1957.[25] From 1957 to 2022, the number of papers in biomechanics of IVDs showed an overall upward trend (Figure 2), and the upward speed increased significantly after 2002. In 2018, the number of publications reached its peak.

Papers with the Most Annual Average Citation Counts in the Field of IVD Biomechanics

There were 119 original IVD biomechanics papers that had each been cited ≥119 times. The most cited paper was "New in vivo measurements of pressures in the intervertebral disc in daily life", which was published in 1999 by Wilke et al[9] (Table 2) and tested human intradiscal pressure under different positions. Its data were then used by Vergroesen et al[16] to discuss the effect of the osmotic potential generated by proteoglycans translating into biomechanical hydrostatic pressure

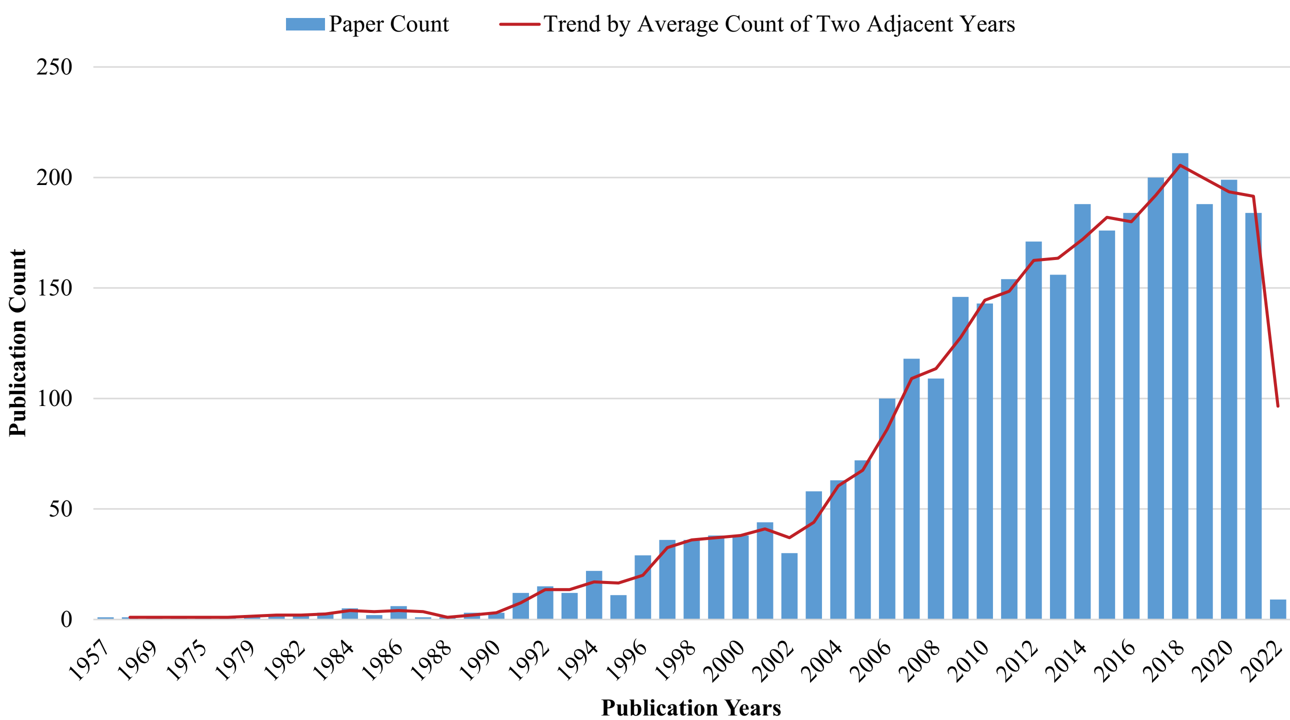

Figure 2 Trends of paper counts of IVD biomechanics. Each blue bar represents how many papers in IVD biomechanics were published each year. The trend of publications is represented by the red line, where the nodes were calculated by average count of two adjacent years.

in healthy discs, finally leading to the conclusion that the increased fragmentation of aggrecan and reduced effective negative charge in degenerating discs may decrease the intradiscal pressure and lead to a reduction in disc height.

References Cited by IVD Biomechanical Studies

The Co-Citation Network of References and its Clustering

The modularity of the co-citation network was 0.8204, which means that references within the same cluster were co-cited much more frequently than references between clusters.[23] Every cluster in Table 3 was highly homogeneous, with the lowest silhouette score being 0.825.

Table 2 Top 10 Original Papers in IVD Biomechanics with the Highest Annual Average Citation Counts

Papers	Total Citations	Average per Year
Wilke et al. *Spine*. 1999[9]	903	37.63
Vergroesen et al. *Osteoarthritis Cartilage*. 2015[16]	292	36.5
Eck et al. *Spine*. 2002[57]	491	23.38
Adams et al. *Spine*. 2000[54]	451	19.61
Dreischarf et al. *J Biomech*. 2014[28]	176	19.56
Iatridis et al. *Spine J*. 2013[26]	177	17.7
Nerurkar et al. *Nat Mater*. 2009[44]	245	17.5
Adams et al. *J Bone Joint Surg Br*. 1996[53]	469	17.37
Norman et al. *Clin Biomech*. 1998[67]	403	16.12
Sato et al. *Spine*. 1999[55]	373	15.54

Table 3 Largest Clusters in the Co-Citation Network

Cluster ID	Size	Silhouette	Optimal Labels (LLR, P value)	Most Relevant Citer	Average Year
0	148	0.918	Annulus fibrosus tissue engineering (566.81, 0.0001)	Iatridis et al (2013)[26]	2007
1	144	0.825	Micromechanical environment (542.97, 0.0001)	Setton et al (2004)[27]	2000
2	118	0.828	Ovine lumbar (487.96, 0.0001)	Casaroli et al (2017)[68]	2012
3	117	0.905	Mechanical evaluation (227.49, 0.0001)	McNally et al (2002)[69]	1999
4	107	0.922	Intervertebral disc (610.11, 0.0001)	Noailly et al (2012)[70]	2006
5	99	0.898	Digital volume correlation (492.17, 0.0001)	Tamoud et al (2021)[71]	2017
6	97	0.937	Herniation risk (651.98, 0.0001)	Fujii et al (2020)[35]	2015
7	62	0.973	Total disc arthroplasties (395.63, 0.0001)	Li et al (2017)[72]	2014
8	55	0.963	Induced volume change (66.66, 0.0001)	Pritchard S (2002)[73]	1999
9	47	0.952	Human cadaveric spine model (157.73, 0.0001)	Huang RC (2005)[74]	2001

Abbreviations: ID, identification; LLR, log-likelihood ratio.

