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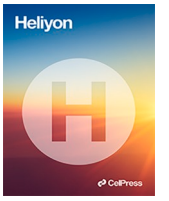

Hyperlipidemia and lipid-lowering therapy in diabetic retinopathy (DR): A bibliometric study and visualization analysis in 1993–2023

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ABSTRACT

Background: Diabetic retinopathy (DR) is a common complication in diabetic patients. DR is also a neurodegenerative disease. Patients with hyperglycemia, hyperlipidemia, and hypertension are vulnerable to retinopathy development. While the roles of blood glucose and blood pressure in the development of retinopathy have been extensively studied, the relationship between body fat and DR pathogenesis and the impact of lipid-reducing drugs on DR has just emerged as a research hotspot in DR study. We aim to visualize the contributions and cooperation of reporters, organizations, and nations, in addition to the research hotspots and trends in DR-related lipid research from 1993 to 2023, by bibliometric analysis.

Methods: We extracted all publications about DR-related lipid research from 1993 to 2023 from the Web of Science Core Collection, and bibliometric features were studied using VOSviewer and the CiteSpace program.

Results: 1402 documents were retrieved. The number of studies has risen consistently for three decades, from an average of 16.8/year in the 1990s to 28.8/year in the 2000s, 64.5/year in 2010s, and reached 112/year in 2020–2022, confirming they are hot research topic in the field. These reports were from 93 nations/regions, with the USA, China, Japan, Australia, and England taking the leading positions. *Diabetes Research and Clinical Practice* was the journal that published the most studies, and *Diabetes Care* was the most quoted. We identified 6979 authors, with Wong TY having the most papers and being the most commonly co-cited. The most popular keyword, according to our research, is diabetic retinopathy. Oxidative stress, diabetic macular edema (DME), lipid peroxidation, and other topics have often been investigated.

Conclusion: DR-related lipid research is conducted mainly in North America, Asia, Oceania, and Europe. Much study has centered on the relationship between lipid-lowering therapy and DR pathogenesis. These studies strongly support using lipid-reducing medications (fenofibrate, statins, and omega-3 PUFAs), combined with hyperglycemia and hypertension therapy, to prevent

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and treat DR. However, the impact of fenofibrate or statin on retinopathy is not correlated with their action on blood lipid profiles. Thus, more randomized clinical trials with primary endpoints related to DR in T1D or T2D are merited. In addition, the lipid biomarker for DR (lipid aldehydes, ALEs, and cholesterol crystals), the action of lipid-reducing medicines on retinopathy, the mechanism of lipid-lowering medications preventing or curing DR, and ocular delivery of lipid-lowering drugs to diabetic patients are predicted as the research focus in the future in the DR-related lipid research field.

1. Introduction

Diabetic retinopathy (DR) is a significant feature of diabetes and the common reason for vision loss in the population of 15–64 years of age [1]. DR is also a neurodegenerative disease [2,3]. According to a recent investigation, almost 400 million people worldwide have diabetes, of which about 1/3 progress to DR, and 10 % have vision loss because of macular edema and retinal neovascularization [4,5]. Traditional DR treatment modalities, such as retinal photocoagulation, intraocular administration of anti-VEGF antibodies, and vitrectomy, have multiple adverse consequences [6], so exploring the pathological process and new treatment for DR is critical.

Increased blood glucose and blood pressure are common conditions leading to DR, and strict managing these parameters can alleviate DR [7–9]. Hyperlipidemia is the typical pathological cause of coronary atherosclerosis [10], but it also contributes to the development of retinopathy [11]. Lipids, including cholesterol and triglycerides (TG), must be transferred with lipoproteins in the blood as they are insoluble in aqueous environments. Lipoproteins are a large family of proteins, including very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and others [12].

The relationship between retinal hard exudates (an early symbol of DR) and serum total cholesterol or LDL-cholesterol (LDL-C) was first reported by the WESDR study [13] and the ETDRS study [14]. The CHS Study concluded that DR correlates with higher total cholesterol and LDL-C levels but not HDL-cholesterol (HDL-C) and TG levels [15]. The SMES Study also confirmed the relationship between HDL-C and DR [16]. Three studies indicated that DME is correlated with LDL-C, including the CURES [17], a Turkey observation [18], and the SN-DREAMS trial [19].

Interestingly, two European studies found that increased HDL-C can promote DR progress, including the UKPDS trial [20] and an Italian study [21]. However, several studies have not found any relationship between DR or DME development and these lipid profiles, including the SRT trial [22], the AusDiab Study [23], the MESA study [5], and a study from Iran [24]. Thus, no conclusion can be drawn from these studies regarding the relationship between lipid profiles and DR development [25].

Nonetheless, lipid-lowering drugs, particularly statin, fibrate, and omega-3 PUFAs, have positively impacted DR patients. Statin (HMG-CoA reductase inhibitor) can decrease total cholesterol and LDL-C [26], while fibrate can decrease TG [27]. Omega-3 fatty acids also have many beneficial effects in lowering lipids and inflammatory factors in some cell types [28].

