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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJD* as 4.2; JIF without journal self cites: 4.1; 5-year JIF: 4.2; JIF Rank: 40/186 in endocrinology and metabolism; JIF Quartile: Q1; and 5-year JIF Quartile: Q2.

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SCIENTOMETRICS

Ubiquitination in diabetes and its complications: A perspective from bibliometrics

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Abstract

BACKGROUND

Diabetes has a substantial impact on public health, highlighting the need for novel treatments. Ubiquitination, an intracellular protein modification process, is emerging as a promising strategy for regulating pathological mechanisms. We hypothesize that ubiquitination plays a critical role in the development and progression of diabetes and its complications, and that understanding these mechanisms can lead to new therapeutic approaches.

AIM

To uncover the research trends and advances in diabetes ubiquitination and its complications, we conducted a bibliometric analysis.

METHODS

Studies on ubiquitination in diabetes mellitus and its complications were retrieved from the Web of Science Core Collection. Visual mapping analysis was conducted using the CiteSpace software.

RESULTS

We gathered 791 articles published over the past 23 years, focusing on ubiquitination in diabetes and its associated complications. These articles originated from 54 countries and 386 institutions, with China as the leading contributor. Shanghai Jiao Tong University has the highest number of publications in this field. The most prominent authors contributing to this research area include Wei-Hua Zhang, with Zhang Y being the most frequently cited author. Additionally, *The Journal of Biological Chemistry* is noted as the most cited in this field. The predominant keywords included expression, activation, oxidative stress, phosphorylation, ubiquitination, degradation, and insulin resistance.

CONCLUSION
The role of ubiquitination in diabetes and its complications, such as diabetic nephropathy and cardiomyopathy, is a key research focus. However, these areas require further investigations.

Key Words: Diabetes mellitus; Ubiquitination; Bibliometric analysis; CiteSpace; Research trends

Core Tip: Ubiquitination, as a crucial protein modification mechanism, plays a key regulatory role in the pathological processes of diabetes. To gain insights into research trends and future directions in the field of diabetes and ubiquitination, we conducted a systematic bibliometric analysis of relevant literature from 2001 to 2023. Through this analysis, we aim to break through traditional treatments and explore novel and effective therapeutic approaches.

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INTRODUCTION

Diabetes kills more than four million people each year and has devastating effects on societies and nations[1]. Diabetes mellitus (DM) is a prevalent chronic disorder of glucose and lipid metabolism, characterized by both insulin resistance and insulin deficiency[2]. Another prominent feature is persistent hyperglycemia, which disrupts the body's internal homeostasis and contribute to the subsequent emergence of diabetes-related complications. The onset and progression of these complications are intricately linked to epigenetic histone modifications[3], with ubiquitination being a common form of histone modification. Various categories of drugs are available for treating diabetes and its associated complications, but certain drugs may cause adverse reactions during treatment. Therefore, identifying safer and more tolerable targets and drugs is crucial. Currently, several studies are exploring the treatment of diabetes by modulating the biological pathways involved in endocrine imbalance, including the ubiquitination pathway. This approach may help control the pathological processes of diabetes by modulating endocrine-related biological pathways, unlike traditional drug therapy.

Ubiquitin is an evolutionarily conserved protein comprising 76 amino acids. Ubiquitination is a biological modification that governs the function and enhances the regulation and stability of a specific protein by covalently attaching a ubiquitin molecule to it. Successful completion of this process necessitates the coordinated involvement of an activating enzyme (E1), a conjugating enzyme (E2), and a ligase (E3)[4-7]. During ubiquitination, proteins are targeted to the ubiquitin-proteasome system (UPS) for degradation[8]. An association between UPS dysfunction and the pathogenesis of diabetes has been established[9]. Multiple studies have corroborated the pivotal role of ubiquitination in diabetes-related complications[10-12]. Regulating the progression of diabetes *via* the ubiquitination pathway is recognized as a crucial aspect of treatment. However, additional research is required to substantiate and broaden these findings to advance more effective treatment strategies. Therefore, we performed a bibliometric analysis of studies exploring the role of ubiquitination in DM, using an integrated approach that included both quantitative and qualitative analyses[13]. This approach evaluates the distribution of profiles, relationships, and clustering within research fields and has been widely adopted to assess the credibility, quality, and impact of scholarly publications[14,15]. Bibliometric analysis assesses the influence of countries, institutions, and authors contributing to a specific research field, while keyword and citation analyses reveal current trends and hotspots in research. To date, no bibliometric analysis has been conducted on research focusing on ubiquitination. A bibliometric analysis of research on diabetes, its complications, and ubiquitination offers fresh insights into the field's development. These findings highlight the critical role of ubiquitination as a pivotal area for future exploration and therapeutic innovations. This analysis not only identifies the most influential studies and emerging themes but also provides valuable insights for researchers seeking to advance knowledge and drive progress in this rapidly evolving domain. Our assessment is expected to guide clinical practice, inform the development of treatment guidelines, and contribute to the advancement of safer and more tolerable drug therapies, thereby providing valuable reference points for future research directions and content.

MATERIALS AND METHODS

This study followed the PRISMA criteria for bibliometric analysis.

Data source and search strategy

The literature analyzed in this study was sourced from the Web of Science Core Collection (WOSCC), the most reliable and comprehensive database for bibliometric analysis. Our data covered the period from 2001 to December 31, 2023, using the search formulas outlined in the Supplementary Table 1. The search formulas were selected based on a thorough summary of our research, prioritizing those that yielded the highest number of relevant results, which were then carefully filtered. The inclusion criteria were articles or reviews published in English to ensure consistency and comprehensibility. Initially, 854 articles were screened and 63 were excluded. Exclusion criteria included early access articles, meeting abstracts, book chapters, proceedings papers, editorial materials, letters, retractions, articles published between 1993 and 2000, and articles published in languages other than English. These exclusion criteria focused on non-peer-reviewed studies and literature beyond the time frame, resulting in a final inclusion of 791 articles. The detailed screening process is illustrated in Figure 1.

Data collection and statistics analysis

Two researchers accessed the literature from the WOSCC, exported the screened results in plain text format, and resolved any disagreements through group consultations. The obtained literature was subjected to bibliometric analysis using CiteSpace 6.2.R4 software. Professor Chao-Mei Chen developed specialized software for bibliometric analysis and visualization[16,17]. Descriptive analyses were performed using Microsoft Excel 2019 and Adobe Illustrator 2023. The study data were initially imported into CiteSpace 6.2.R4 to remove duplicates. Subsequently, co-occurrence and cluster analyses were conducted using CiteSpace 6.2.R4 for countries, institutions, authors, cited authors, cited journals, citations, and keywords related to the documents. In this analysis, a purple-colored outer ring on the node indicates the high centrality of the study, and a node with centrality greater than 0.1 indicates a pivotal point within the field[18,19]. The analyzed data were subjected to descriptive statistics, including the ranking of research items, frequency of occurrence, and centrality.

RESULTS

Trends in annual article issuance

Ultimately, we incorporated 791 relevant study publications, including 674 original articles and 117 reviews, and analyzed publication trends from 2001 to 2023 (Figure 2). Between 2001 and 2011, the number of research publications demonstrated a modest growth trend, reaching 112. From 2012 onward, the number of publications saw a substantial increase, totaling 36 in that year. However, 2015 experienced a substantial decline with only 26 publications. From 2016 to 2023, there was a wave of growth, totaling 536 publications. Notably, 2020 recorded a substantial surge, with annual publications reaching 79, and 2022 recorded an even more pronounced peak, reaching 99. This trend indicates a consistent increase in research focused on ubiquitination in diabetes and its associated complications. As a research area that has garnered attention over the past 23 years, it remains an actively pursued, with promising developments anticipated in the future.