The largest cluster (#0) had 148 members and we labeled it as "annulus fibrosus tissue engineering" by LLR (Figure 3 and Table 3), while the second-largest cluster (#1) which contained 144 members was labeled as "micromechanical environment." The most relevant citer to cluster #0 was published by Iatridis et al,[26] who cited 32 (21.6%) references of cluster #0. The most relevant citer to cluster #1 was published by Setton et al,[27] who cited 27 (18.8%) references of cluster #1.

We found that clusters #2, #5, #6, and #7 were the most recent clusters, which were labeled as "ovine lumbar", "digital volume correlation", "herniation risk", and "total disc arthroplasties", respectively (Table 3). The suboptimal

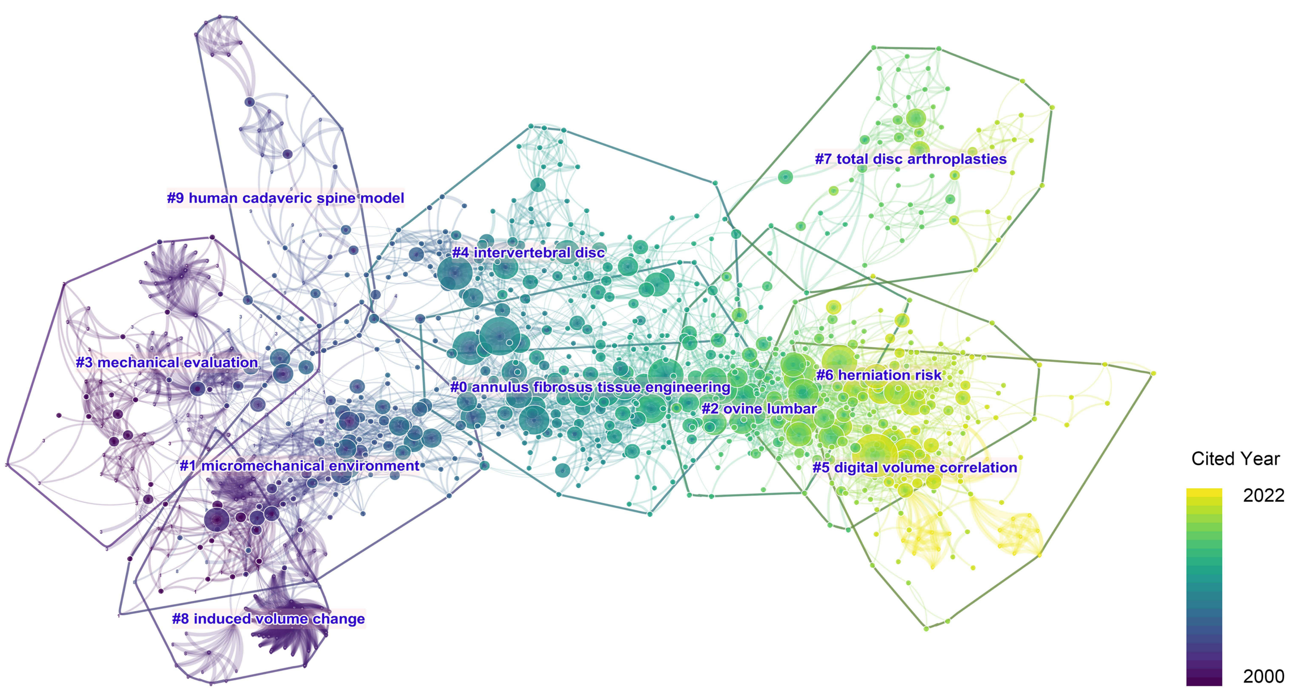

Figure 3 Co-citation network of the references and its clustering. Nodes in the network represent references, and their size indicates citation counts contributed by IVD biomechanical studies. A node may have a number of rings with different colors, which means that they were cited in different time slices.[23] Connections represent co-citation relationships.

labels of these clusters by LLR were "complex loading condition" (LLR = 442.64, P = 0.0001), "intervertebral disc annulus" (LLR = 483.68, P = 0.0001), "annulus fibrosus repair" (LLR = 601.33, P = 0.0001), and "two-level cervical disc replacement" (LLR = 340.03, P = 0.0001), respectively.

The References with the Highest Citation Counts Contributed by Papers of IVD Biomechanics

The top 10 references highly cited by papers of IVD biomechanics from 2000 to 2022 are shown in Table 4. Half of them existed in cluster #0 ("annulus fibrosus tissue engineering"). The most cited reference was "Biomechanics of the human intervertebral disc: a review of testing techniques and results" by Newell et al,[5] followed by the papers of Dreischarf et al[28] and Rohlmann et al.[29]

Citation Bursts

Papers with strong citation bursts mainly existed in clusters #0–2 and #6 (Figure 4). The top 10 of these papers are shown in Table 5. We found that Newell et al[5] and Dreischarf et al[28] had the strongest citation bursts. Except for Galbusera et al[30] and O'Connell,[31] another eight references also existed on the list of highest citations.

Betweenness Centrality

Table 6 shows references that have the highest betweenness centrality scores. The study by MacLean et al in cluster #1 was the top-ranked reference, which involved a mechanobiological investigation and reported that cells of the NP and AF have heterogeneous mechanobiological behavior in vivo.[32] This study's corresponding node in the co-citation network was positioned between clusters #0 and #1 (Figure 5). Notably, this kind of position may become a bridge of research topic evolution.[23] The paper by Holzapfel et al[33] in cluster #0 had a similar position as that of MacLean et al[32] between clusters #0 and #1 (Figure 5); Holzapfel et al tested the mechanical behavior of lamellae of human annulus fibrosus in vitro.