The Steno-2 Study (S-2-S) demonstrated that intensive statin treatment can reduce DME risk by 50 % [29]. Similar results were observed in some Korean DME patients [30] and a cohort of Taiwan patients with DR (NPDR, PDR) and vitreous hemorrhage [31]. The FIELD study demonstrated beneficial results of Fenofibrate to prevent DR in type 2 diabetes [32,33]. The ACCORD study revealed that Fenofibrate could substantially prevent DR development. Fibrate and statin together improved the DR condition by 40 % compared to statin alone [34,35]. The PREDIMED study found that dietary omega-3 PUFA can reduce DR risk among T2D patients [36].

These initial results were confirmed recently in a large group of T2D patients; lipid-lowering agents (statin or fibrate) reduced the risk of DR and DME [37,38]. Surprisingly, however, the beneficial results of fibrates or statin on retinopathy were not correlated to their impact on blood TG, HDL-C, and LDL-C, indicating these drugs might have some retinal-specific functions and raising concerns if serum lipids and lipoproteins are involved in the DR development [39]. It is possible that BRB (blood-retinal barrier) breakdown and subsequent local lipoprotein-mediated retinal injury, rather than serum lipid concentration, is the critical mechanism related to DR pathogenesis [40]. Thus, more research regarding the role of dyslipidemia and lipid-lowering therapy in DR is urgently merited.

Bibliometric analysis can qualitatively and quantitatively investigate hotspots and development tendencies in published scientific works. This analysis has two major procedures, including performance analysis and science mapping. (1) Performance analysis evaluates different academic study players (states, institutes, authors, and journals) and the influence of their work based on the bibliographic evidence. It measures the quantity and quality of scientific output through several parameters. (2) Science mapping reveals the speculative, collaborative, or intelligent shape of academic study, in addition to its transformation and flexible attributes, based on bibliographic networks, which include citation, co-citation, authors, co-authors, and keywords. It generates a spatial network to show how disciplines, areas, specialties, and publications or writers interact. It has been commonly employed to exhibit and reveal obscure central components (papers, researchers, organizations, directions) in individual investigation areas [41].

Bibliometric study has been an essential instrument in many research fields that intend to advance, including Medicine [42]. The current bibliometric analysis wants to determine, assess, and visualize documents published on DR-related lipid research over the last three decades to predict future research focus and tendency.

2. Materials and methods

2.1. Data sources and search strategy

We used the Science Citation Index Expanded of the Web of Science Core Collection (WoSCC) database in our study. All searches were performed on March 18, 2023. Two authors completed the literature search independently to identify DR-related lipid research literature with these search approaches: ((TS=(diabetic retinopathy)) OR TS= (diabetic macular edema)) AND (TS=(lipids) OR TS= (lipid metabolism) OR TS = (fatty acid) OR TS=(cholesterol) OR TS=(triglyceride) OR TS=(phospholipid) OR TS=(lipoprotein) OR TS=(Fibrates) OR TS=(Statins) OR TS=(Omega-3)). The period was from January 1, 1993, to March 18, 2023, and the language was English. In total, 2702 studies were obtained after the de-duplication of the search results. After excluding 1300 irrelevant items, we got 1211 articles and 191 reviews for analysis (Fig. 1).

2.2. Data analysis and visualization with CiteSpace and VOSviewer

CiteSpace (Version 6.2 R2) was applied to examine authors, institutions, and countries, find highly co-cited authors and co-cited journals, and use related algorithms to derive high-frequency keywords, outbreak words, and the top ten cited and outbreak literature. Clusters of keywords were created with VOSviewer (Version 1.6.18).

3. Results

3.1. The trend of publication output

Overall, 1402 papers were determined: 1211 papers are articles (86.4 %), and 191 are reviews (13.6 %). The annual publications from 1993 to 2022 are shown in Fig. 2 (13 publications from 2023 till March 18, 2023, not shown in Fig. 2). There is a general tendency to grow the production of scientific research gradually. The number of studies has risen consistently during the period of three decades, from an average of 16.8/year in the 1990s to 28.8/year in the 2000s, 64.5/year in the 2010s, and reached 112/year in 2020–2022, confirming they are hot research topic in the field. 35.37 % of all papers were published in the last six years (2018–2023).

3.2. Countries or regions analysis

During 1993–2023, DR-related lipid research articles/reviews came from 93 nations or regions. Table 1 summarizes the names of countries with the top number of papers. The United States (USA) was the leading country (349, 24.89 %), China ranked second (295, 21.04 %), and Australia was third (105, 7.49 %). Overall, these countries are mainly located in North America (USA), Asia (China, Japan, India, and Singapore), Oceania (Australia), and Europe (England, Italy, Spain, and Germany).

While the number of publications is essential, betweenness centrality (BC) is another indicator of research impact. The BC of a node is calculated when nodes are linked to each other, which represents the relative weight of every node within a network. As shown in Table 1 and Fig. 3, England had the highest BC score (0.37), followed by the USA (0.26), Australia (0.20), and Italy (0.20). Thus, these four countries published the most essential papers in the DR-related lipid research field. Citation is also influential; the USA had the most citations (17452), followed by Australia (7700) and Singapore (5554) (Table 1 and Fig. 3).