Countries/regions analysis

From 2001 to 2023, ubiquitination research on diabetes and its complications involved 54 countries and territories worldwide. A visual mapping analysis encompassing all countries revealed a map with 54 nodes and 181 connecting lines (Figure 3). Table 1 details the 10 countries with the most published articles. China leads the list with 361 articles, followed closely by the United States with 242 articles; these two nations have far exceeded all others. The top 10 countries also included Japan, Germany, South Korea, Canada, the United Kingdom, France, India, and Australia, none of which had more than 100 articles. Centrality analysis indicates that the countries with purple outer circles include the United States, Germany, China, France, the United Kingdom, and Italy, highlighting the high centrality of these countries. The United States had a centrality of 0.43, followed by Germany at 0.37, and China ranked third with a centrality of 0.22. This underscores the substantial influence of the United States as a major player in the field of study.

Analysis of major institutions

Between 2001 and 2023, 386 different institutions participated in studies on ubiquitination in diabetes and its complications. A co-occurrence analysis for all institutions resulted in a graph comprising 386 nodes and 850 connecting lines (Figure 4A). Table 1 provides a detailed list of the 10 leading institutions ranked by the number of publications, with Shanghai Jiao Tong University leading, followed by the University of California System, and the Chinese Academy of Sciences ranked third. In terms of centrality, the University of California System performs well with a centrality of 0.17. Harvard University follows with a centrality of 0.15, and the Chinese Academy of Sciences ranks third with a centrality of 0.09. These institutions have made substantial contributions to the study of ubiquitination in diabetes and its associated complications. This level of involvement is evident not only in the number of publications but also in their centrality within the broader research network, highlighting the centrality of excellence in the University of California System. Institutions with a higher volume of publications typically engage in broader collaborations, including Shanghai Jiao Tong University, the University of California System, the Chinese Academy of Sciences, Harvard University, and Sun Yat-sen University. To delve deeper into the research content of each institution, keywords from articles published by these institutions were clustered and analyzed (Figure 4B). Two of the top three institutions by publication count concentrated on FOXO3a research themes, creating a module designated as Cluster 0. The second-ranking institution in terms of

Table 1 Top 10 countries and institutions with the highest number of publications

Items	Rank	Name	Centrality	Year	Publications
Country/region	1	China	0.22	2003	361
	2	United States	0.43	2001	242
	3	Japan	0.08	2004	54
	4	Germany	0.37	2002	48
	5	South Korea	0.07	2007	39
	6	Canada	0.03	2005	37
	7	England	0.19	2008	25
	8	France	0.13	2004	23
	9	India	0	2012	23
	10	Australia	0.06	2004	21
Institution	1	Shanghai Jiao Tong University	0.07	2018	29
	2	University of California System	0.17	2003	28
	3	Chinese Academy of Sciences	0.09	2012	24
	4	Harvard University	0.15	2001	23
	5	Sun Yat Sen University	0.03	2006	21
	6	Harvard Medical School	0.05	2001	20
	7	Huazhong University of Science & Technology	0.05	2015	18
	8	Harbin Medical University	0.01	2017	18
	9	Nanjing Medical University	0.07	2015	15
	10	Fudan University	0.02	2013	14

publications focused primarily on insulin-like growth factor I research (Cluster 1), highlighting its substantial contributions to these research areas.

Authors and co-cited authors analysis

Between 2001 and 2023, research on ubiquitination in relation to diabetes and its complications was conducted by 934 authors. Table 2 presents a comprehensive breakdown of the top 10 authors ranked by publication count, with Wei-Hua Zhang as the most prolific author, followed by Yi Liu and Peter MT Deen The top 10 authors based on publication numbers were closely grouped, indicating collaborative efforts among them. Despite these collaborations, centrality was 0. Co-citation relationships reflect the interplay and relevance of literature, typically indicating their importance within the same field or topic, while other researchers or scholars consider them pertinent and valuable within a specific context. Therefore, performing a co-citation analysis on the literature authored by these researchers and a keyword clustering analysis on the articles citing these co-cited authors (Figure 5A) helped elucidate the hot topics of the study. Table 2 lists the top 10 authors based on citations, where Zhang Y holds the highest number with 54 citations, followed by Liu Y with 42 citations. However, the centrality of all referenced authors was minimal. In the clustering diagram of cited authors (Figure 5A), it was observed that the studies of the most cited authors primarily focused on ferroptosis, forming a maximal cluster 0. This suggests that ferroptosis is a prominent research area with a notable correlation with ubiquitination.

Influential co-cited journals analysis

By analyzing journal co-citations in the literature, researchers can gain deeper insights into the focal points and emerging trends within a particular field. Generally, journals with a large number of citations reflect their influence and importance within the academic community. Of the 579 journals cited, 11 received more than 300 citations. Table 3 offers comprehensive details of the top 10 cited journals. The most cited journal was notably *J Biol Chem* with 625 citations, followed by *Proc Natl Acad Sci USA* with 529 citations, and *Nature* was closely behind, with 468 citations. Among the 10 most-cited journals, seven were situated in the Q1 region, underscoring their broad recognition in the academic community. *Nature* had the highest impact factor (IF) at 64.8, followed by *Cell* at 64.5, and *Science* ranked third, with an IF of 56.9. Figure 5B illustrates the double graph overlay, where the colored connections indicate the relationship between the two journals, highlighting their collaborative research efforts. The orange main pathway illustrates that articles from journals covering molecular biology, genetics, forensic anatomy, and medical sciences were referenced by articles from journals focusing on molecular biology and immunology.

Table 2 Top 10 authors and co-cited authors with the highest number of articles

Items	Rank	Name	Centrality	Year	Publications/count
Author	1	Wei-Hua Zhang	0	2017	6
	2	Yi Liu	0	2007	5
	3	Peter MT Deen	0	2006	5
	4	De-Chao Zhao	0	2020	4
	5	Miao Yu	0	2020	4
	6	Hai-Ming Xiao	0	2022	4
	7	Yu Sun	0	2020	4
	8	Shuo Peng	0	2020	4
	9	Fang-Ping Lu	0	2020	4
	10	Fang-Hao Lu	0	2020	4
Co-cited author	1	Zhang Y	0	2006	54
	2	Liu Y	0	2011	42
	3	Li Y	0	2012	33
	4	Li X	0	2018	29
	5	Zhang L	0	2018	27
	6	Wang Y	0	2009	26
	7	Liu J	0	2019	25
	8	Li J	0	2015	25
	9	Li W	0	2017	25
	10	Zhao Y	0	2013	24

Table 3 Top 10 most co-cited journals involving ubiquitination in diabetes

Rank	Co-cited journal	Year	Count	Centrality	IF	JCR
1	*Journal of Biological Chemistry*	2001	625	0	4.8	Q2
2	*Proceedings of the National Academy of Sciences of the United States of America*	2001	529	0	11.1	Q1
3	*Nature*	2001	468	0.01	64.8	Q1
4	*Cell*	2001	441	0.01	64.5	Q1
5	*Science*	2001	399	0.01	56.9	Q1
6	*Diabetes*	2002	394	0.01	7.7	Q1
7	*Journal of Clinical Investigation*	2001	368	0.01	15.9	Q1
8	*PLOS One*	2009	361	0.01	3.7	Q2
9	*Molecular Cell*	2004	329	0.01	16	Q1
10	*Molecular and Cellular Biology*	2002	310	0.01	5.3	Q2

Impact factor and Journal citation report are both 2022. IF: Impact factor; JCR: Journal citation report.