Other nodes of high betweenness centrality (Table 6) were highly connected to other nodes in an intra-cluster fashion, rather than between clusters. As a result, they may be considered very important in their clusters; however, they cannot help as much with the transition between research topics.

Major Contributors

Authors of Original Papers and Their References

Among the original papers included in this investigation, there were 90, 81, and 80 papers on whom Wilke HJ, Elliott DM, and Iatridis JC were authors, respectively. Meanwhile, Adams MA, Panjabi MM, and Wilke HJ were the authors most commonly found among the references of IVD biomechanical studies (Table 7), having been cited 917, 747, and

Table 4 References Most Highly Cited by Papers of IVD Biomechanics

References	Citation Counts	Cluster ID
Newell et al. *J Mech Behav Biomed*. 2017[5]	50	5
Dreischarf et al. *J Biomech*. 2014[28]	44	2
Rohlmann et al. *J Biomech*. 2006[29]	43	0
Schmidt et al. *Clin Biomech*. 2006[64]	40	0
Vergroesen et al. *Osteoarthr Cartilage*. 2015[16]	40	6
Goel et al. *Spine*. 2005[59]	35	4
Nerurkar et al. *J Biomech*. 2010[39]	32	0
Iatridis et al. *Spine J*. 2013[26]	32	6
Schmidt et al. *J Biomech*. 2010[75]	31	0
Guerin et al. *J Biomech*. 2006[76]	29	0

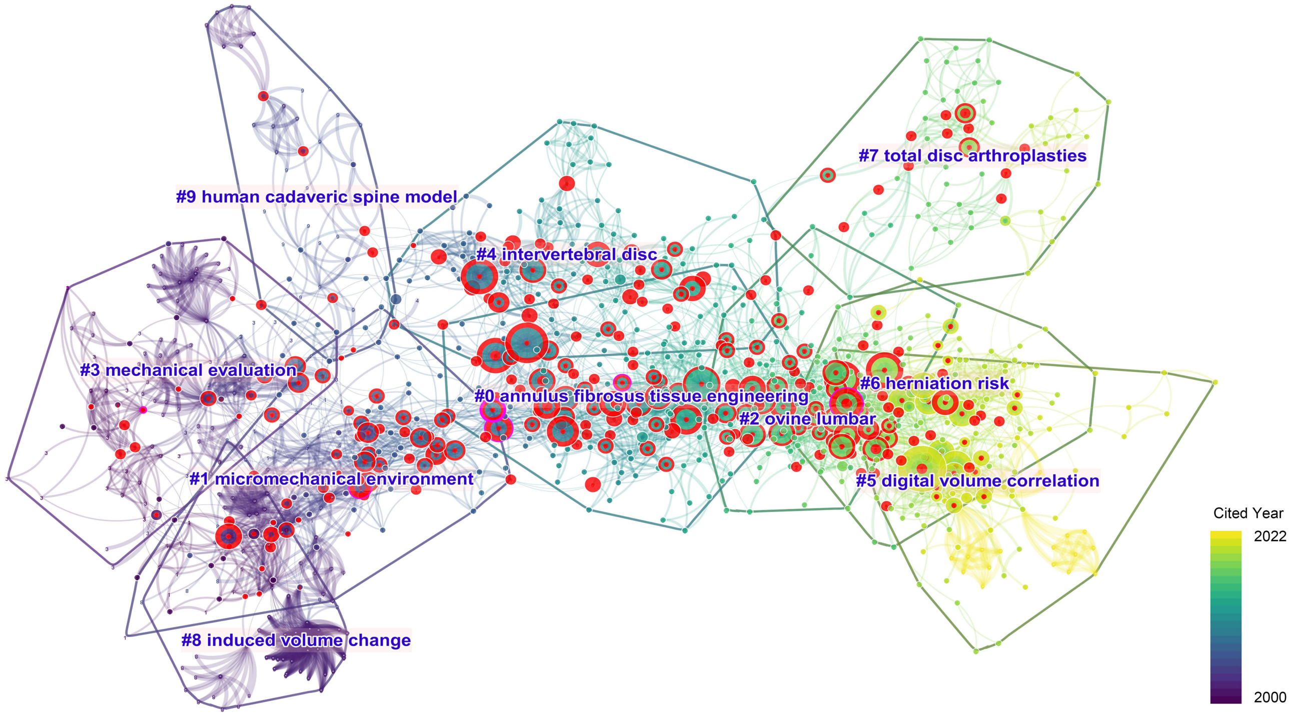

Figure 4 Citation bursts in the co-citation network. Red rings around the nodes represent the years when citation bursts can be found.

692 times up to January 2022, respectively. From January 2002–December 2021, Adams MA, Panjabi MM, Wilke HJ, Iatridis JC, Goel VK, and Urban JPG were among the 10 authors most cited by papers of IVD biomechanics in each 5-year slice. Of these, Adams MA from the University of Bristol was cited the most.

Major Journals

As shown in Table 8, *Spine* was the most productive journal, having published 414 papers of IVD biomechanics, followed by the *Journal of Biomechanics* (*J Biomech*) (208 papers) and the *European Spine Journal* (*Eur Spine J*) (158 papers). *Spine, Eur Spine J*, and *J Biomech* were also determined to be the most cited journals, having been cited 2689,

Table 5 Top 10 References with the Strongest Citation Bursts

References	Cluster ID	Strength	Start	End	2000–2022
Newell et al. *J Mech Behav Biomed*. 2017[5]	5	23.75	2018	2022	
Dreischarf et al. *J Biomech*. 2014[28]	2	19.74	2015	2019	
Rohlmann et al. *J Biomech*. 2006[29]	0	19.67	2007	2011	
Vergroesen et al. *Osteoarthr Cartilage*. 2015[16]	6	18.81	2017	2020	
Schmidt et al. *Clin Biomech*. 2006[64]	0	18.29	2007	2011	
Goel et al. *Spine*. 2005[59]	4	16.88	2006	2010	
Iatridis et al. *Spine J*. 2013[26]	6	14.81	2014	2018	
Nerurkar et al. *J Biomech*. 2010[39]	0	14.42	2011	2015	
Galbusera et al. *J Mech Behav Biomed*. 2011[30]	2	14.09	2013	2016	
OConnell et al. *J Mech Behav Biomed*. 2011[31]	2	14.09	2013	2016	

Note: In the right-most column, the color represents the strength of the citation burst (red, strong burst; green, weak burst).