3.3. Institutions analysis

In total, DR-related lipid research articles/reviews were published by 2048 institutions. The top 10 institutes are from 4 countries (Table 2, Fig. 4), including two Australian universities, Singapore (Natl Univ Singapore and Singapore Natl Eye Ctr), USA (Univ Oklahoma, Univ Wisconsin, Harvard Med Sch, and Harvard Univ), and two Chinese universities. University of Sydney (Australia) had the highest BC score (0.07), followed by the University of Oklahoma (USA) with a BC score of 0.06, indicating they were major

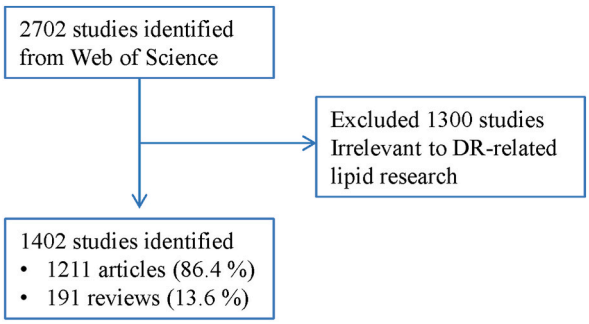

Fig. 1. Flow chart of the searching, screening, and inclusion.

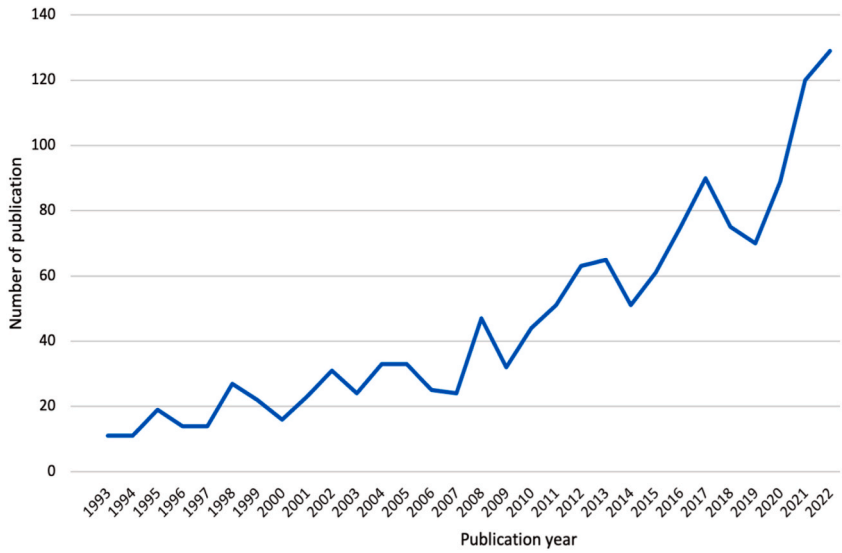

Fig. 2. The annual number of articles published in DR-related lipids research.

Table 1
The top 10 countries involved in DR-related lipid research.

Rank	Country	Centrality	Count (%of 1402)	Citation
1	USA	0.26	349 (24.893)	17452
2	Peoples R China	0.06	295 (21.041)	5061
3	Australia	0.2	105 (7.489)	7700
4	Japan	0.12	97 (6.919)	2906
5	England	0.37	91 (6.491)	5501
6	India	0.04	80 (5.706)	2682
7	Italy	0.2	78 (5.563)	3948
8	Singapore	0.05	60 (4.280)	5554
9	Spain	0	54 (3.852)	1774
10	Germany	0.06	50 (3.566)	2670

Fig. 3. Collaboration network involved in DR-related lipids research. In the network, a node represents a country or region. The size of the node represents the number of publications. The curved lines between nodes and their thickness indicate collaboration and the intensity of the partnership. A purple rim around the node indicates the betweenness centrality.

Table 2
The top 10 institutions involved in DR-related lipid research.

Rank	Institutions	Centrality	Count (% of 1402)	Citations
1	Univ Sydney	0.07	51 (3.638)	5863
2	Univ Melbourne	0.03	44 (3.138)	5608
3	Natl Univ Singapore	0.02	40 (2.853)	4874
4	Univ Oklahoma	0.06	30 (2.140)	1954
5	Univ Wisconsin	0.02	23 (1.641)	1052
6	Capital Med Univ	0.04	22 (1.569)	2276
7	Singapore Natl Eye Ctr	0	21 (1.498)	685
8	Harvard Med Sch	0.03	20 (1.427)	1101
9	Shanghai Jiao Tong Univ	0.01	20 (1.427)	1369
10	Harvard Univ	0.02	15 (1.070)	629