Analysis of co-cited literature and citation bursts

Among the 791 cited documents, we performed an extensive analysis of the top 10 most referenced articles, with specific citations detailed in Table 4. The article with the highest citation count was written by Song *et al*[20], followed by an article by Gong *et al*[21]. Notably, all 10 cited papers received at least five citations. Burst detection of citations enables the identification of highly impactful literature and offers insights into contemporary research frontiers and emerging directions. Figure 6A illustrates the results of burst detection of citations, where substantial burst intensity values indicate a sudden and notable surge in citations for a particular literature within a specified timeframe. Song *et al*'s article[20] excelled in both burst intensity and duration. This study examined the crucial role of the E3 ubiquitin ligase MG53 in

Table 4 Top 10 most co-cited references involving ubiquitination in diabetes

Rank	Author	Ref.	Citations	Year
1	Ruisheng Song	Central role of E3 ubiquitin ligase MG53 in insulin resistance and metabolic disorders	13	2013
2	Wenyan Gong	CKIP-1 affects the polyubiquitination of Nrf2 and Keap1 *via* mediating Smurf1 to resist HG-induced renal fibrosis in GMCs and diabetic mice kidneys	7	2018
3	Stewart H Lecker	Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression	6	2004
4	Chenlin Gao	MG132 ameliorates kidney lesions by inhibiting the degradation of Smad7 in streptozotocin-induced diabetic nephropathy	6	2014
5	Ruey-Hwa Chen	Ubiquitin-mediated regulation of autophagy	5	2019
6	Guanghong Jia	Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity	5	2018
7	Michael H Glickman	The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction	5	2002
8	Wolfgang H Dillmann	Diabetic Cardiomyopathy	5	2019
9	Saeed Yadranji Aghdam	High glucose and diabetes modulate cellular proteasome function: Implications in the pathogenesis of diabetes complications	5	2013
10	Qi Wu	CHIP Regulates Aquaporin-2 Quality Control and Body Water Homeostasis	5	2018

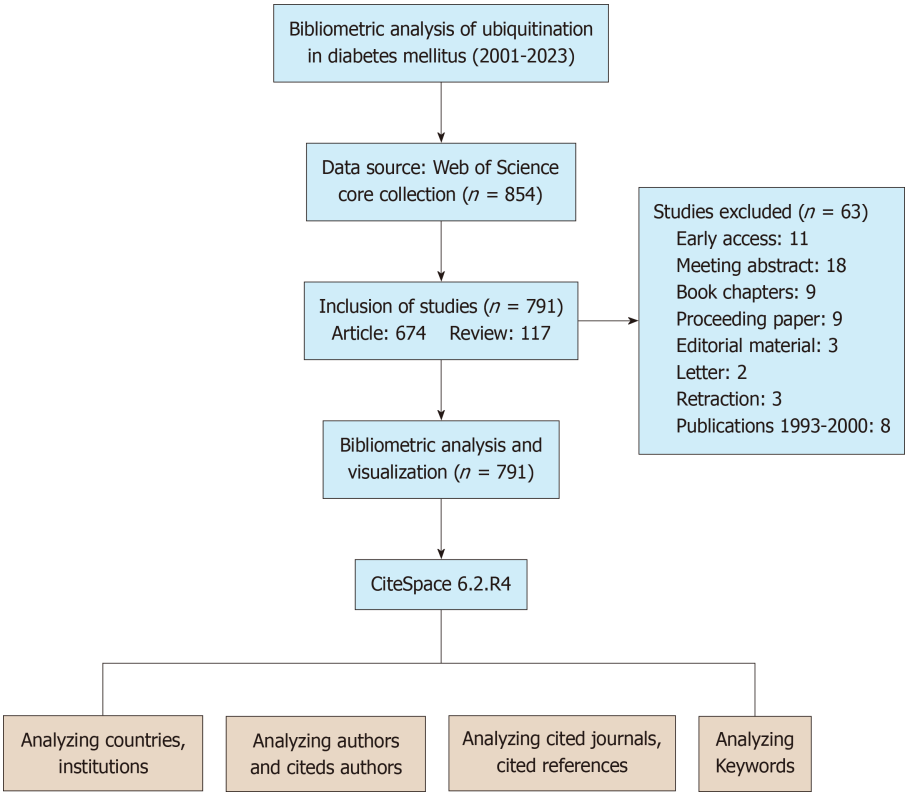


Figure 1 Literature screening process and bibliometric analysis methods.

insulin resistance and metabolic disorders, positioning it as a prominent research focus. Additionally, articles published by Gong *et al*[21], Jia *et al*[22], Buenaventura *et al*[23], and Hovsepian *et al*[24] exhibited strong citation bursts, indicating their prominence in recent research developments over the past three years. These research elements are likely to continue evolving and offer valuable insights for future research.

Keyword and hotspot analysis

Keyword analysis enables researchers to concentrate on cutting-edge issues within a field and identify key research hotspots. The top 20 keywords, ranked by frequency of occurrence in the CiteSpace analysis results, are listed in Table 5. Figure 7A shows the co-occurrence analysis of these keywords. Notably, "expression", "activation", "oxidative stress", "phosphorylation", and "ubiquitination" appeared with relatively high frequency, indicating prominent topics in the

Table 5 The 20 keywords with the highest frequency

Rank	Keyword	Centrality	Year	Count
1	Expression	0.21	2003	161
2	Activation	0.13	2001	114
3	Oxidative stress	0.08	2008	89
4	Phosphorylation	0.1	2003	87
5	Ubiquitination	0.11	2002	77
6	Degradation	0.14	2006	75
7	Insulin resistance	0.11	2007	74
8	Protein	0.07	2008	74
9	Gene expression	0.16	2001	61
10	Mechanisms	0.03	2002	54
11	Diabetic nephropathy	0.04	2013	53
12	Apoptosis	0.06	2003	52
13	Cells	0.05	2003	47
14	Metabolism	0.02	2012	42
15	Pathway	0.04	2007	42
16	Glucose	0.06	2010	38
17	Nf kappa b	0.06	2010	37
18	Mice	0.03	2002	35
19	Diabetes mellitus	0.08	2003	32
20	Inhibition	0.02	2003	31

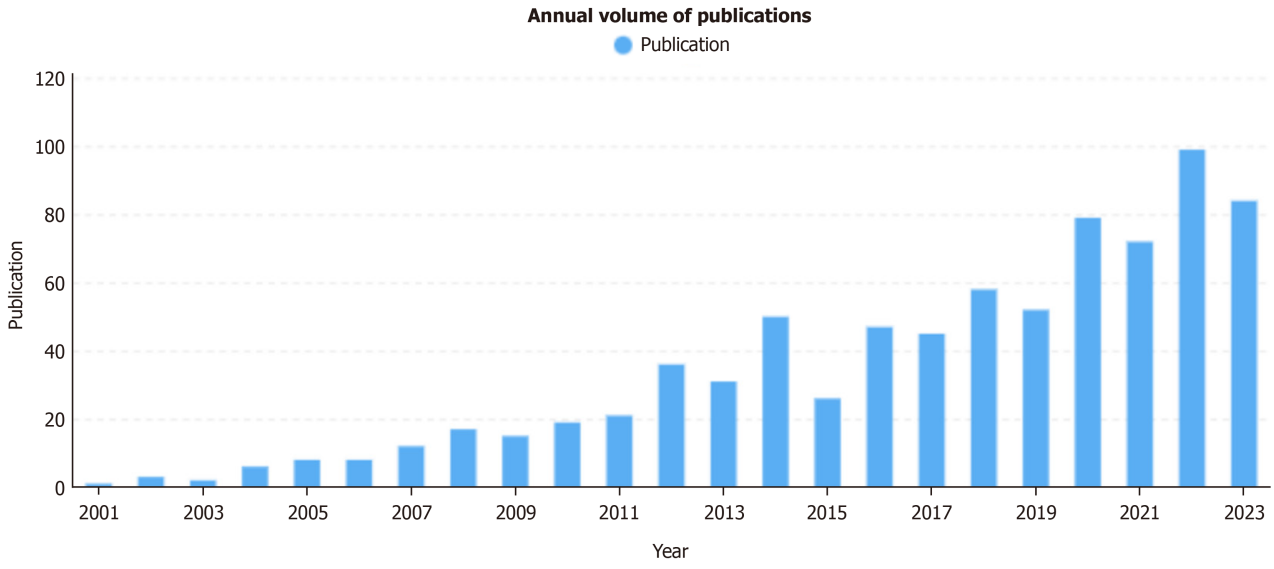


Figure 2 Annual publication trends in diabetes ubiquitination research, with the year of publication in the horizontal coordinate and the number of publications in the vertical coordinate.