Table 6 References with the Highest Betweenness Centrality in the Co-Citation Network

References	Cluster ID	Centrality
MacLean et al. *J Orthop Res.* 2005[32]	1	0.22
Hsieh et al. *Spine.* 2009[77]	0	0.13
Iatridis et al. *Spine J.* 2013[26]	6	0.12
Elliott et al. *J Biomech Eng-T ASME.* 2001[14]	1	0.12
Mcnally et al. *Spine.* 1996[78]	3	0.12
Adams et al. *Spine.* 2000[54]	3	0.10
Nerurkar et al. *Nat Mater.* 2009[44]	0	0.10
Guilak et al. *Spine.* 1999[52]	1	0.10
Holzapfel et al. *Biomech Model Mechan.* 2005[33]	0	0.10
Olmarker et al. *Spine.* 1995[79]	3	0.10

2018, and 1960 times by papers of IVD biomechanics, respectively, from 2000 to 2022. From January 2002–December 2021, they were also the three most cited journals in each 5-year slice (Figure 6).

Distribution of Countries/Regions in Papers of IVD Biomechanics

Up to January 2022, authors from the United States had published 1278 papers of IVD biomechanics, followed by authors from the People's Republic of China and Canada, who published 456 and 260 papers, respectively. Similarly, the United States and the People's Republic of China were ranked first and second in terms of scientific output from 2012 to 2016 and 2017 to 2021 (Table 9).

Discussion

For the present study, a primary purpose is to explore the evolution of research topics, and emerging trends based on the co-citation network and its clustering. Cluster #0 and #1, the largest two clusters, were labeled as "annulus fibrosus tissue engineering" and "micromechanical environment" respectively (Table 3). These labels were extracted from the titles of citing articles by the LLR algorithm.[24] Specifically, the citing articles of cluster #1 were mainly concerned with investigating the micromechanical effects on the IVD cells. Among them, Setton et al[27] had cited 27 (18.8%) references of cluster #1, being the most relevant citer. Setton et al reviewed the knowledge of micromechanical factors in the IVDs and their role in cell biology, with a key point on the differences between AF and NP. Citers of cluster #0 had a strong focus on tissue engineering. The most relevant citing article was written by Iatridis et al[26] which had cited 32 (21.6%) references of cluster #0. Iatridis et al reviewed the key targets to repair and the promising biomaterials. Considering the statistical results and actual content of citers, the labels of cluster #0 and #1 are both acceptable.

A major evolution of research topics in the co-citation network was found between cluster #1 and #0. First, these were the largest two clusters in this study, which indicate that research supported by these references are major topics of IVD biomechanics. Second, the average publication years of references in these two clusters were 2000 and 2007, respectively, which are distinct and provide a probability of transition. Most importantly, we found nodes of high betweenness centrality (MacLean et al[32] and Holzapfel et al[33]) between them by which they are connected tightly (Figure 5). This evolution may represent the process of the key research topic of IVD biomechanics changing from mechanobiology to tissue engineering. This result is logical as progress in mechanobiology can help to guide the strategy and design of functional engineered tissues.[34] In this study, cluster #0 was comprised of highly concentrated nodes with citation bursts (Figure 4). The citation years of references in cluster #0 ranged from 2007 to 2015, indicating that cluster #0 attracted much attention and captured the emerging trend of IVD biomechanical research at that time.