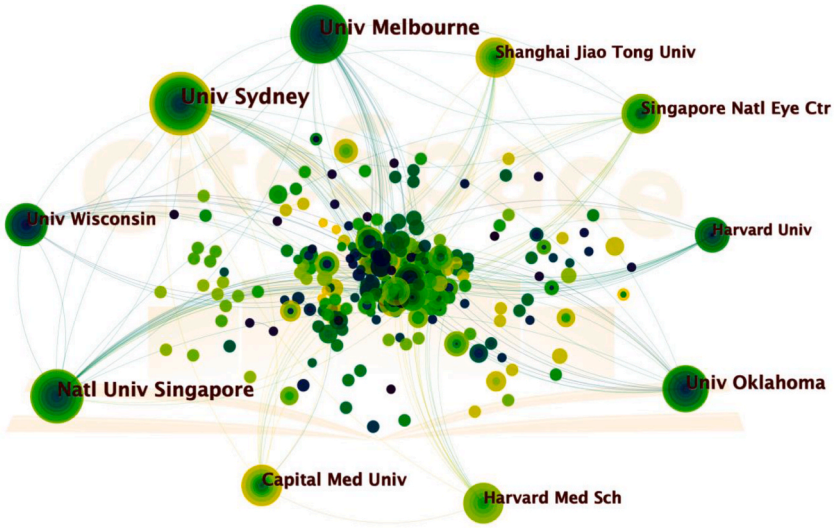

Fig. 4. Network of institutions involved in DR-related lipid research. The landmark nodes included Univ Sydney, Univ Melbourne, Natl Univ Singapore, Univ Oklahoma, Univ Wisconsin, Capital Med Univ, Singapore Natl Eye Ctr, Shanghai Jiao Tong Univ, Harvard Med Sch, and Harvard Univ. The major institutions collaborating with Univ Sydney were Univ Wisconsin and Singapore Natl Eye Ctr. In contrast, the central institutions collaborating with Univ Melbourne were Natl Univ Singapore and Univ Oklahoma.

institutes publishing necessary research in this field (Table 2). The two institutes from Australia have the most citations (5863 and 5608), followed by Natl Univ Singapore (4874) and Capital Med Univ in China (2276).

3.4. Authors analysis

Overall, 6979 researchers participated in the DR-related lipid studies. Table 3 and Fig. 5 show that DR-related lipid papers were published mainly by researchers from Singapore, Australia, the USA, and Indian institutions. Wong TY contributed the most reports (34, 2.425 %), succeeded by Wang JJ (13, 0.927 %) and Klein R (9, 0.642 %). Wong TY also had the most citations (3134), followed by

Table 3
The top 10 authors involved in DR-related lipid research.

Rank	Author	Institutes	Count (% of 1402)	Citation
1	Wong, Tien Y	Natl Univ Singapore	34 (2.425)	3134
2	Wang, Jie Jin	Univ Sydney	13 (0.927)	1428
3	Klein, Ronald	Univ Wisconsin	9 (0.642)	1060
4	Cheng, Ching-Yu	Singapore Natl Eye Ctr	8 (0.571)	291
5	Chenung, Ning	Univ Melbourne	7 (0.499)	2775
6	Lamoureux, Ecosse L	Univ Melbourne	7 (0.499)	485
7	Lyons, TJ	Univ Oklahoma	6 (0.428)	601
8	Klein, Barbara E K	Univ Wisconsin	6 (0.428)	659
9	Sharma, Tarun	Shri Bhagwan Mahavir Vitreoretinal Services	6 (0.428)	276
10	Mitchell, Paul	Univ Sydney	5 (0.357)	2603

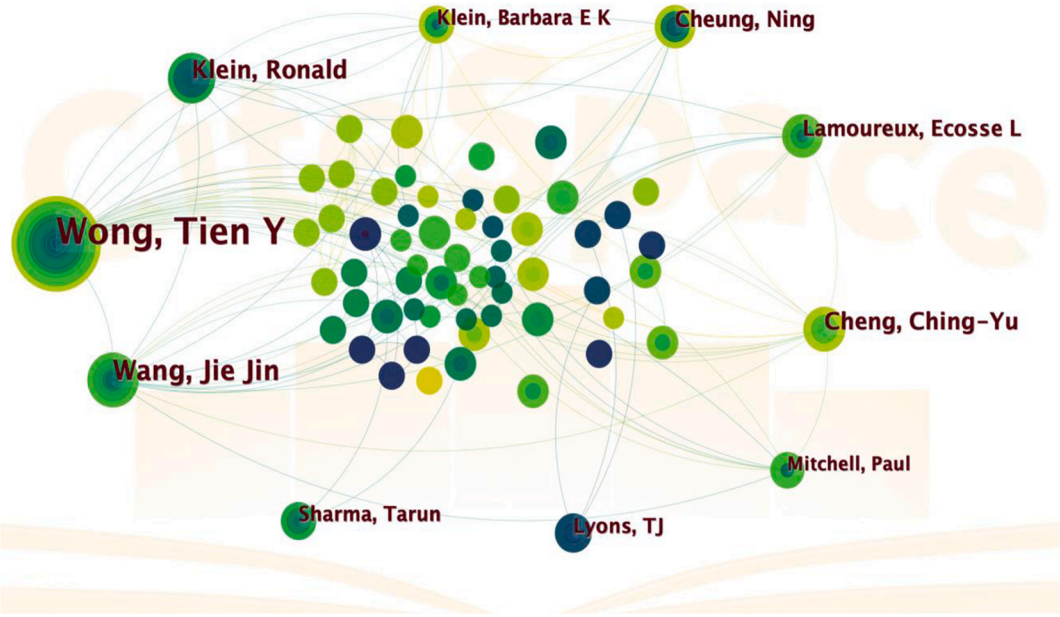

Fig. 5. Network of authors of DR-related lipids research. Wong TY, Wang JJ, and Klein R were at the center of the network.