study of ubiquitination in diabetic complications. Figure 6B illustrates the burst detection of the top 20 keywords in research on the ubiquitination of diabetes and its complications. Higher burst intensity values indicate a substantial increase in the prevalence of keywords over a specific period, revealing research trends and frontiers. The keywords with the earliest burst and the longest duration were "plasma membrane" and "phosphatidylinositol 3 kinase," with burst lasting from 2002 to 2012. Both were among the earliest topics to attract attention in the field and have maintained a high level of research activity over the past decade. In terms of burst intensity, "gene expression" ranks highest, followed by "*in*

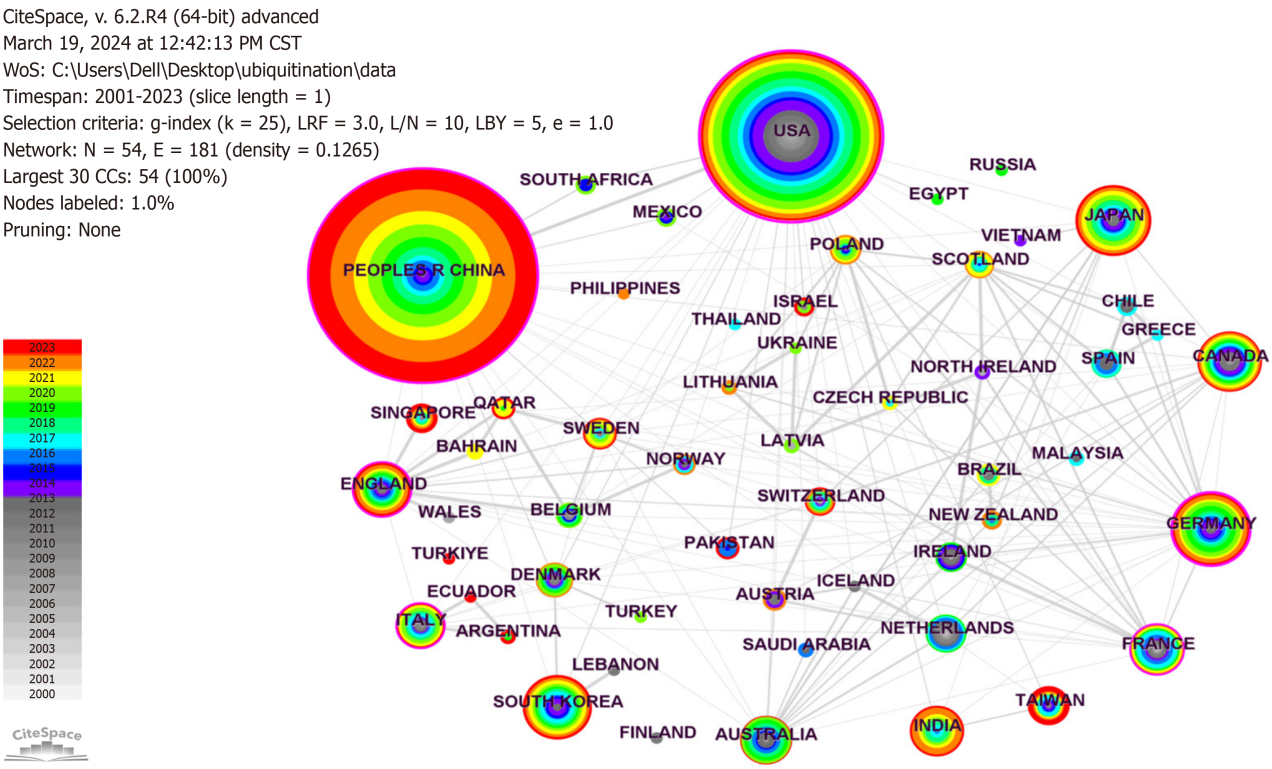


Figure 3 Visualization of country collaboration analysis for diabetes ubiquitination studies. Nodes represent countries, with the size of each node proportional to the number of articles published by that country, and the thickness of the connecting lines proportional to the intensity of collaboration between countries. Nodes with a purple periphery indicate high centrality, and nodes of different colors represent different publication years.

vivo," both representing active areas of research focus. Additionally, "ubiquitin ligase" ranks third in burst intensity, with its burst lasting for up to 10 years, marking it as one of the longest-lasting research hotspots in the field. Furthermore, diabetic cardiomyopathy (DCM) and diabetic nephropathy (DN) have shown a pronounced escalation starting in 2020 and continuing to the present. This observation suggests that these conditions continue to evolve, making them prospective and considerable research areas.

We identified 22 clusters through keyword clustering and chronological visualization. The top 10 clusters, encompassing 515 nodes and 3180 connecting lines, are depicted on the right side of Figure 7B. In the timeline, cluster 0 was dominated by E3 ligases, making it the largest cluster, followed by cluster 1, which focused on DCM. The nodes "expression", "activation", "oxidative stress", "phosphorylation" and "ubiquitination" are larger, indicating a greater number of related studies published. Nodes with purple outer circle, including "expression", "gene expression", "degradation", "activation", "ubiquitination", and "insulin resistance" exhibit high centrality, highlighting their substantial impact in the field. Emerging research clusters in 2023 cover topics such as E3 ligases, DCM, resistance, insulin resistance, insulin signaling, and oxidative stress. Nodes within these research areas show a gradual increase, potentially indicating the future frontiers of ubiquitination research in diabetic complications. To facilitate a clearer observation of the temporal changes in keywords, a keyword time-zone map (Figure 7C) was created. In this Figure, the year aligned with each keyword on the vertical axis indicates the specific time of its initial appearance. Larger nodes indicate a greater involvement of keywords and literature. This analysis offers important perspectives on how research topics have evolved, revealing clear trends in research themes. Early studies focused on the pathogenesis and treatment mechanisms of diabetes, involving various experimental approaches such as *in vitro* cellular and *in vivo* animal experiments. In recent years, research emphasis has shifted toward diabetic complications, including DN and DCM, while investigations into insulin resistance mechanisms remain a persistent focus.

DISCUSSION

Given the intricate nature of diabetes, novel clinical interventions are needed to ensure effective treatment and prevention of associated complications. The role of ubiquitination in diabetes has been extensively studied, with growing evidence indicating that histone-modified ubiquitination plays a vital role in diabetes and its complications. For example, tripartite motif (TRIM) proteins, a superfamily of E3 ubiquitin ligases, regulate protein levels and function through ubiquitination and are crucial for regulating insulin sensitivity. This has spurred advancements in the development of TRIM-targeted drugs[25]. X-box binding protein 1, a transcription factor, is essential for improving insulin sensitivity and maintaining glucose homeostasis, which may offer a strategic approach for anti-diabetic therapy[26]. In summary, these studies provide considerable insights into the mechanistic regulation of diabetes and facilitate the exploration of new approaches