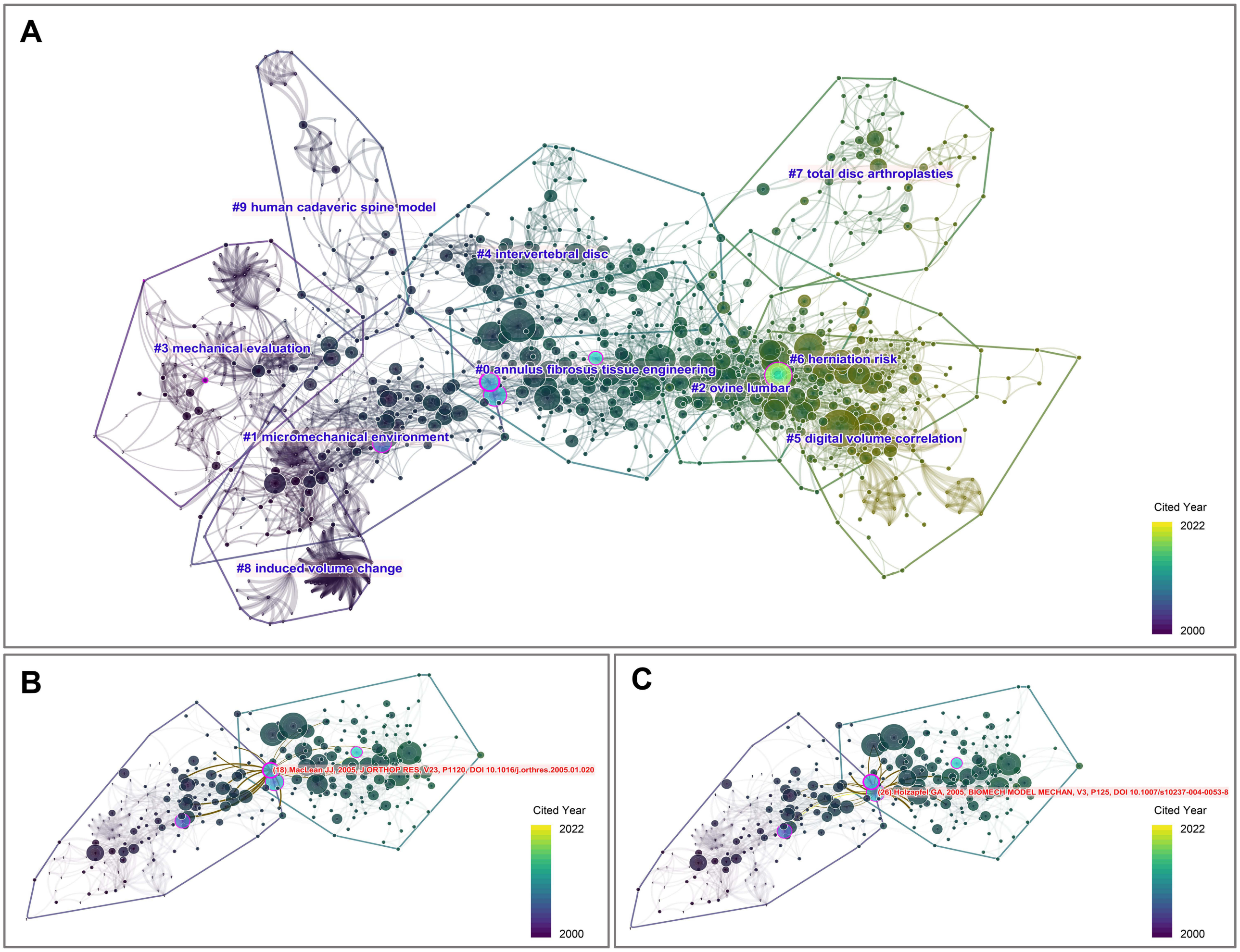

Figure 5 Nodes positioned between clusters #0 and #1. There were five nodes with highest betweenness centrality highlighted by purple rings, where the thickness indicated the strength of betweenness centrality. Specifically, MacLean et al (2005)[32] and Holzapfel et al (2005)[33] were positioned between clusters #1 and 0, which are more likely to provide insights into topics evolution or emerging trends, while the other highlighted nodes were highly connected to other nodes within the same cluster, which may make them less important than the former. (**A**) Spotlight model of the co-citation network, which highlights nodes with high betweenness centrality. Close-ups of MacLean et al (2005)[32] (**B**) and Holzapfel et al (2005)[33] (**C**), which are positioned between clusters #0 and #1.

Clusters #5 and #6 were the two most recent clusters in this study (Table 3 and Figure 3), and cluster #6 was also comprised of highly concentrated nodes with citation bursts (Figure 4). It is evident that references in cluster #6 have attracted extensive attention at present, and cluster #6 probably captured the current emerging trend. The optimal label of cluster #6 was "herniation risk", and the suboptimal label was "annulus fibrosus repair." The most relevant citer published by Fujii et al[35] had cited 15 (15.5%) references of cluster #6. They tested the biomechanical properties of AF repaired by genipin crosslinked fibrin adhesive hydrogel. The second relevant citer provided a systematic review of injectable cell delivery biomaterials used in IVD repair.[36] Therefore, the actual interests of the citing articles were consistent with the suboptimal label of clusters #6, "annulus fibrosus repair".

As presented in cluster #0 and #6, AF tissue engineering and repair had been identified as emerging trends of IVD biomechanics. However, their citing articles investigated the NP replacement as well. For example, the most relevant citing article as well as a highly cited article of cluster #6, had reviewed the promising materials both for AF repair and NP replacement.[26] Most importantly, there is an objective expansion in the studies about NP replacement. Therefore, considering "IVD repair" as scope of the emerging trends was conservative, but more reasonable for the present study. Moreover, the precise scope of "repair" should be determined. Biological repair strategies for intervertebral disc degeneration can be classified into three categories: biomolecular therapy, cell therapy, and biomaterial-based

Table 7 Top 10 Authors with the Highest Citation Counts Contributed by Papers of IVD Biomechanics

Rank	Up to Jan 2022	Jan 2002–Dec 2006	Jan 2007–Dec 2011	Jan 2012–Dec 2016	Jan 2017–Dec 2021
1	Adams MA (917)	Adams MA (91)	Adams MA (196)	Adams MA (258)	Adams MA (267)
2	Panjabi MM (747)	Panjabi MM (84)	Panjabi MM (165)	Wilke HJ (229)	Wilke HJ (238)
3	Wilke HJ (692)	Iatridis JC (71)	Goel VK (149)	Panjabi MM (217)	Schmidt H (234)
4	Iatridis JC (611)	Goel VK (65)	Iatridis JC (147)	Iatridis JC (181)	Panjabi MM (201)
5	Goel VK (562)	Shiraziadl A (63)	Wilke HJ (146)	Schmidt H (153)	Iatridis JC (187)
6	Urban JPG (500)	Nachemson A (60)	Urban JPG (102)	Rohlmann A (150)	Urban JPG (149)
7	Schmidt H (473)	Urban JPG (58)	Nachemson A (100)	Urban JPG (146)	Oconnell GD (147)
8	Nachemson A (430)	Wilke HJ (57)	Rohlmann A (98)	Goel VK (142)	Goel VK (140)
9	Shiraziadl A (416)	White AA (46)	Natarajan RN (89)	Oconnell GD (100)	Rohlmann A (137)
10	Rohlmann A (406)	Lotz JC (44)	Schmidt H (84)	Nachemson A (99)	Shiraziadl A (117)

Note: Data are presented as "first or corresponding author (citation count in corresponding time slice)".