Chenung N (2775) and Mitchell P (2603).

3.5. Journals and co-cited journals

Publications of DR-related lipid research were found in 453 journals. Top 10 fruitful journals in this field are listed in Table 4. Impact factors (IFs) are used to measure the weight of a journal by calculating the times the selected documents are cited within the last few years. The higher the IF, the more highly ranked the journal [43]. Among them, *Diabetes Research & Clinical Practice* published the highest number of papers (43, 3.02 %), followed by *Diabetes Care* (42, 2.95 %) and *Invest Ophth Vis Sci* (38, 267 %). There were three Ophthalmic Journals, *Invest Ophth Vis Sci (IOVS), British Journal of Ophthalmology (BJO),* and *Ophthalmology*; each published 38, 26, and 20 papers, respectively. *Diabetes Care,* with an IF of 17.152, published 42 documents (2.95 %), ranked 2nd for the overall number of documents. The lowest IF of 3.219 was the *Journal of Diabetes & Its Complications*, which ranked seventh with 30 papers (2.11 %). Consistent with the IF and the number of published articles, *Diabetes Care* received the most citations (3508), followed by *Diabetologia* (2798) and *IOVS* (2289).

When two or more papers are cited simultaneously by another publication, the papers are "co-cited." Documents from two journals are cited simultaneously by the articles published in a third journal, termed journal co-citation. *Diabetes Care* had the most co-citations (1011), followed by *Diabetes* (921) and *Diabetologia* (811) (Table 5). These three journals were also among the most prolific and highly cited (Table 4).

3.6. Keyword analysis

Keyword analysis can determine the research focus. In this analysis, various versions of the same name were combined, such as analogs (e.g., "adhesion molecule-1" and "adhesion molecules"), singular and pleural terms (e.g., "mouse" and "mice"), different

Table 4
The top 10 Journals in DR-related lipid research.

Rank	Journal	IF 2022	Count (% of 1402)	Citation
1	Diabetes Research & Clinical Practice	8.18	43 (3.067 %)	2103
2	Diabetes Care	17.152	42 (2.996 %)	3508
3	Invest Ophth Vis Sci (IOVS)	4.925	38 (2.710 %)	2289
4	Diabetologia	10.46	38 (2.710 %)	2798
5	Plos One	3.752	34 (2.425 %)	958
6	Diabetic Med	4.213	34 (2.425 %)	1372
7	Journal of Diabetes & Its Complications	3.219	30 (2.140 %)	865
8	British Journal of Ophthalmology	5.908	26 (1.854 %)	820
9	Diabetes	9.337	25 (1.783 %)	2145
10	Ophthalmology	14.277	20 (1.427 %)	1979

Table 5
The top 10 co-cited Journals in DR-related lipid research.

Rank	Co-cited journal	IF	Centrality	Count
1	Diabetes Care	17.152	0.04	1011
2	Diabetes	9.337	0.04	921
3	Diabetologia	10.46	0.04	811
4	Invest Ophth Vis Sci	4.925	0.03	757
5	Ophthalmology	14.277	0.03	719
6	New Engl J Med	176.07	0.04	655
7	Lancet	202.73	0.04	631
8	Arch Ophthalmol-Chic	8.253	0.01	602
9	Diabetic Med	4.213	0.03	505
10	Diabetes Res Clin Pr	8.18	0.04	476

Table 6
Top 30 keywords.

Rank	Keyword	Count	Rank	Keyword	Count
1	Diabetic Retinopathy	852	16	Microvascular Complications	102
2	Diabetes	466	17	Expression	98
3	Risk Factor	447	18	Population	96
4	Prevalence	263	19	Cholesterol	93
5	Oxidative Stress	222	20	Insulin Resistance	86
6	Progression	205	21	Blood Pressure	82
7	Complications	196	22	Coronary Artery Disease	82
8	Diabetic Macular Edema	183	23	Glycemic Control	72
9	Disease	164	24	Diagnosis	67
10	Association	157	25	Epidemiology	67
11	VEGF	138	26	Atherosclerosis	66
12	Diabetic Nephropathy	133	27	Nitric Oxide	65
13	Cardiovascular Disease	131	28	Mortality	63
14	Inflammation	114	29	Serum Lipids	63
15	Lipid Peroxidation	105	30	Retina	62

spelling (e.g., “cardiovascular disease” and “cardiovascular-disease”). Table 6 shows the top 30 keywords: DR, DME, VEGF, lipid peroxidation, cholesterol, and serum lipids. In Fig. 6, we also use VOSviewer software to show the primary keywords co-occurrence in a more compact and aesthetically pleasing manner. When two keywords appear in the same paper, it is considered that these two words have a relationship.

We employed CiteSpace to uncover the top 25 keywords with the highest citation (Fig. 7). The blue line represents the citation period; the red line segment delineates the keywords’ burst year. The strong citation strength keyword was lipid peroxidation (16.47) during 1997–2007, followed by microalbuminuria (12.05) and nephropathy (10.96). Some keywords demonstrated intense citation bursts, including DME and management.