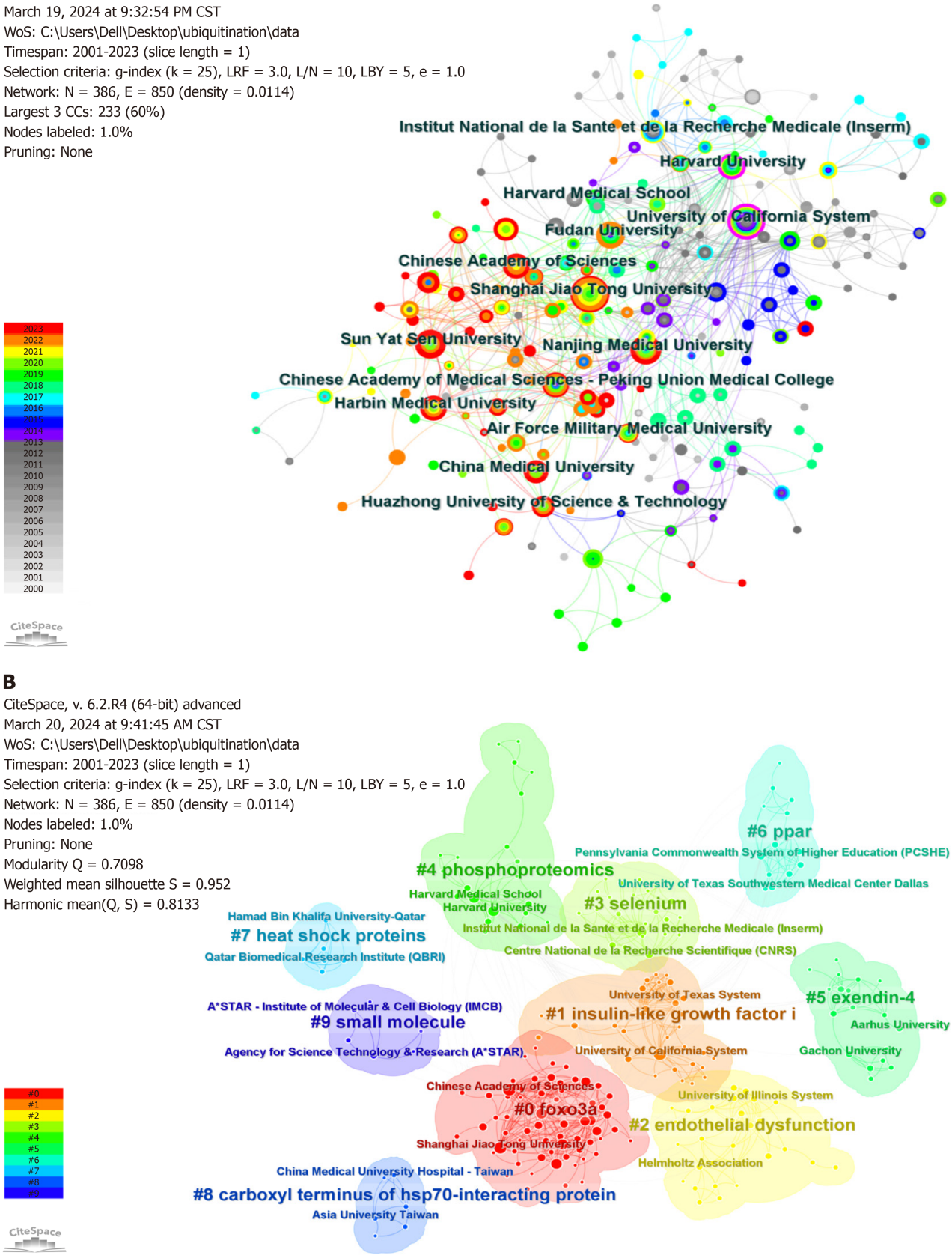


Figure 4 Visualization of institutional research in diabetes ubiquitination studies. A: Visualization of institutional collaboration analysis. Only institutions with at least ten publications are shown in the figure. Each node represents an institution, with the size of the node proportional to the number of articles published by that institution, and the thickness of the connecting lines proportional to the intensity of collaboration between institutions. Nodes with a purple periphery indicate high centrality, and nodes of different colors represent different publication years; B: Top ten keywords clustering analysis of institutional research themes.

The text with different numbers indicates the keyword clusters of these institutions, each node represents one institution, and different colors represent different clusters.

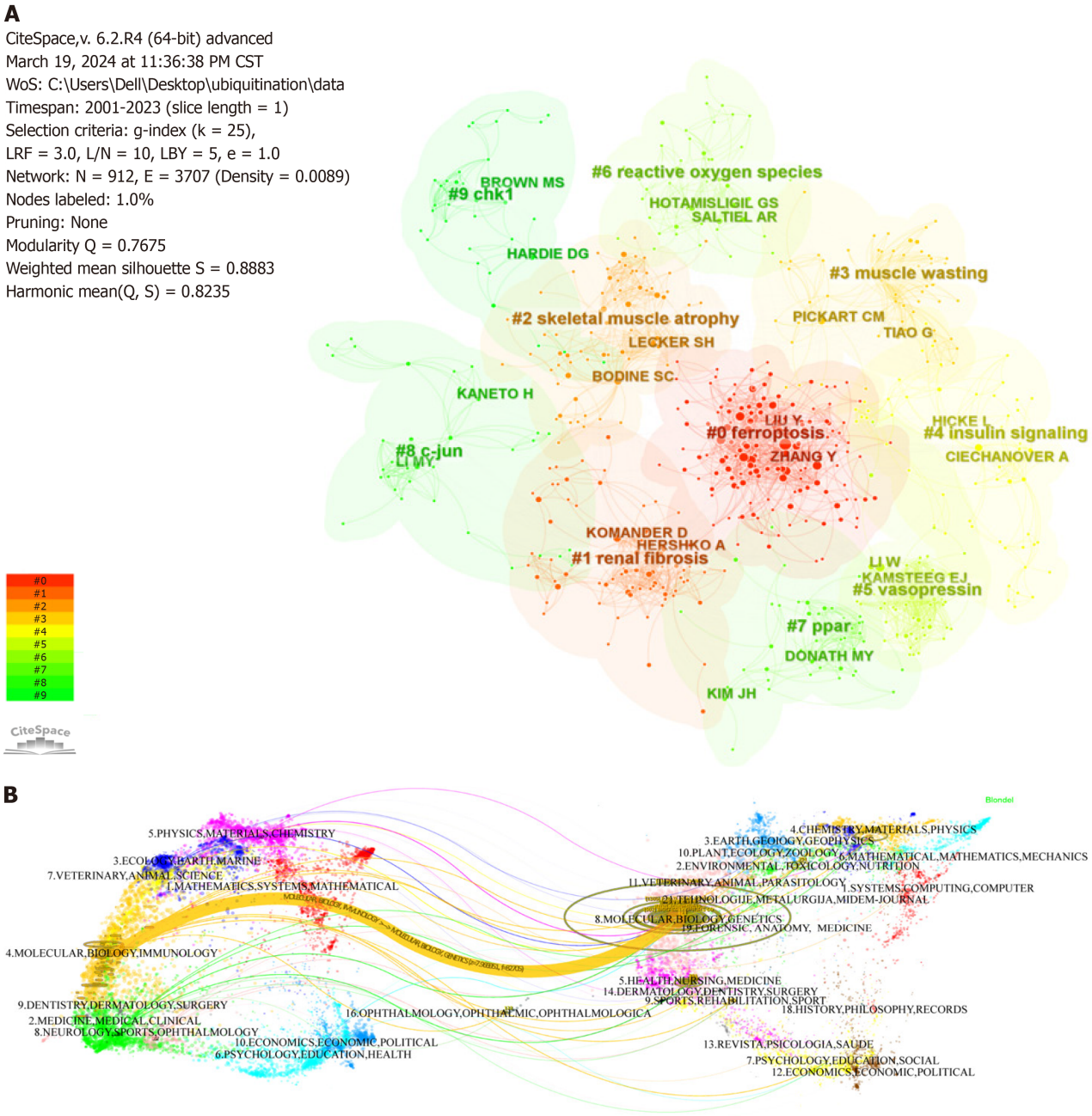


Figure 5 Visualization of co-cited authors and journals research in diabetes ubiquitination studies. A: Top ten keyword clustering analysis for co-cited author research topics. Each cluster shows only the most influential authors. The text with different numbers indicates the keyword clusters for these co-cited author research topics. Each node represents an author, and different colors represent different clusters; B: A double overlay figure showing journals with research related to diabetes ubiquitination, with citing journals on the left and cited journals on the right. Labels indicate disciplines, and links indicate citation paths.

for targeted therapies. Here, we present a thorough bibliometric review of recent advancements in the functions and regulatory mechanisms of ubiquitination in diabetes and its complications and discuss the challenges and future prospects in this field.