Table 8 Top 10 Most Productive Journals in IVD Biomechanics

Journal	Count (%)	IF (2020)	JCR (Rank/Category)
Spine	414 (12.98%)	3.468	Q1/Orthopedics Q2/Clinical Neurology
J Biomech	208 (6.52%)	2.712	Q3/Biophysics Q3/Engineering, Biomedical
Eur Spine J	158 (4.96%)	3.134	Q2/Orthopedics Q3/Clinical Neurology
J Biomech Eng-T ASME	103 (3.23%)	2.097	Q3/Engineering, Biomedical Q4/Biophysics
Clin Biomech	97 (3.04%)	2.063	Q3/Engineering, Biomedical Q3/Orthopedics
Spine J	86 (2.70%)	4.166	Q1/Orthopedics Q2/Clinical Neurology
J Orthop Res	84 (2.63%)	3.494	Q1/Orthopedics
J Mech Behav Biomed Mater	79 (2.48%)	3.902	Q2/Engineering, Biomedical Q2/Materials Science, Biomaterials
Comput Methods Biomech Biomed Engin	52 (1.63%)	1.763	Q4/Computer Science, Interdisciplinary Applications Q4/Engineering, Biomedical
J Neurosurg Spine	46 (1.44%)	3.602	Q1/Surgery Q2/Clinical Neurology

Abbreviations: IF, impact factor; JCR, journal citation report.

therapy.[37,38] According to the labels and primary citing articles[26,35,36] of cluster #0 and #6, which was discussed before, the identified emerging trend was more relevant to biomaterial field rather than biomolecular/cell field. This finding is in line with the mainstream[38] and will be discussed below.

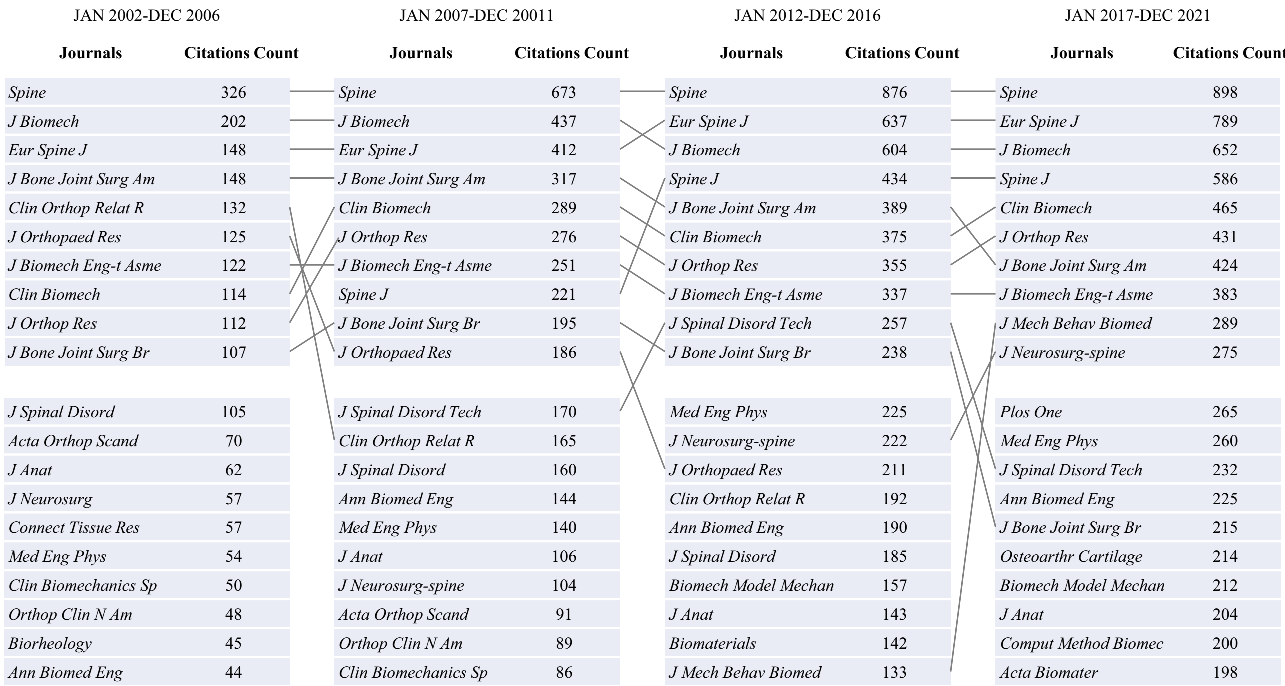

Figure 6 Top 20 journals with the most citations contributed by papers of IVD biomechanics in each 5-year slice. The fluctuation of top 10 journals with the most citations were presented. The gray straight line showed the ranking change of a certain journal in each 5-year slice. *Spine, Eur Spine J*, and *J Biomech* were the journals cited most by papers in IVD biomechanics in each time slice.

Biomechanics serves to evaluate new repair strategies, for example, comparing the mechanical properties between new tissue engineering scaffolds and native tissues. Therefore, it is crucial to establish a goal for repair strategies, based on mechanical properties of native IVDs. Considering this, a review article by Nerurkar et al[39] (in cluster #0, with 32 citations contributed by IVD biomechanical studies and strong citation bursts) proposed a series of mechanical criterions or benchmarks of native IVD tissue. Utilizing these benchmarks, subsequent repair strategies can be designed more effectively.

Table 9 Most Productive Countries/Regions in Two Recent 5-Year Time Slices

2012–2016		2017–2021	
Countries/Regions	**Paper Counts**	**Countries/Regions**	**Paper Counts**
United States	336	United States	293
China	118	China	275
Canada	85	Germany	81
Germany	74	Canada	60
England	56	England	58
Netherlands	47	Australia	47
Switzerland	45	Switzerland	43
South Korea	43	France	34
Taiwan	35	Netherlands	33
Italy	33	India	32

Methods of AF repair include suture, void filling, and biomimetic tissue engineering scaffolds.[40] Void filling methods use injectable hydrogels or other materials to repair the defects in the AF. To reach better adhesion with native tissue, combining hydrogels with biocompatible cross-linkers is a feasible way, such as collagen cross-linked with riboflavin[41] and fibrin cross-linked with genipin.[42] Biomimetic tissue engineering could mimic the collagen fiber architecture of native AF using aligned fibrous scaffolds. The scaffolds can be produced by various techniques, such as electrospinning, collagen contraction, silk-fiber winding, among which electrospinning is preferred.[43] A study by Nerurkar et al[44] (in cluster #0) had raised considerable attentions with 17.5 citations per year and high betweenness centrality. They developed an aligned electrospun nanofibrous scaffolds seeded with mesenchymal stem cells for AF repair. This scaffold succeeded to generate angle-ply multi-lamellar tissues that replicate the organized structure of the AF, as well as the anisotropic mechanical properties. To uncover the role of oriented lamellar structure, their later work constructed three bilayers with three different fiber orientations to perform uniaxial tensile testing.[45] The experimental data was then applied to the constitutive model. Results showed that interlamellar shearing maximizes the reinforcement of the tensile response when fibers in adjacent lamellae were aligned in opposing directions. This finding highlighted the role of organized lamellar structure in the success of AF repair.[45] In addition, compared to scaffolds without organized lamellar structure, biomimetic scaffolds with lamellar structure may not require adhesion or void filling.[46] Hence, biomimetic tissue engineering scaffolds may be a promising field of AF repair.

