• Bibliometric Research •

# Visual analysis of research trends in diabetes-associated dry eye *via* bibliometrics

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Received: 2024-06-12 Accepted: 2025-06-25

## Abstract

● **AIM:** To provide a comprehensive review of the advances in research on diabetes-associated dry eye (DADE), highlighting its pathophysiological mechanisms, risk factors, and demographic characteristics, laying the foundation for further investigation into its pathogenesis and treatment strategies.

● **METHODS:** A systemic review of the documents related to DADE had been performed based on the Web of Science database prior to achieving the plain text files of authors, titles, journals, and abstracts which afterwards had been imported into Citespace and VOSviewer software for data cleansing. The visual analysis was implemented from the following aspects: journals' publications, author and national cooperation, keyword co-occurrence, timeline analysis, and burst detection.

● **RESULTS:** The 318 documents in 167 journals had been incorporated with the overall annual citations and annual publications respectively growing significantly since 2014 and 2016. The keyword co-occurrence networks formed 4 clusters, with the representative keywords being dry eye, diabetes mellitus, prevalence, and diabetic retinopathy. Both the timeline map and the burst detection demonstrated that in the exploration of the pathogenesis of DADE, initial research was dedicated to Sjögren's syndrome, followed by cross-sectional statistical analysis of the pertinent contributing factors of DADE using online databases. Precisely the oxidative stress seemed to surge into the research spotlight presently. The key pathogenic mechanisms of DADE include inflammation, oxidative stress and corneal neuropathy, contributing to the development of dry eye symptoms.

● **CONCLUSION:** Age, gender, diabetes duration, and diabetic retinopathy are strongly associated with the development of DADE, but the impact of other systemic factors require further investigation. With high prevalence of dry eye in Asia, valuable resources like the Korea National Health and Nutrition Examination Survey (KNHANES) database offer crucial data for developing risk prediction models for DADE. Building risk prediction models using machine learning algorithms is a promising future research direction, enabling physicians to identify high-risk individuals and implement early interventions.

● **KEYWORDS:** bibliometrics; diabetes; dry eye; visual analysis

**DOI:10.18240/ijo.2025.09.16**

**Citation:** Yang Z, Jiang JY, Zhang XH. Visual analysis of research trends in diabetes-associated dry eye *via* bibliometrics. *Int J Ophthalmol* 2025;18(9):1737-1746

## INTRODUCTION

Diabetes had been identified as one of the risk factors of dry eye according to the expert consensus published by the Tear Film & Ocular Surface Society in 2017[1]. The prevalence of dry eye or meibomian gland dysfunction among patients with diabetes mellitus was around 50%[2-3], which had led to widespread interest in diabetes-associated dry eye (DADE). The relevant pathogenic factors of DADE appeared to extend beyond mere tear deficiency, encompassing a vicious cycle of metabolic dysregulation, neural impairment, and chronic inflammation. Specifically, hyperglycemia-induced lacrimal gland dysfunction and corneal neuropathy synergistically disrupted tear film stability, as highlighted by Wang *et al*[4], and high glucose could cause inflammatory reactions, disrupt the ocular surface microenvironment, and adversely affect the normal metabolism of keratoconjunctival epithelium and lacrimal cells[5]. However, the precise interplay between these mechanisms remained poorly characterized, particularly in the context of diabetes progression stages.

Bibliometrics, as a discipline capable of analyzing a large amount of literature in a specific field and revealing research trends through mathematical and statistical methods, had been

widely used in clinical research. The visualization of epidemic research based on bibliometric software was among the hot topics of bibliometric analysis.

While existing research had primarily concentrated on analyzing the relationship between diabetes mellitus and dry eye, a comprehensive assessment of the evolving research trends in different fields related to DADE is lacking, and the key factors driving these changes have also not been identified. In this study, our objective was to synthesize the current literature on DADE, identifying key areas of interests and tracing the evolution of the research focusing on the relationship between diabetes mellitus and dry eye in recent years. By elucidating the pathophysiological mechanisms, risk factors, and demographic characteristics of DADE, this research sought to lay a robust foundation for future research on diagnostic methods and therapeutic approaches.

## MATERIALS AND METHODS

**Literature Source and Retrieval Strategy** The Web of Science core collection was used as the database to retrieve the literature from its inception to 2024. To avoid bias in the number of documents retrieved due to the database update, the retrieval was completed within one day on February 11, 2024. A total of 875 publications were retrieved using the search formula: (TS=(Diabet*) OR TS=(Diabetes Mellitus) OR TS=(Diabetes Mellitus, Type 2) OR TS=(Diabetes Complication)) AND (TS=(Dry eye) OR TS=(Dry Eye Syndrome) OR TS=(Dry eye disease) OR TS=(xerophthalmia). The study flow chart was shown in Figure 1.

**Manual Screening and Quality Control** The text files were imported into Citespace (Version 6.2.R6, Drexel University, Philadelphia, United States) and VOSviewer (Version 1.6.20, Leiden University, Leiden, the Netherlands) for duplicates removal and literature type screening. Exclusion criteria included editorials, letters, conference abstracts, book reviews, paper corrections, literature without abstracts or keywords, and literature irrelevant to DADE evaluated by reading the titles and abstracts of the documents. Two ophthalmologists screened the documents on the basis of the titles and abstracts, as well as reading the main texts if necessary, so as to exclude retrieval results unrelated to DADE. An experienced professor of ophthalmology was available to make judgements when there were disagreements.