Our analysis of annual publication statistics revealed a consistent, wave-like increase, indicating growing interest among researchers in studying ubiquitination in DM and its complications. This trend suggests promising prospects for future advancements in this area. Our study also shows that China leads in the number of published papers, followed by the United States. The top 10 institutions in terms of publication numbers are predominantly from China and the United States, highlighting a high level of collaboration between these two countries, which also maintain extensive cooperative relationships with other nations. Additionally, countries such as Germany, the United Kingdom, France, and Canada have broad cooperative networks. Most countries are collaborating extensively in this regard. The University of Ca-

A Top 20 references with the strongest citation bursts

References	Year	Strength	Begin	End	2001-2023
Glickman MH, 2002, PHYSIOL REV, V82, P373, DOI 10.1152/physrev.00027.2001, DOI	2002	3.21	**2004**	2006	
Brunet A, 2004, SCIENCE, V303, P2011, DOI 10.1126/science.1094637, DOI	2004	1.78	**2005**	2008	
Lecker SH, 2004, FASEB J, V18, P39, DOI 10.1096/fj.03-0610com, DOI	2004	3.73	**2008**	2009	
Song RS, 2013, NATURE, V494, P375, DOI 10.1038/nature11834, DOI	2013	5.22	**2013**	2018	
Chan CH, 2012, CELL, V149, P1098, DOI 10.1016/j.cell.2012.02.065, DOI	2012	1.89	**2013**	2017	
Gao CL, 2013, J DIABETES RES, V2013, P0, DOI 10.1155/2013/589474, DOI	2013	1.71	**2014**	2018	
Perry RJ, 2014, NATURE, V510, P84, DOI 10.1038/nature13478, DOI	2014	2.36	**2015**	2016	
Gao CL, 2014, J DIABETES RES, V2014, P0, DOI 10.1155/2014/918396, DOI	2014	2.88	**2016**	2019	
Huang KP, 2015, ENDOCRINOLOGY, V156, P268, DOI 10.1210/en.2014-1381, DOI	2015	2.29	**2017**	2018	
Cybulsky AV, 2013, KIDNEY INT, V84, P25, DOI 10.1038/ki.2012.390, DOI	2013	2.29	**2017**	2018	
Aghdam SY, 2013, BIOCHEM BIOPH RES CO, V432, P339, DOI 10.1016/j.bbrc.2013.01.101, DOI	2013	2.17	**2017**	2018	
Goru SK, 2017, PHARMACOL RES, V120, P170, DOI 10.1016/j.phrs.2017.03.024, DOI	2017	2.18	**2018**	2021	
Wu Q, 2018, J AM SOC NEPHROL, V29, P936, DOI 10.1681/ASN.2017050526, DOI	2018	2.9	**2019**	2020	
Ando F, 2018, NAT COMMUN, V9, P0, DOI 10.1038/s41467-018-03771-2, DOI	2018	2.31	**2019**	2020	
Swatek KN, 2016, CELL RES, V26, P399, DOI 10.1038/cr.2016.39, DOI	2016	2.04	**2019**	2021	
Gong WY, 2018, FREE RADICAL BIO MED, V115, P338, DOI 10.1016/j.freeradbiomed.2017.12.013, DOI	2018	2.5	**2020**	2023	
Manning BD, 2017, CELL, V169, P381, DOI 10.1016/j.cell.2017.04.001, DOI	2017	2.2	**2020**	2021	
Jia GH, 2018, CIRC RES, V122, P624, DOI 10.1161/CIRCRESAHA.117.311586, DOI	2018	2.67	**2021**	2023	
Buenaventura T, 2019, PLOS BIOL, V17, P0, DOI 10.1371/journal.pbio.3000097, DOI	2019	2.17	**2021**	2023	
Hovsepian J, 2017, J CELL BIOL, V216, P1811, DOI 10.1083/jcb.201610094, DOI	2017	2.13	**2021**	2023	

B Top 20 keywords with the strongest citation bursts

Keywords	Year	Strength	Begin	End	2001-2023
plasma membrane	2002	3.15	**2002**	2012	
phosphatidylinositol 3 kinase	2002	3.15	**2002**	2012	
gene expression	2001	10.09	**2008**	2015	
ubiquitin ligase	2008	6.35	**2008**	2018	
skeletal muscle	2008	4.76	**2008**	2011	
apical membrane	2008	2.92	**2008**	2012	
insulin resistance	2007	3.13	**2009**	2011	
alzheimers disease	2010	2.88	**2010**	2015	
in vivo	2012	6.74	**2012**	2016	
p53	2012	3.16	**2012**	2016	

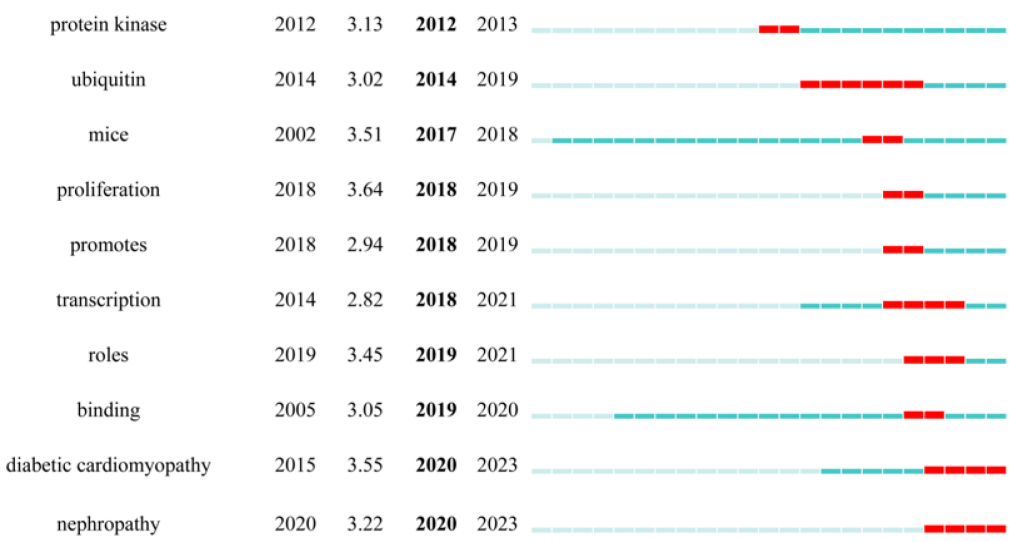


Figure 6 Top 20 references and keywords with the strongest bursts. A: Top 20 references with the strongest bursts in the diabetes ubiquitination study; B: Top 20 keywords with the strongest bursts in the diabetes ubiquitination study.