3.7. Co-cited references and references with citation bursts

3.7.1. Top-cited references

Co-cited references analysis is a valuable feature of CiteSpace. Table 7 lists the top 10 co-cited references from 1993 to 2023. Of the ten documents, three were published in *The New England Journal of Medicine (NEJM)* and two in the *Lancet*; the other five were published in *Diabetes Care, Circulation, Eye Vision, Ophthalmology,* and *Cardiovascular Diabetology,* respectively. Among them, four were reviews on DR [4,44] or DR epidemiology [45,46]; two were about ACCORD and ACCORD Eye study [34,47]; one was about Fenofibrate and FIELD survey [32]; one about Statin [30]; one about strict control of blood glucose on DR development [8] and one about the relationship between DR and blood TG and HDL-C [48].

The most frequently co-cited reference is a systemic review by the META-EYE Study Group, which revealed that there were about 100 million DR patients, about 20 million PDR patients, 20 million DME patients, and 30 million VTDR (vision-threatening DR) patients worldwide in 2012. Diabetes duration, hyperglycemia, and hypertension strongly indicate DR occurrence [45]. The second most co-cited paper is about the FIELD study, which reported the beneficial results of Fenofibrate to prevent DR course in T2D patients [32,33]. The third most cited paper was the ACCORD study, which revealed that Fenofibrate could significantly prevent DR progression. Fibrate combined with statin had even better effects [34,35]. The ACCORD study paper [34] is also the most impactful report, with the highest BC score of 0.53, followed by the study that showed a relationship between lipids and diabetic microvascular complications with a BC score of 0.38 [48].

3.7.2. Citation bursts

The burst detection approach was utilized for documents quoted at a progressively rapid pace to determine papers with lots of

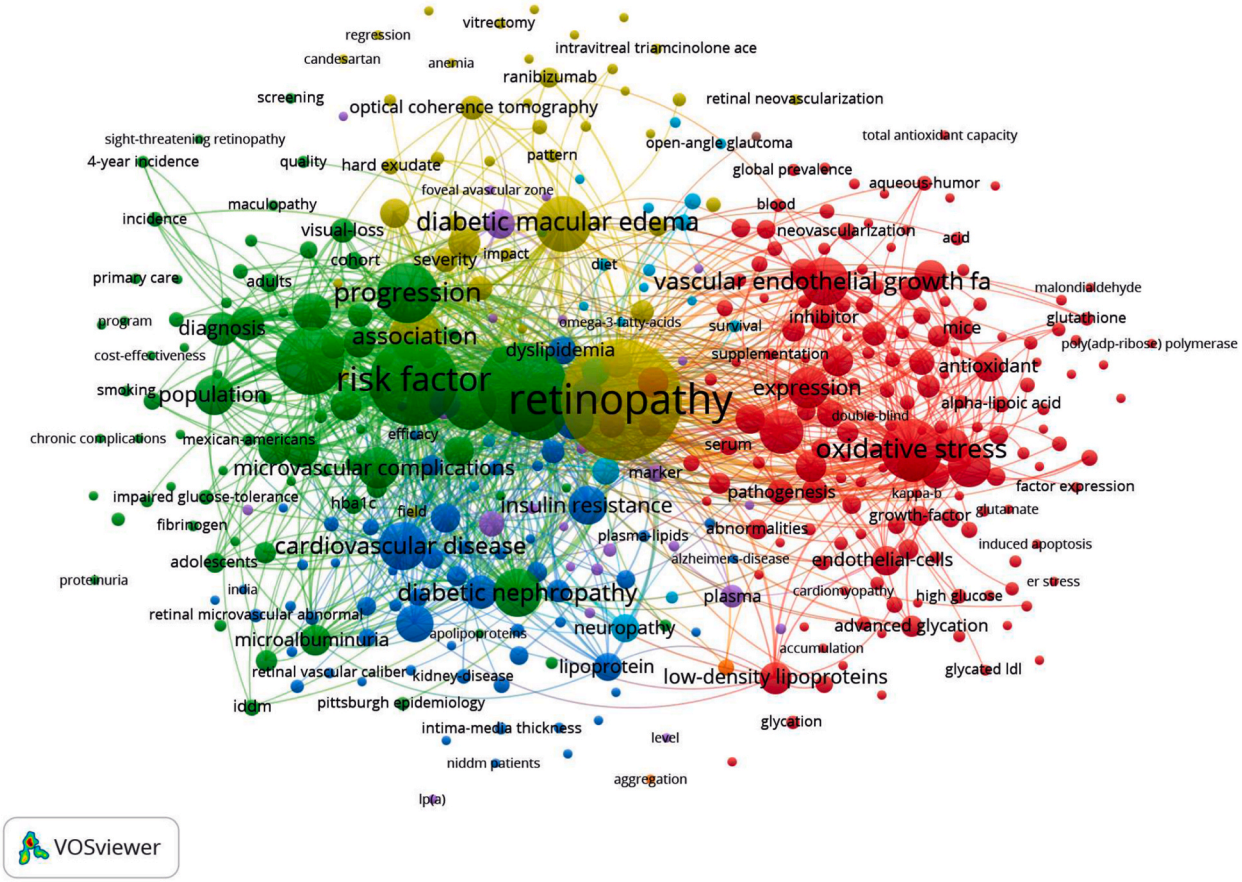

Fig. 6. Map of keyword clustering in DR-related lipid research. The font size of each keyword indicates the number of papers with this keyword. The thickness of the curved connecting line suggests the collaborative intensity between keywords; the same color represents the same cluster. Keywords were stratified into six main clusters; for instance, oxidative stress and VEGF are in the red cluster (1), risk factor and microvascular complications are in the green cluster (2), insulin resistance and cholesterol are in the blue cluster (3), DR and DME are in the light yellow cluster (4), type 1 diabetes and PDR are in the purple cluster (5), neuropathy and Mediterranean diet are in the cyan cluster (6).