In addition to AF repair, there is a remarkable expansion in the studies about NP replacement as well. To date, many injectable natural and synthetic materials for NP replacement have been developed. Biocompatible natural materials such as alginate, agarose, hyaluronan, collagen, chitosan and cellulose can provide favorable environment for IVD cells.[26] However, researches in recent years have found the common limitation of them, weakness in mechanics. Therefore, great efforts have been made to develop composite materials with improved mechanical properties, such as cellulose/chitosan,[47] fibrin/Silk[48] and gelatin/hyaluronic acid.[49] In one study, an injectable bioinspired formulation of cellulose nanofibril-reinforced Chitosan had been proposed for NP replacement and exhibited an increase of the elastic modulus with the increase of the cellulose nanofibril content.[47] This approach was also appropriate for AF repair.[50] These findings highlighted the importance of composite materials. In addition, due to well controlled properties, a variety of synthetic polymeric materials have also been investigated as potential NP substitutes, including in situ hydrating polymers and in situ forming polymers.[40] While biomaterial-based therapy has shown promise in preclinical studies, it has not yet been well demonstrated clinically, leaving a gap in IVD repair.

Over several decades, numerous outstanding papers in IVD biomechanics have been published. Combining validated metrics, the present study has found the most representative literatures (Table 2, Tables 4 and 5). These literatures contribute to several fields, including mechanical testing of normal and pathological IVDs, mechanical evaluation of new repair strategies and development of finite element model. Landmark studies on IVD repair have been discussed. Other landmark studies will be discussed in the following paragraphs.

Understanding the mechanical properties of normal and degenerative IVDs is key to IVD biomechanics. Many classic studies, the majority of which were found in cluster #1, contributed a lot to this area. As cornerstones of further studies, most of them had high annual average citation counts and betweenness centrality (Tables 2 and 6). Specifically, Wilke et al[9] (with 37.63 overall citations per year) conducted an in vivo direct measurement of intradiscal pressure in a volunteer male orthopedist. The result showed that the resting intradiscal pressure is roughly 0.1–0.24 MPa at night and increases to 0.3–1.1 MPa when standing or sitting, and to 2.3 MPa when lifting a 20-kg weight in a flexed position. This study was considered a supplement to Nachemson's earlier works.[51] MacLean et al[32] (in Cluster #1) performed a mechanobiological in vivo studies, which was been mentioned before for their highest betweenness centrality and crucial position in the co-citation network to link the cluster #1 and #0. The results showed that responses in the disc cell to mechanical loading was dependent on duration of loading and there were distinct responses between the AF and NP. Three studies with high betweenness centrality investigated the multi-scale biomechanical behaviors of IVDs.[14,33,52] Elliott et al[14] (in Cluster #1, 0.12 in centrality) provided evidences that compared to the inner AF, the outer AF was more effective to withstand the circumferential stresses, according to higher circumferential tensile modulus in the linear area. Holzapfel et al[33] (in Cluster #1, 0.10 in centrality) demonstrated that at the shallow radial position (≤3.9±0.21 mm) of AF, collagen fiber angles depend predominately on the circumferential position. The fiber angle was smallest in the midsagittal ventral position (23°) and biggest in the midsagittal dorsal position (47°). This studies also provided valuable mechanical information about nonlinearity, anisotropy, heterogeneity and viscoelasticity at the scale of single lamellar. Guilak et al[52] (in Cluster #1, 0.10 in centrality) characterized the micromechanical properties of IVD cells using alginate as the 3D matrix and provided available evidence that NP cells were more viscous and stiffer than AF cells, suggesting the existence of biomechanical distinction between cell types. A recent review article by Newell et al[5] (in cluster #5), with highest citations contributed by IVD biomechanical studies and strongest citation bursts, amalgamated many experimental testing techniques adopted by biomechanical research to instruct experimentalists and computational modelers. It can be thought to be one of the most important landmark studies in IVD biomechanics.

Mechanical pathology of disc degeneration was investigated by numerous landmark studies as well. Specifically, Adam et al[53] (17.37 overall citations per year) compared the distribution of stress between normal, aged and degenerated IVDs. The results showed that degeneration reduced the diameter of the functional NP by approximately 50%, and the pressure insides this region by 30%. Instead, both the width of the functional annulus and the height of compressive stress peaks within it increased. Another study with high betweenness centrality by Adam et al[54] (in cluster #3, 0.10 in centrality) reached a similar conclusion that minor injury of CEPs may lead to a decrease in intradiscal pressures and stress concentrations in the AF. These findings supported the role of high 'stress' concentrations within the AF in the development of IVD degeneration. A large in vivo study conducted by Sato et al[55] (15.54 overall citations per year) corroborated this conclusion. They demonstrated that degeneration does influence the intradiscal pressure and there exists a clear dose-effect relationship between degenerative grade and intradiscal pressure. In the field of mechanical pathology, a review article by Vergroesen et al,[16] with 36.5 overall citations per year, 40 citations contributed by IVD biomechanical studies and strong citation bursts, provided a comprehensive discussion about the interaction between biomechanics, extracellular matrix, and cells during degeneration.