As a result, 29 documents were excluded. The 318 documents were retained, including 245 articles, 72 reviews and 1 proceedings paper. Prior to data analyzing, the synonyms in countries and keywords were merged for more accurately analysis. The Citespace software was employed to perform analysis of the publication statistics, author and country cooperation networks, keyword timeline view and burst detection. The VOSviewer software was to visualize keyword co-occurrence networks, publications and co-citation networks of journals. Within the above software data mining was performed for DADE in the multiple dimensions of time, trend, and clustering.

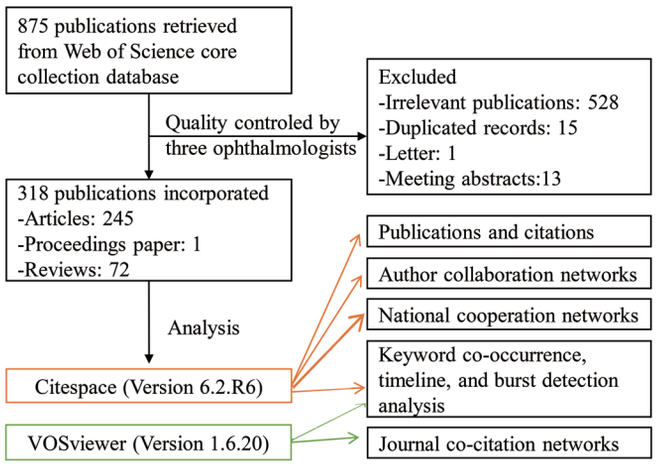


**Figure 1 Flow chart of the data acquisition and bibliometric analysis** A total of 318 publications were incorporated in the study. Citespace software was used to perform analysis of publication and citation volume, authors, countries, and keywords. And VOSviewer software was applied to analyze journals and keywords.

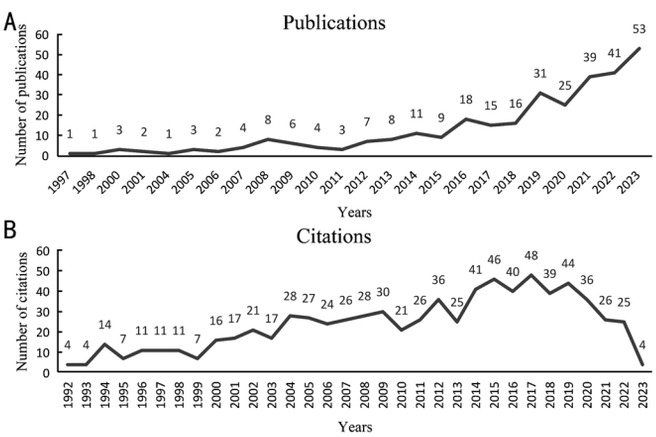


**Figure 2 Chart of publications and citations** A: Annual publications in the area of DADE from 1997 to 2023; B: Annual citations of publications in the area of DADE from 1992 to 2023. DADE: Diabetes-associated dry eye.

## RESULTS

**Publication Overview** The 318 publications included in this study originated from 1552 authors, 525 institutions, 167 journals, and 52 countries. Meanwhile, these papers cited 12 588 ones from 2661 journals.

Since the first mention of DADE in 1997, the publication volume had slowly increased till 2015 (Figure 2A). The number of published papers had increased significantly after that, with an average annual increase of 5 papers, up to 53 papers in 2023. Seven papers were published from the beginning of 2024 to February 11, which were not included in the Figure 2. There were 760 citations in the literature related to DADE from 1992 to 2023 (Figure 2B). Overall

**Table 1 The top 10 authors, institutions, and publication date of their first relevant article ranked by the publication volume**

| Ranking | Author | Volume | Year of the first publication | Institution |
|---|---|---|---|---|
| 1 | Zou Haidong | 7 | 2020 | Shanghai Jiao Tong University |
| 2 | Joseph W. Sassani | 5 | 2009 | University of Pennsylvania |
| 3 | Patricia McLaughlin | 5 | 2009 | University of Pennsylvania |
| 4 | Ian S. Zagon | 5 | 2009 | University of Pennsylvania |
| 5 | Indira Purushothaman | 4 | 2021 | University of Pennsylvania |
| 6 | Lu Lina | 4 | 2020 | Shanghai Jiao Tong University |
| 7 | Cuong Q. Nguyen | 4 | 2007 | University of Florida |
| 8 | Ammon B Peck | 4 | 2007 | University of Florida |
| 9 | FH Grus | 3 | 1998 | Johannes Gutenberg-Universität Mainz |
| 10 | Yuta Ohno | 3 | 2023 | Asahi University |