considerations. Vigorous citation bursts of 25 articles are shown in Fig. 8. The publication year is labeled. Strength illustrates the citation frequency. The line aligns with the time between 1993 and 2023; the red fragment shows the period of citation bursts.

The most excellent citation burst was the paper about the FIELD study reported in the *Lancet* by Keech et al. [32], with a burst beginning from 2009 to 2012 (22.92), accompanied by a DR review reported in *Diabetes Care* by Yau et al. [45] with a citation burst covering 2013 to 2017 (22.67), and a DR therapy paper reported in *NEJM* by Chew et al. [34], with a burst from 2010 to 2015 (19.83). These three citation bursts are among this field's top 10 co-cited papers (Table 7). Five pieces whose citation burst ended in 2023 are worth more attention. These include statin use and DME [30], incidence and progression of DR [49], DR treatments [50], and the IDF Diabetes Atlas (2015–2040) [51] and IDF Diabetes Atlas (2030–2045) [52].

3.7.3. Nine co-citation clusters

CiteSpace can split the co-citation data into clusters, exhibiting securely associated papers in the same cluster and vaguely associated reports in separate clusters. The name of the cluster was determined using the terms of the titles of all documents in the cluster. The nine clusters were indicated in Fig. 9, including #0 Fenofibrate, #1 Metabolomics, #2 Hard exudates, #3 Taurine, #4 Lipoprotein (a), #5 Cardiovascular diseases, #6 Oxidation, #7 Ranibizumab, and #8 Serum creatinine. These included one cluster about DR phenotype (cluster #2), two clusters about DR therapies (#0, #7)), two about risk factors (#5, #6), and four about metabolites (#1, #3, #4, #8).

3.7.4. Timeline map of the nine clusters

The cluster map (Fig. 9) could be turned into a timeline map, in which the x-axis is the year, and the y-axis is the cluster number (Fig. 10). This graph describes the general progression and nine clusters over time. Remarkably, clusters #3 (taurine), #4 (lipoprotein (a)), and #8 (serum creatinine) were mainly in the early time (Fig. 10), but #1 (metabolomics) persisted to recent times, indicating the focus of study shifted from analyzing single metabolite to large-scale metabolites (metabolomics) in this field.