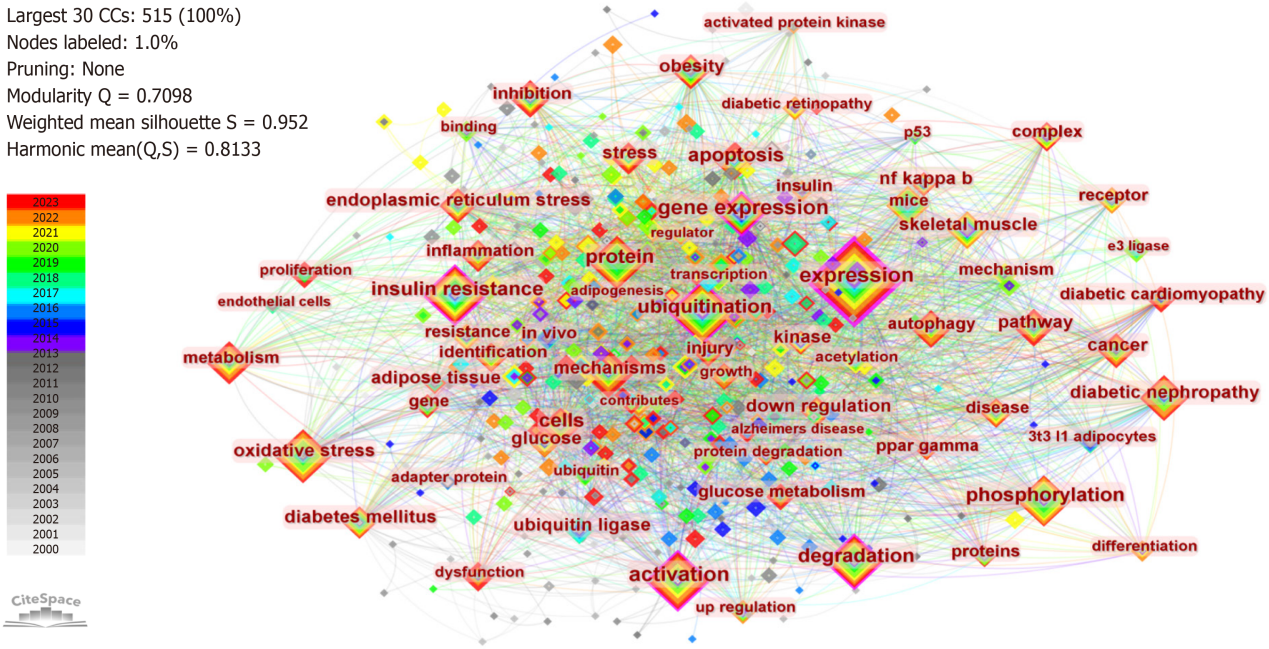
lifornia System and Harvard University in the United States have the highest centralities, followed by the Chinese Academy of Sciences. This positions China and the United States as leaders in this field, surpassing other nations in terms of publication volume, influence, and collaboration levels. The analysis of authors' co-occurrence results revealed that each had a relatively few published articles and low centrality. This indicates weak collaboration between authors, which may hinder further research. Countries can actively recruit professionals or send advanced scholars to study at leading institutions. For example, scholars could engage in exchanges and learning opportunities at the University of California System and Harvard University in the United States or at Shanghai Jiao Tong University and the Chinese Academy of Sciences in China. Such initiatives can foster complementary advantages, strengthen cooperative relationships, and promote rapid advancements in this field.

By examining co-cited authors, journals, and references, we can identify the key themes and intrinsic values of papers within the research domain and gauge the impact of related projects through co-citation frequency. The author with the highest citation frequency was Zhang Y, indicating that this study holds substantial academic value. However, this author has lower centrality, suggesting limited connections with other researchers and, therefore, lower influence. To advance this research field, authors should work to enhance collaborative relationships. Among the cited journals, *Nature*, *Cell*, and *Science* were highly cited and authoritative, substantially influencing foundational aspects of academic development. Double-stacked graphs depicting cited journals underscore interdisciplinary collaboration and knowledge transfer within research areas. The main route encompasses several disciplines including molecular biology, genetics, anatomy, and medicine. Among the co-cited articles, there are two articles noted for their high intensity, prolonged impact, and inclusion in the top 10 most cited articles. These studies primarily focus on how casein kinase 2 interacting protein-1 (CKIP-1) mediates resistance to high glucose-induced glomerular fibrosis by targeting Smad ubiquitylation regulatory factor-1 in diabetic mice, particularly concerning renal fibrosis. These investigations explore the influence of CKIP-1 on nuclear factor erythroid 2-related factor 2 (Nrf2) and Kelch-like ECH-associated protein 1 (KEAP1) in glomerular mesangial cells, as well as its role in renal fibrosis in diabetic mouse kidneys. One study highlights CKIP-1's role in affecting the polyubiquitination of Nrf2 and KEAP1[21], while another provided an update on the clinical mechanisms related to DCM[22]. These articles suggest that the content covered therein may represent a current or future research topic. The keywords represent the thematic focus of each research area. Using keyword co-occurrence analysis, timeline visualization, and time-zone mapping, we observed that oxidative stress, insulin resistance, and gene expression were prominent features. Notably, these themes clustered predominantly within clusters 3, 6, and 8, highlighting their substantial roles in diabetes pathogenesis. DN and DM ranked among the top 20 in the keyword frequency analysis. Additionally, DCM ranked first and DM ranked second in keyword clustering, suggesting that DCM and DN were substantial diabetic complications in this study. DCM is recognized as a distinct cardiac complication independent of essential hypertension and other diabetic heart diseases[27]. Cardiovascular disease is the leading cause of mortality in individuals with diabetes[28,29]. DN is highly prevalent among patients with diabetes and is the most common microvascular complication of advanced diabetes, often leading to end-stage renal disease[30]. Its pathogenesis involves diverse factors, including glucose metabolism disorders, oxidative stress, hemodynamic abnormalities, genetic factors, and inflammation[31]. Both areas are likely to emerge as primary directions and focal points for future research.

Combining the keyword clusters, a substantial cluster included cluster 0 for E3 ligases. The number of E3 enzymes identified in the UPS far surpasses those of the E1 and E2 enzymes[32]. The primary role of E3 ubiquitin ligases *in vivo* is to recognize and transport proteins to the proteasome for degradation, which is one of the most critical components of ubiquitination. E3 ligases are typically classified into three primary families: The HECT domain family, which shares homology with the carboxyl terminus of E6-associated proteins; the RING domain family; and the U-box family[33].

A

CiteSpace, v. 6.2.R4 (64-bit) advanced
March 20, 2024 at 10:40:27 AM CST
WoS: C:\Users\Dell\Desktop\ubiquitination\data
Timespan: 2001-2023 (slice length = 1)
Selection criteria: g-index (k = 25), LRF = 3.0, L/N = 10, LBY = 5, e = 1.0
Network: N = 515, E = 3180 (density = 0.024)
Largest 30 CCs: 515 (100%)
Nodes labeled: 1.0%
Pruning: None
Modularity Q = 0.7098
Weighted mean silhouette S = 0.952
Harmonic mean(Q,S) = 0.8133



B

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Timespan: 2001-2023 (slice length = 1)
Selection criteria: g-index (k = 25), LRF = 3.0, L/N = 10, LBY = 5, e = 1.0
Network: N = 515, E = 3180 (density = 0.024)
Nodes labeled: 1.0%
Pruning: None
Modularity Q = 0.3543
Weighted mean silhouette S = 0.7074
Harmonic mean(Q, S) = 0.4721

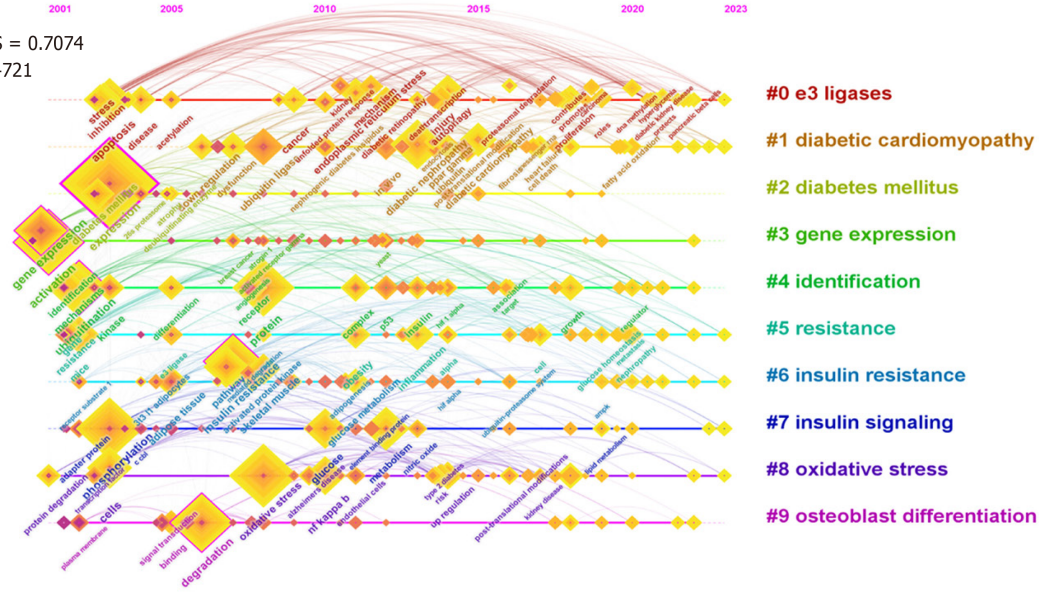

Figure 7 Visualization of keywords in diabetes ubiquitination studies. A: Visualization of the co-occurrence analysis of keywords in diabetes ubiquitination research. Only keywords with a frequency of 6 or more occurrences are shown. Each node represents a keyword, and the size of the node is proportional to its frequency. The thickness of the connecting lines indicates how frequently two keywords co-occur, and different colors represent the years the keywords appeared; B: Timeline visualization of the top ten keywords clustering analysis. Keywords on the same line correspond to the clusters on the right. Each node represents a keyword, and the size of the node is proportional to its frequency. The position of the node on the horizontal axis indicates the keyword's first occurrence; C: Timeline visualization of keywords. Each node represents a keyword, and its size is proportional to the frequency of the keyword. The position of the node on the horizontal axis indicates the time of the keyword's first appearance.