**Table 2 The top 15 journals ranked by publication volume, with their total number of citations, average number of citations, and total link strength**

| Ranking | Journals | Volume | Citations | Average citations | Total link strength |
|---|---|---|---|---|---|
| 1 | *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE* | 18 | 576 | 32.0 | 117 |
| 2 | *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES* | 8 | 73 | 9.1 | 33 |
| 3 | *JOURNAL OF OPHTHALMOLOGY* | 8 | 202 | 25.3 | 120 |
| 4 | *BMC OPHTHALMOLOGY* | 7 | 234 | 33.4 | 147 |
| 5 | *INDIAN JOURNAL OF OPHTHALMOLOGY* | 7 | 22 | 3.1 | 41 |
| 6 | *INTERNATIONAL OPHTHALMOLOGY* | 7 | 90 | 12.9 | 78 |
| 7 | *PLOS ONE* | 7 | 198 | 28.3 | 47 |
| 8 | *CORNEA* | 6 | 152 | 25.3 | 82 |
| 9 | *EXPERIMENTAL EYE RESEARCH* | 6 | 177 | 29.5 | 47 |
| 10 | *INTERNATIONAL JOURNAL OF OPHTHALMOLOGY* | 6 | 99 | 16.5 | 55 |
| 11 | *CURRENT EYE RESEARCH* | 5 | 113 | 22.6 | 51 |
| 12 | *EYE & CONTACT LENS-SCIENCE AND CLINICAL PRACTICE* | 5 | 52 | 10.4 | 43 |
| 13 | *FRONTIERS IN MEDICINE* | 5 | 29 | 5.8 | 54 |
| 14 | *AMERICAN JOURNAL OF OPHTHALMOLOGY* | 4 | 781 | 195.3 | 94 |
| 15 | *BMJ OPEN* | 4 | 21 | 5.3 | 24 |

citations demonstrated a consistent growth trend leading up to 2014, followed by a notable surge in that year. After 2014 overall citations remained a relatively stable level but declined annually since 2020.

**Analysis of Author Cooperation Networks** After generating the author information using Citespace software, the top 10 authors with the highest publication volume were presented in Table 1. The top 5 authors were all from the University of Pennsylvania, except for the first one, Haidong Zou, who was from Shanghai Jiao Tong University. In the clustering map (Figure 3), authors in the top 6 clusters came from neither University of Pennsylvania nor Shanghai Jiao Tong University, but mainly from University of Florida, as well as China Medical University, Baylor College of Medicine, Johannes Gutenberg University of Mainz, and University of São Paulo also incorporated. The above findings suggested that the DADE studying at Shanghai Jiao Tong University and the University of Pennsylvania may be mainly done by a few outstanding researchers themselves so that cross-collaboration among multiple subject groups had not been formed.

**Analysis of the Journal Publication Volume and Co-citation Networks** In terms of publication source of the literature (Table 2), there were a total of 167 journals, among which the top 15 journals ranked by the publication volume had published 103 articles and accounted for 32.4% of the total literature volume. The only journal with more than 10 articles was *Investigative Ophthalmology & Visual Science*, with a total of 18 articles. Prior to *Investigative Ophthalmology & Visual Science* becoming an open access journal in 2020, there were 13 relevant articles published, whose number of citations accounting for 90.1% (519/576) of the total citation. The remaining top 5 journals were all open access. The journal with the highest average number of citations was the non-open access journal *American Journal of Ophthalmology* (195.3). The analysis of its highly cited literature revealed that it was mainly based on rigorously designed clinical empirical research, and its citation number was 5.8 times than that of the open access journal *BMC Ophthalmology* (33.4), which ranked the 2$^{nd}$ by the average number of citations of the journal. It could be seen that researchers in the field of DADE were

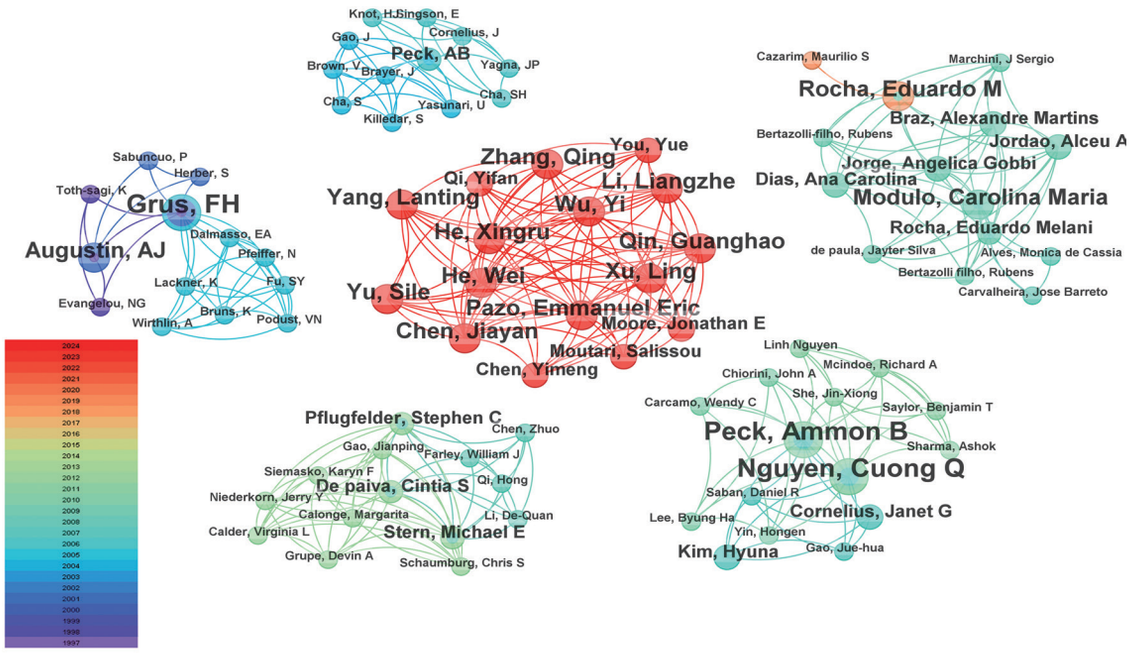


**Figure 3 Cluster map of the top 6 author collaboration networks by the publication volume and the collaboration relationships.**