Adjacent-level effects had also been investigated by several landmark biomechanical studies with high annual average citation counts. Adjacent segment disease (ASD) is a long-term outcome of surgery. Early epidemiological report of ASD by Hilibrand et al[56] had raised significant attentions. Naturally, a biomechanical study should be performed to uncover the pathogenesis. In 2002, Eck et al[57] (with 23.38 overall citations per year) performed an in vitro study. With upper cervical spine segment stabilized, the intradiscal pressures during flexion increased by 73.2% at C4-C5, and by 45.3% at C6-C7. A strong link between impaired mechanical function and adjacent segment disease was established by these findings. Due to adjacent-level effects of spinal fusion, non-fusion motion preservation devices were developed. Charite was the first lumbar implant commercially available.[58] Since then, more artificial discs were designed. Hence, comparison of mechanical properties between the substitute and native IVDs became a major consideration. In 2005, Goel et al[59] (in cluster #4, with 35 citations and strong citation bursts contributed by IVD biomechanical studies) investigated the biomechanical effects of the Charité artificial disc across the implanted and adjacent segments by a hybrid test method. The result showed that the Charité increased the motion at the implanted level, and decreased the motions at the adjacent levels, which led to corresponding changes in loads. These findings conformed the biomechanical advantage of motion preservation devices. Compared to spinal fusion, short-term superiority of total disc replacement has also been proved by longitudinal follow-up clinical studies.[60,61] However, there are still concerns about the long-term outcome, such as reoperations.[62]

In vivo and in vitro biomechanical studies investigating native IVDs, and biomaterials have yielded many successes. Meanwhile, finite element (FE) analysis, a research method based on computer, has also experienced rapid growth. Compared to in vitro or in vivo approaches, computational methods can offer cost-effective solutions with less ethical concerns. The earliest of them was completed by Belytschko et al[63] in 1974 investigating stress analysis of IVDs. In 2006, Rohlmann et al[29] (in cluster #0, with 43 citations as well as strong citation bursts contributed by IVD biomechanical studies) developed a three-dimensional nonlinear FE model to investigate the influence of disc degeneration on the mechanics of lumbar motion segment. In the same year, Schmidt et al[64] (in cluster #0, with 40 citations as well as strong citation bursts contributed by IVD biomechanical studies) developed a method to calibrating the FE model of human lumbar AF. Since then, FE analysis had been adopted by numerous studies to investigate IVD biomechanics. When it came to 2014, Dreischarf et al[28] (in cluster #2, with 44 citations as well as strong citation bursts contributed by IVD biomechanical studies) compared the relative predictive power of eight well-established FE models of L1–L5. The result showed that the median of all FE model predictions was always relatively close to the in vitro median values of the intervertebral rotations, intradiscal pressure and facet joint forces. Studies by Dreischarf et al,[28] Rohlmann et al[29] and Schmidt et al[64] had become the references with the highest citation counts contributed by IVD biomechanical papers, except for review article written by Newell et al[5] Accordingly, FE model studies may have made important contributions to our understanding of IVD biomechanics.

Considering the list of the 10 references with the highest citations contributed by IVD biomechanical studies (Table 4), half focused on developing models or new methods of biomechanical tests. These studies provided principles for IVD biomechanical experiments. For example, based on Newell et al's review of disc composition and functional anatomy,[5] Wang et al determined the thickness of cartilaginous endplates in their finite element model.[65] In addition, Newell et al summarized characteristics of IVD during bending and axial rotation tests, highlighting the "neutral zone" where the torque is zero (hysteresis), and Bezci et al combined the "zero torque location" and "zero rotation location" to form the concept of a "hysteresis loop."[66] The shape change of the "hysteresis loop" was then used to explore the combined effect of axial compressive preload and rotation angle on the mechanical behavior of IVDs.

The major contributors in IVD biomechanics were very concentrated. Wilke HJ, Elliott DM, and Iatridis JC have been the most productive authors of papers of IVD biomechanics, and Adams MA, Panjabi MM, and Wilke HJ were the most cited authors of identified references (Table 7). Particularly, Adams MA ranked as the most cited author of included references in each 5-year slice. Spine, Eur Spine J, and J Biomech published the most papers of IVD biomechanics and were the journals cited most by original papers as well (Table 8, Figure 6). Among the top 10 references with the highest citation counts contributed by papers of IVD biomechanics, half were published in J Biomech. In the lists of references with the highest betweenness centrality and papers with the most annual average citation counts, respectively, half and 40% were published in Spine, respectively. Regardless of the timespan selected, the United States was the most productive country. However, publications from the People's Republic of China have increased rapidly over time.

Conclusion

The major research topic of IVD biomechanics may have evolved from mechanobiology to mechanical repair strategies of IVDs, and the latter has been identified as an emerging trend in IVD biomechanics, which is a major finding of the present study.

Landmark studies identified have contributed to several fields, including mechanical testing of normal and pathological IVDs, mechanical evaluation of new repair strategies and development of FE model. In the field of mechanical physiology, in vivo study by Wilke et al,[9] with the highest annual average citations, provided valuable data of intradiscal pressure by direct measurement. Review article for biomechanical testing techniques by Newell et al,[5] had the most citations and strongest bursts of citations contributed by IVD biomechanics. In vivo study by MacLean et al[32] (in Cluster #1), with highest betweenness centrality, uncovered the mechanobiological distinction between NP and AF cell, which should be considered as an important bridge in topics evolution. In the field of mechanical pathology, review article by Vergroesen et al[16] highlighted the role of vicious circle between biomechanics, extracellular matrix, and cells in the development of IVD degeneration. In vitro study by Adam et al[53] demonstrated the crucial role of 'stress' concentrations in IVD degeneration. In term of IVD repair, Nerurkar et al had reviewed the benchmarks of native IVDs[39] and developed an aligned electrospun nanofibrous scaffolds for AF repair,[44] both of which are representative studies. Finally, FE model studies by Dreischarf et al,[28] Rohlmann et al[29] and Schmidt et al,[64] with high citation counts contributed by IVD biomechanical papers, should also be regarded as landmark studies. Additionally, the present study explored the major contributors to IVD biomechanics. Adams MA was the most cited author among the references providing the most literature basis for IVD biomechanical research. Spine, Eur Spine J, and J Biomech were the major journals for both original papers and references. The United States has made significant contributions to the field; however, Chinese researchers are catching up.

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Disclosure

The authors report no conflicts of interest in this work.

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