Here, we summarize the key research hotspots and trends related to E3 ligases, DCM, and DN.

E3 ligases and DCM

Based on our bibliometric results, E3 enzymes are anticipated to emerge as novel therapeutic targets for DCM treatment. Hundreds of E3 enzymes have been identified, each demonstrating specificity for substrates, and their abundance endows them with diverse and intricate functions[34]. The E3 ligase Atrogin-1 inhibits cardiac hypertrophy by interacting with calmodulin phosphatase and Akt, which are crucial molecules associated with cardiac hypertrophy[35,36]. In an *in vitro* study, transgenic mice overexpressing the E3 ubiquitin ligase Atrogin-1 demonstrated resistance to insulin-like growth factor treatment in the context of cardiac hypertrophy. Conversely, mice deficient in Atrogin-1 showed heightened cardiac hypertrophy after engaging in voluntary running[36]. Furthermore, E3 ubiquitin ligase is implicated in the regulation of cardiac apoptosis, where it interacts with tumor protein 53 and various members of the caspase family of proteases to orchestrate the control of cardiac apoptosis[32]. Several recent studies have been conducted; Feng *et al*[37] showed that an E3 ligase-inactive mutant shields the diabetic heart from acute ischemia/reperfusion injury. Other studies have indicated that the E3 ubiquitin ligase muscle ring finger protein 2 suppresses both the protein levels and activity of cardiac peroxisome proliferator-activated receptor gamma 1 (PPARγ1), thereby playing a protective role against DCM [38]. However, the specificity of E3 ubiquitin ligases and their complex and diverse functions warrant further in-depth study to elucidate their mechanisms of action in the treatment of DCM, which will aid in establishing a fundamental and comprehensive therapeutic approach for the treatment of DCM.

E3 ligases and DN

E3 ligases play a substantial role in DN by regulating the expression of numerous proteins involved implicated in inflammatory and fibrotic pathways[39]. Arkadia, a novel RING-type E3 ligase, is highly expressed in the renal tissues of patients with DN[40]. Furthermore, a reduction in Arkadia expression attenuates experimentally induced renal fibrosis in diabetic mice[41]. *In vitro* experiments revealed that TRIM18, a member of the RING-type E3 ligase superfamily, robustly suppressed epithelial-mesenchymal transition, inflammation, and fibrosis in the renal tissues of diabetic mice[42]. Research has indicated that the E3 ubiquitin ligase Speckle-type BTB-POZ protein (SPOP) acts as a suppressor of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. Given the involvement of NLRP3-containing inflammasomes in DN progression, SPOP is a potential therapeutic target for improving DN through the inhibition of NLRP3 inflammatory vesicles[43]. Recent research has found that the E3 ubiquitin ligase TRIM Containing

63 is responsible for mediating the ubiquitination and degradation of PPARα, leading to podocyte injury and proteinuria. Consequently, the inhibition of Trim63 may offer a promising therapeutic strategy to mitigate podocyte injury and proteinuria in DN[44]. The development of therapeutic approaches targeting specific E3 ligases holds substantial potential for effective treatment of DN.

As research on ubiquitination advances, its substantial role in regulating various diseases is increasingly recognized. Diabetes induces chronic hyperglycemia, which gradually compromises bone density and osteogenesis, disrupts osteoblast differentiation and function, and ultimately results in osteoblast dysfunction[45]. Patients with diabetes have an elevated risk of developing osteoporosis and fractures, as highlighted by keyword clustering module 9 on osteoblast differentiation. Ubiquitination plays a crucial role in bone metabolism by regulating osteoblast differentiation, maturation, and function, thereby influencing skeletal health and disease states. Metabolic bone disease, a prevalent endocrine disorder secondary to DM, is affected by E3 ligases during disease onset and progression[46]. Our keyword co-occurrence analysis also showed that ubiquitination defects are closely linked to the initiation, progression, and eventual metastasis of cancer[47]. Research has demonstrated that ubiquitin ligase complexes can effectively inhibit abnormal activation of the integrated stress response in certain cancer cells, offering a potential therapeutic strategy for selectively targeting and eliminating these cancer cells[48]. Phosphorylation has emerged as a focus of current research in our keyword clustering results, highlighting the functional interactions between ubiquitination and phosphorylation. Emerging evidence suggests that phosphorylation similarly regulates ubiquitin-like modifiers[49]. Thus, in addition to DCM and DN, research involving these elements is likely to become a popular topic in the future. Combined with hotspot studies, research on ubiquitination in other disease mechanisms, and interdisciplinary content of journal dual-axis graphs, this approach offers new perspectives for advancing research on the treatment of diabetic complications. Ubiquitination is a multifaceted regulatory process that involves numerous ubiquitin ligases, deubiquitinating enzymes, and their respective target proteins. The limited number of identified ubiquitinases necessitates the use of highly sensitive techniques and tools to detect changes in ubiquitination levels and identify the affected target proteins. Despite the potential of ubiquitination in diabetes research, its complex regulatory network, dynamic nature, functional diversity, and current technological limitations present substantial challenges for both research and clinical translation.

Limitations

It is important to recognize that this study had its own set of constraints. First, it utilized only the WOSCC, and the search timeframe covered January 2001 through December 2023. Consequently, the retrieved literature may be incomplete and may not include some of the most recently published studies. Additionally, only articles published in English were included, limiting the research coverage. This study's findings may be somewhat subjective because of the narrow scope of the search terms used. The articles included were not comprehensive and may not accurately represent all findings. Second, the included articles and reviews were not stratified and did not account for overlaps, potentially masking trends and patterns in the dataset. As a result, certain research hotspots may have gone unidentified, and the study may have failed to distinguish between the fundamental concepts commonly discussed in reviews and novel findings reported in original research articles. The quality of these articles was not assessed, meaning that low-quality studies could potentially affect the results. Additionally, data analysis was conducted solely using CiteSpace software, which may have inherent limitations. Delays in publication time for certain articles may have introduced bias in and volume of articles included in our analysis. Furthermore, the failure to include recently published articles due to delays in the database could also introduce bias in identifying research hotspots.

CONCLUSION

Our bibliometric analysis provided a comprehensive and in-depth overview of ubiquitination in diabetes and its complications, involving authors from 54 countries, 386 institutions, and 934 contributors. Overall, the publication of related papers is on the rise, with China and the United States emerging as leaders in this field. There is a pressing need to enhance cooperation among authors, potentially through scholarly exchanges and study programs in China and the United States. Current research primarily focuses on DN and DCM. The key mechanisms under investigation include ubiquitination, oxidative stress, phosphorylation, and insulin resistance, which are hotspots and frontiers in this area.

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FOOTNOTES

Author contributions: Xiong LY conducted the bibliometric analysis and composed the manuscript. Zheng YJ conceptualized the study and oversaw data retrieval by Xiong LY. Xiong LY and Zhao W performed the statistical analysis. Xiong LY, Zhao W, Hu FQ, and Zheng YJ critically reviewed the manuscript. Zheng YJ and Zhou XM provided overall supervision and guidance for revisions throughout the process. Li-Yuan Xiong and Wei Zhao contributed equally to the research and writing of this paper and are designated as co-first authors; All authors contributed to and approved the final version of the article.

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