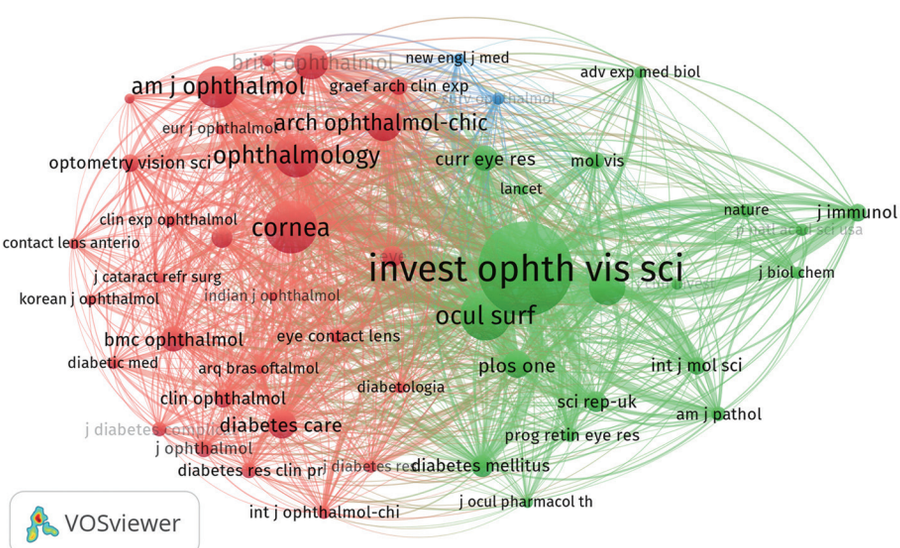


**Figure 4 Journal co-citation networks map, with different colors representing different clusters** The larger the node, the higher the frequency of co-citation. The most co-cited journal was *Investigative Ophthalmology & Visual Science*.

more inclined to publish articles with high academic impact in high quality non-open access journals to a certain extent. The concept of open access publishing, although widely and strongly developed, had not fully addressed the concerns of certain groups of researchers that open access may pose risks to the development of academic research[6].

The co-citation networks of the cited journals comprised three clusters (Figure 4). The blue nodes represented journals in the fields of fundamental research in ophthalmology and molecular biological mechanisms in medicine. Among these, the two most cited journals were *Investigative Ophthalmology & Visual Science* (1411 citations) and *The Ocular Surface* (581 citations). These journals were cited to support cutting-edge research on the pathogenesis and treatment of dry eye and DADE. The red cluster consisted mainly of ophthalmic or diabetic journals with a higher proportion of clinical studies or reviews. The aim of citing these journals was to review the findings of current clinical studies, such as the analysis of risk factors for DADE, which helped incorporate the advanced ideas of contemporary researchers. In the blue cluster, only *New England Journal of Medicine* (71 citations) and *Survey of Ophthalmology* (75 citations) were cited. These two journals were comprehensive journals covering multiple medical fields and review type journals focusing on ophthalmology, respectively. Due to their high influence and academic reputation, citing literature from these journals could provide a higher level of evidence to enhance the credibility of the study.

**Analysis of National Cooperation Networks** To compare the contributions of various countries in the field of DADE, we analyzed relevant studies from 52 countries and regions, visualized the top 15 countries with the largest publication volume and calculated their betweenness centrality (Figure 5). The betweenness centrality was often used to evaluate the importance of a node of a network in controlling the other members at both ends of the connecting line. The results showed that China and the United States together accounted for about half of the total global publications (Table 3), with 104 (31.0%) and 67 (19.9%) articles, respectively. The biggest betweenness centrality was found in the United States (0.79), followed by Spain (0.24), China (0.18) and the United Kingdom (0.15), which indicated a large gap between other countries and the United States.

**Keyword Co-occurrence, Timeline, and Burst Detection Analysis** Keyword co-occurrence analysis was performed by VOSviewer. A g-index based words frequency determination method was used to determine the threshold of high-frequency words[7]. As a result, 36 keywords with a frequency of 12 or higher were identified as high-frequency keywords and used for visualization (Figure 6B). The keyword co-occurrence network (Figure 6B) revealed that knowledge structure in DADE risk factor research exhibited characteristics of both high specialization and interdisciplinary integration. Based on cluster analysis of co-occurring keywords, high-frequency keywords formed four distinct clusters centered around "dry eye", with the following representative keywords in each cluster: diabetes mellitus, prevalence, and diabetic retinopathy. The tight interconnections among these four core keywords highlighted four principal research directions in DADE investigations.

1) Pathophysiological impact mechanisms: Yellow key terms including "diabetic retinopathy", "cornea", "cataract", and "glaucoma" indicated research focusing on diabetes-induced pathological alterations affecting multiple ocular structures, particularly exploring mechanistic links between systemic metabolic disorders and ocular surface diseases, lens abnormalities, and retinal complications.

2) Molecular metabolic mechanisms: This core cluster of red key terms containing "dry eye", "ocular surface", "oxidative stress", "insulin", and "cells" emphasized molecular pathogenesis studies. Current investigations concentrated on the role of oxidative damage mechanisms, insulin, and molecular signaling pathway in DADE development.

3) Diagnostic technological advancements: The green cluster encompassed keywords such as "diabetes mellitus", "tear film analysis", "confocal microscopy", "neuropathy", and "sensitivity". Among them, "neuropathy" and "sensitivity" revealed the deep connection between diabetic peripheral neuropathy and dry eye symptoms, underscoring the importance of refined detection technologies for studying disease symptoms and mechanisms.

4) Epidemiological studies: The blue cluster centered on keywords like "prevalence", "diagnosis", "epidemiology", and "classification". Epidemiological studies on dry eye based on regions and ethnic groups complement basic research on its pathogenesis, reflecting the attention given to standardized evaluation and heterogeneity analysis of dry eye.

The first article focusing on the relationship between the severity of diabetes and dry eye was published in 2000 (Figure 6A), this prospective study identified keratoconjunctivitis sicca as an ocular manifestation of diabetes mellitus. Staging diagnosis of diabetic retinopathy and dry eye was conducted using the Early Treatment Diabetic Retinopathy Study Score and the Sicca Score, suggesting that the severity of dry eye correlates with the severity of diabetic retinopathy. As can

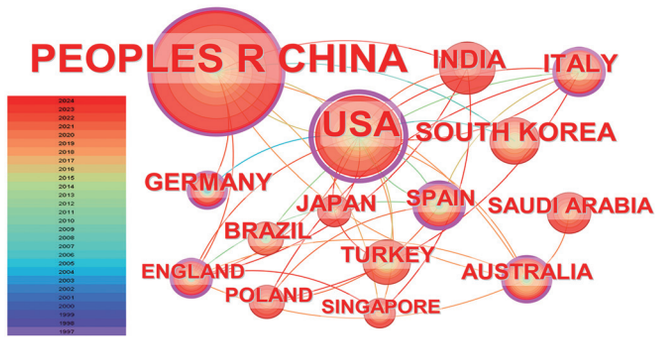


**Figure 5 National cooperation networks map of top 15 countries ranked by publication volume** The color and width of the nodes' tree rings represented the year and the publication volume. The purple ring appeared outermost indicated that the country had a strong betweenness centrality.

**Table 3 The top 15 countries, publication volume and average number of citations, ranked by the number of citations**

| Ranking | Country | Volume | Citations | Average citations |
|---|---|---|---|---|
| 1 | USA | 67 | 3319 | 49.54 |
| 2 | BRAZIL | 13 | 561 | 43.15 |
| 3 | SOUTH KOREA | 19 | 710 | 37.37 |
| 4 | AUSTRALIA | 11 | 373 | 33.91 |
| 5 | SINGAPORE | 8 | 233 | 29.13 |
| 6 | ENGLAND | 9 | 204 | 22.67 |
| 7 | POLAND | 9 | 187 | 20.78 |
| 8 | TURKEY | 12 | 249 | 20.75 |
| 9 | ITALY | 16 | 324 | 20.25 |
| 10 | INDIA | 19 | 384 | 20.21 |
| 11 | PEOPLES R CHINA | 104 | 1978 | 19.02 |
| 12 | GERMANY | 14 | 225 | 16.07 |
| 13 | JAPAN | 13 | 153 | 11.77 |
| 14 | SAUDI ARABIA | 11 | 79 | 7.18 |
| 15 | SPAIN | 11 | 57 | 5.18 |

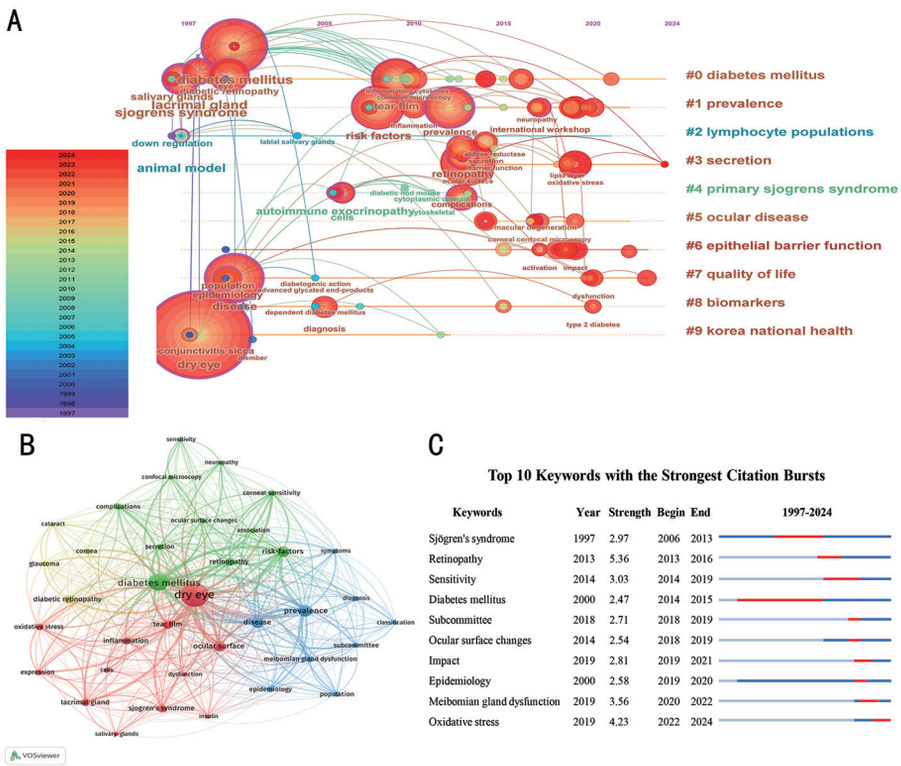


**Figure 6 Visualizations of keywords generated by Citespace** A: Timeline map of the keyword networks. The titles of the keyword clusters were shown on the right side. The curve lines represented the links between keywords, the horizontal lines represented the years in which the keywords appeared. The node size represented the frequency of keyword occurrence; B: Keyword co-occurrence map. The node size represented the frequency of keywords, the thickness of lines between two nodes indicated the strength of association between keywords, and different colors represented different keyword clusters; C: Keyword burst detection. The light blue bars indicated that the keywords had not yet appeared, and the dark blue bars represented the year in which the keywords appeared. The red bars represented the beginning and the end of the keyword burst.

be seen from the cluster #0 diabetes mellitus, there were fewer relevant studies in the following decade until around 2010 when researchers turned their attention to the impact of diabetes mellitus on corneal sensitivity and tear film. The largest node, dry eye, appeared in cluster #9 Korea National Health, due to the fact that the Korea National Health and Nutrition Examination Survey (KNHANES) database had been used by many researchers to analyze the risk factors for the development of dry eye and had been influential in this field.

Keyword burst analysis was used to detect significant changes in the frequency and importance of certain keywords within a certain period of time, which could reveal the evolution and transformation of the certain research field. By this means it helped discover advanced research directions and trends, and serve as a reference for future research in related fields. The top 3 keywords in terms of the duration were Sjögren's syndrome, sensitivity, and retinopathy (Figure 6C). These burst keywords could reflect the research focuses in the certain period of time. Since 2006, studies on Sjögren's syndrome had focused on the cytology. The keyword retinopathy began to emerge in 2013, and an analysis of the literature at that time showed that in addition to considering the unilateral effect of diabetes on dry eye and retinopathy, the correlation between diabetic complications and dry eye had become a popular topic of studying, such as diabetic retinopathy, diabetic neuropathy and diabetic nephropathy[8]. The prominence of keywords that emerged in the last 5y were "subcommittee", "impact", "meibomian gland dysfunction", and "oxidative stress". The emergence of oxidative stress had been persisted from 2022 and was expected to remain a key focus of research into the pathogenesis of DADE in the foreseeable future. The surge of interest in subcommittee in 2018 may be attributed to the release of new consensus guidelines on dry eye diagnosis and treatment published by the Tear Film & Ocular Surface Society in 2017.

## DISCUSSION

The association between diabetes mellitus and dry eye had been confirmed by numerous studies, highlighting that the onset of dry eye was notably linked to gender, age, duration of diabetes and the presence of comorbid diabetic retinopathy in patients with diabetes mellitus[8-12]. On the basis of the report of Hom and De Land[13], the prevalence of dry eye could be more than half in patients with diabetes or prediabetes. The

keyword co-occurrence map (Figure 6) indicated the strongest connection between dry eye, diabetes mellitus, and risk-factors, underscoring that the investigation of risk factors for DADE was a significant research focus. Research had demonstrated that risk factors for DADE encompassed the duration of diabetes, abnormalities in systemic metabolic markers (including glycated hemoglobin, serum insulin), disturbances in the ocular surface microenvironment, and the severity of diabetes related systemic complications (including diabetic retinopathy)[14-16]. However, Uchino *et al*[17] argued that they didn't find significant correlation between diabetes mellitus and dry eye by assessing the prevalence and risk factors of dry eye in a questionnaire survey of 3294 adults over 40 years old in a rural mountainous area of Japan. Vehof *et al*[18] also evaluated the prevalence and risk factors of dry eye in 3824 female twins from the TwinsUK cohort, whereas they failed to identify connections between diabetes and dry eye. These results may be due to the diagnosis based on self-report rather than objective examinations, and the underestimation of dry eye can also be blamed to the mild to moderate decrease in corneal sensitivity caused by diabetes.

Corneal neuropathy may be one of the trends for further research on DADE risk factors. Keywords in the green group of the co-occurrence map (Figure 6) highlighted the relationship between DADE and corneal neuropathy. Some researchers had suggested that diabetic keratopathy was correlated with the accumulation of advanced glycation end-products, impaired neurotrophic innervation and corneal limbal stem cell function, and inflammatory changes, whereas corneal sensitivity and lacrimal homeostasis were influenced by corneal nerves[19-20]. The timeline map of the keyword networks (Figure 6A) revealed that studies on the aspect of diabetic corneal neuropathy surged after 2010. Bitirgen *et al*[21-22] quantitatively assessed the morphology of corneal nerve fibres and cells by *in vivo* confocal microscopy (IVCM) and concluded that there were significant changes in patients with diabetes mellitus or rheumatoid arthritis. Ferdousi *et al*[23] performed dry eye evaluation and IVCM examinations in patients with type 1 diabetes mellitus and found that the prevalence of dry eye was significantly higher in these patients but was not associated with abnormalities of corneal nerves, basal epithelium, or corneal cellular morphology. The negative outcome observed in this study could potentially be attributed to the lack of objective test criteria for dry eye diagnosis and the underlying premise that their study population consisted of only type 1 diabetes mellitus. The timeline map (Figure 6A) highlighted the emergence of diabetic keratopathy as a research focus after 2010. This trend was likely driven by the increasing availability of sophisticated tools for examining corneal sensitivity and tear film quality, enabling more comprehensive investigations into the disorder. Jing *et al*[24] utilized IVCM to investigate the mechanisms of visual impairment in patients with dry eye disease. They discovered a strong correlation between corneal nerve morphology changes and corneal aberrations, which could significantly impact visual function and exacerbate subjective symptoms in dry eye patients. The widespread application of IVCM had facilitated research on the pathogenesis of corneal neuropathy in DADE population. It provided a quantitative method for assessing the severity of corneal neuropathy, helped interpret the therapeutic efficacy of dry eye treatments, and offered comprehensive clinical diagnostic and management guidelines. Therefore, analyzing the leading research hotspots and trends of IVCM could help guide future research on the pathogenesis, diagnosis, and clinical management of DADE.

Immuno-inflammation was another area of research on DADE risk factors. The red group in the keyword co-occurrence map (Figure 6) contained tear film, inflammation, oxidative stress, expression, and cells, suggesting that the decrease of tear film quality was associated with oxidative stress and apoptosis induced by inflammation, which ultimately leads to exacerbation of dry eye. Rhee and Mah[25] proposed that inflammation and oxidative stress were the core driving forces behind the vicious cycle progression of DADE. Oxidative stress triggered inflammatory responses in the ocular surface, while inflammation further exacerbated oxidative stress. Concurrently, apoptosis-related markers increased, followed by a decrease in tear film stability, leading to elevated tear osmolarity, which further intensified inflammation. The inflammatory cytokines induced by hyperglycemia could disrupt the structure of various layers of the tear film, leading to decreased tear film stability[26]. Systemic immune-inflammation index played an important role in predicting diabetes related ocular problems as a diagnostic indicator[27]. Immuno-inflammation related proteins significantly increased in tear fluid expression in patients with DADE, including interleukin 1, interleukin 6, interleukin 8, and tumor necrosis factor-α (TNF-α), while raised TNF-α expression was also seen in the conjunctival epithelial basal layer. Decreased expression of peroxisome proliferator-activated receptor-γ contributed to the reduced corneal sensitivity and diminished tear secretion in mice with DADE[28-30]. Therefore, DADE could be treated by intervening the afferent and efferent arms through antioxidant and anti-stress interventions in order to break the inflammatory cycle.

On the other hand, specialized pro-resolving mediators (SPMs) are involved in key pathophysiological processes such as corneal epithelial regeneration, corneal neovascularization after injury, and tear production. In dry eye patients, the expression of SPMs such as lipoxin A4, resolvins, protectins, and maresins

is dysregulated, leading to persistent inflammatory damage to the ocular surface and exacerbating dry eye symptoms. Pham and Bazan[31] reported that pigment epithelium-derived factor and docosahexaenoic acid would be able to enhance regeneration of damaged nerves, improve nerve sensitivity, and reduce neuropathic pain by upregulating the expression of resolvin D6i. This could promote wound healing and tear secretion, holding promise as a potential therapeutic approach for corneal neuropathy caused by DADE. The study of the immunoinflammatory mechanisms in DADE could improve our ability to stratify dry eye patients, perform diverse DADE typing and disease monitoring, ultimately leading to the development of targeted intervention strategies[32]. In essence, DADE is a multifactorial ocular surface disease with a complex pathogenesis, which involves not only increased production of inflammatory factors like TNF-α, or dysregulation of SPMs, but also corneal neuropathy. Therefore, the management, apart from strict glycemic control, should also include methods for local anti-inflammation and improvement of corneal neuropathy. Furthermore, research on the ocular surface immune homeostasis disruption caused by DADE may contribute to the development of new diagnostic and therapeutic strategies for other ocular surface diseases. For instance, abnormal expression of ocular surface immune factors like antimicrobial peptides could be a potential risk factor for neurotrophic keratopathy[33].

The analysis of the contributions of 52 countries and regions in DADE research showed that the United States had the highest betweenness centrality compared with Asian countries which had notably larger number of diabetic patients than other regions (Table 3). This indicated that the United States had a strong information control ability and played an important bridging role in linking the findings of DADE research in other countries. What's more, it was concluded that the top five countries with the highest average number of citations were the United States, Brazil, South Korea, Australia, and Singapore, indicating that researchers from the above countries had a higher impact in researching DADE. The initial publications by American scholars predominantly occurred before 2010 (Table 1), while Chinese researchers, on the other hand, had more publications and most of which were published after 2020. This indicated that DADE was an emerging and focused area in China for the past few years.

In recent years, research on DADE had seen a surge in popularity. Except for a dip in publication volume in 2020 possibly due to the COVID-19 pandemic, the field had witnessed a consistent increase in publications since 2016, reaching a peak of 53 papers in 2023. This trend could be attributed to economic development and a growing awareness of the disease. As the global prevalence of diabetes continued to rise, its complications were posing increasing challenges to people worldwide. In 2021, among the top 10 countries with the highest number of adult diabetes patients aged 20–79y, China, India, and Pakistan ranked in the top 3. The list also featured Indonesia, Bangladesh, and Japan. The prevalence of dry eye displayed an uneven distribution, with notably higher rates in Asia, particularly in East Asia, compared to other regions worldwide[34]. This may be attributed to genetic and environmental factors specific to Asian populations, as well as cultural and lifestyle differences from other regions. Investigating the characteristics and associated factors of DADE in Asian populations could offer enhanced understanding of the disease burden in regions with high prevalence, and thus further to explore the impact of environmental, demographic, and systemic factors on the development of DADE. Notably, given that Asian populations may exhibit different responses to risk factors and treatment methodologies compared to other areas, targeted research focused on specific populations could facilitate the development of tailored prevention and treatment strategies. Furthermore, conducting comparative studies on DADE risk factors in Asian populations and other regions would contribute to a comprehensive understanding of the disease, providing insights into DADE on a global scale with both theoretical and practical significance.

This study's findings generally aligned with the current state of knowledge in the field of DADE, while also revealing some discrepancies. The aspects that were consistent included topics of intense scholarly scrutiny and the study of pathogenesis. Our study, through keyword burst detection, identified recent research hotspots such as meibomian gland dysfunction, oxidative stress, and impact. This suggested that the impact of diabetes on the systemic system was a key focus in dry eye pathogenesis research, aligning with current literature that emphasized the correlation between diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and dry eye. Our analysis indicated that a significant number of studies focused on the pathogenesis of diabetic dry eye, with tear film stability, inflammation, oxidative stress, and cell expression as prominent keywords. These were consistent with the current research directions, where existing studies had shown that immuno-inflammation, oxidative stress, and corneal neuropathy were key pathological mechanisms in the development of DADE. A discrepancy between our findings and existing literature lay in the representative core keywords identified in the keyword co-occurrence map, which were dry eye, diabetes, incidence, and diabetic retinopathy. Existing research, while acknowledging the high incidence of dry eye in diabetic patients and confirming its association with diabetic retinopathy, had not prioritized this prevalence as a key

research area or delved deeply into the underlying mechanisms or clinical implications of the association. Therefore, while bibliometric analysis was able to systematically collect data from a research field to accurately summarize and deduce research trends, the analysis should be combined with the current research status. A multi-dimensional analysis, encompassing both macro and micro perspectives, should be provided based on a clear understanding of the actual hot topics in the research field.

This study had several limitations. First, bibliometric studies relied on data from published literature. This study used the Web of Science core collection as the database for literature extraction. Although the database was generally considered comprehensive and we examined the integrity and validity of extracted literature data, it was possible that some unpublished or non-mainstream journal publications may be overlooked. Particularly when considering that East Asian populations exhibited higher prevalence rates of diabetes and dry eye compared to other regions globally, making them an ideal population for DADE research. Therefore, subsequent studies should incorporate other languages besides English and employ more scientific and diverse search strategies. Furthermore, this study utilized both Citespace and VOSviewer software for data analyzing. Due to the varying algorithms and logic details of these two software, the visualized results from multiple perspectives of the data may differ. Future research should enrich data sources while refining the comparison of data quantification analysis across different bibliometric software.

In conclusion, the pathogenesis of DADE was a major focus of current research, with risk factor analysis being a prominent area of interest. Possible risk factors included age, gender, duration of diabetes, and diabetic retinopathy[8]. The relationship between comprehensive systemic factors and the development of DADE needed to be further investigated. What's more, in depth research into the underlying mechanisms could provide a theoretical foundation for developing more effective treatment methods. The diagnosis criteria, treatment approaches, and prognosis evaluation of DADE were also crucial research directions in this field. Given that the prevalence of dry eye in the Asian region ranked highest globally, a considerable amount of research on risk factors for dry eye emerged in Asian populations. Meanwhile, the KNHANES database had received significant attention from researchers worldwide[35-36]. Utilizing this online database to extract demographic, dietary, and laboratory data for statistical analysis among diabetes and dry eye patients would greatly contribute to the establishment of risk prediction models for DADE. Additionally, training efficient prediction models using machine learning algorithms was a current priority in research[37-38]. Current studies had proved that deep learning algorithms, such as the Enhanced Stacked Auto-Encoder-Optimized Deep Neural Network, were promising in diagnosing dry eye through ocular surface images[39]. Deep mining of such databases using artificial intelligence and establishing predictive models for the occurrence of DADE represented future research trends. Establishing accurate predictive models can assist physicians in identifying high risk individuals earlier, enabling timely interventions and ultimately reducing the incidence of DADE.

**ACKNOWLEDGEMENTS**

**Authors' Contributions:** Yang Z (conceptualization, methodology, software, writing-original draft); Jiang JY (methodology, investigation, data curation); Zhang XH (resources, writing-review & editing, supervision, funding acquisition).

**Foundation:** Supported by the Exploratory Project of The Second Affiliated Hospital of Xi'an Jiaotong University [No.2020YJ(ZYTS)154].

**Conflicts of Interest: Yang Z,** None; **Jiang JY,** None; **Zhang XH,** None.

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