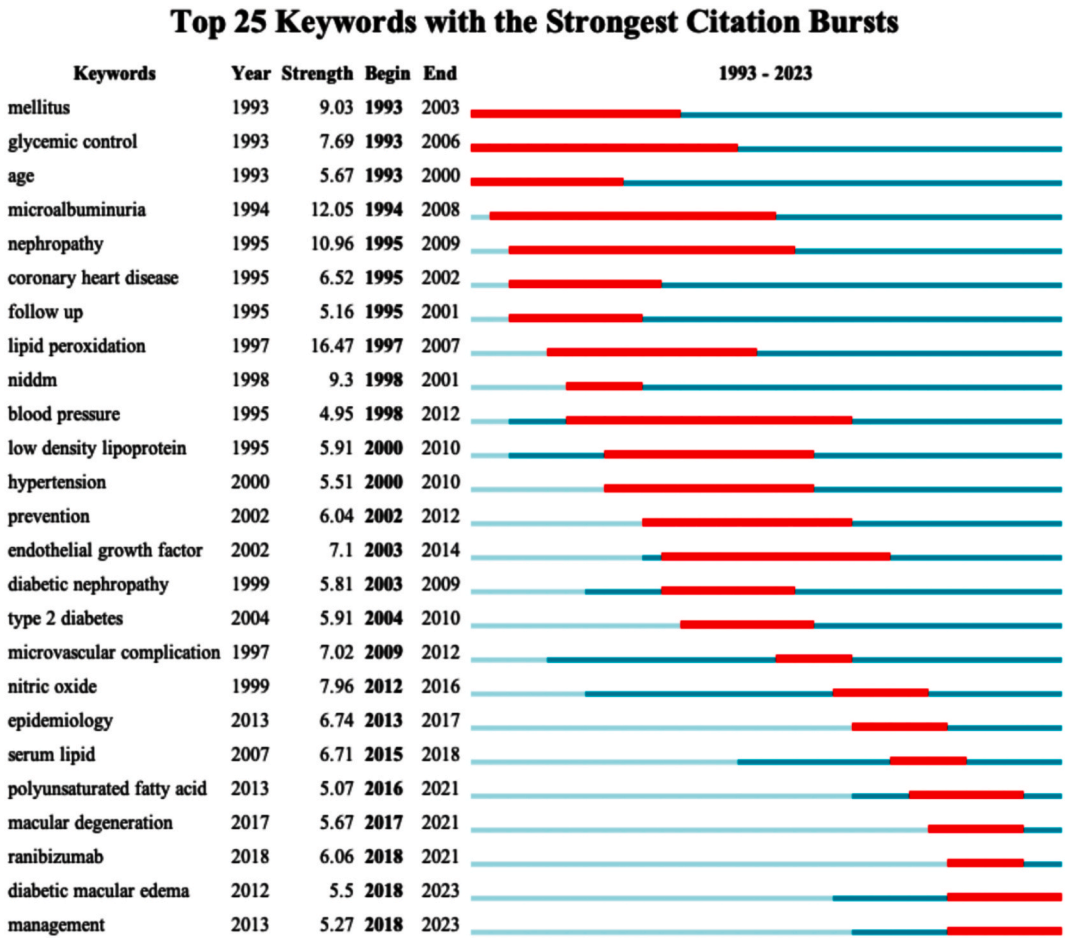

Fig. 7. Keywords with intense citation bursts in DR-related lipid research.

Table 7
Top 10 co-cited references in DR-related lipid research.

Rank	Citation	Centrality	Author	Year	Journal
1	46	0.2	Yau JWY	2012	Diabetes Care
2	44	0.16	Keech AC	2007	Lancet
3	42	0.53	Chew EY	2010	New Engl J Med
4	26	0.38	Sacks FM	2014	Circulation
5	26	0.15	Lee R	2015	Eye Vision
6	25	0.04	Cheung N	2010	Lancet
7	24	0.18	Shamoon, H;	1993	New Engl J Med
8	23	0.19	Antonetti DA	2012	New Engl J Med
9	22	0.03	Chew EY	2014	Ophthalmology
10	20	0.09	Chung YR	2017	Cardiovasc Diabetol

3.7.4.1. High betweenness centrality articles. Some nodes in the map (Fig. 10) had purple rings, denoting that they had high BC scores [53]. The top five documents are shown in Table 8. All documents were published between 2001 and 2010; two of them belong to cluster #0 (Fenofibrate), two belong to cluster #5 (Cardiovascular diseases), and one belongs to cluster #3 (Taurine). They reported the use of fibrates [34,54], antioxidative supplemental vitamins C + E [55], and statin [56] to treat diabetic complications, including DR. The DCCT/EDIC Study supported the notion that lipoprotein is involved in DR pathogenesis [57].

3.7.4.2. Details of cluster #0 (fenofibrate). In cluster #0 (Fenofibrate), the top 10 papers were published in the *Lancet, NEJM* , *Ophthalmology, JAMA,* and *IOVS* from 2007 to 2010 (Table 9). These include the seminal research of FIELD and ACCORD studies [32, 34]. They also include two reports published in *NEJM* in 2008 about anti-hyperglycemia therapy on T2D patients; one showed that strict control of hyperglycemia for 3.5 years had not reduced major cardiovascular complications but unexpectedly increased mortality

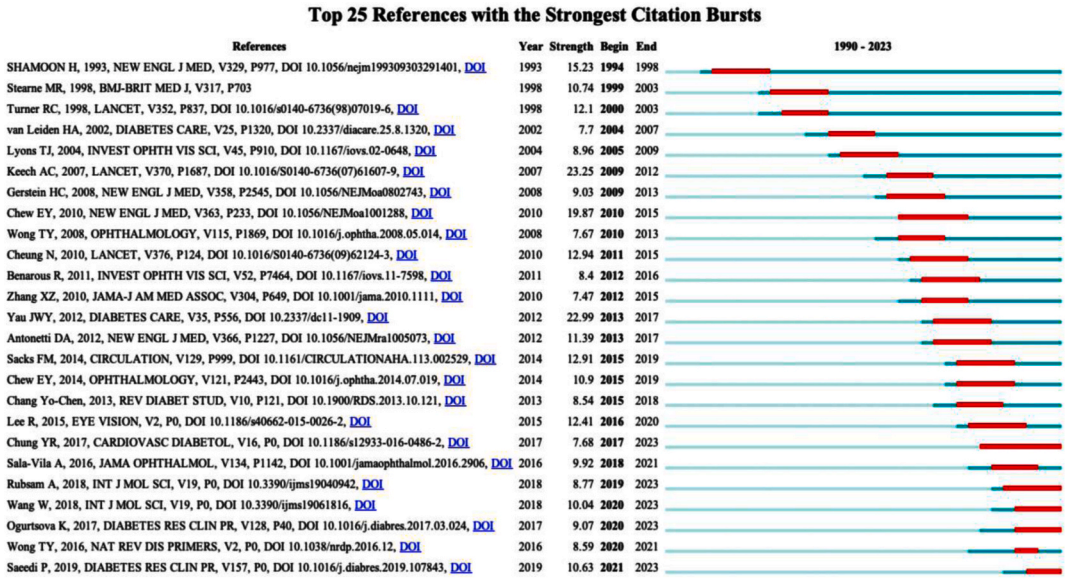

Fig. 8. Top 25 references with intense citation bursts in DR-related lipid research.

[58]. However, intensive five-year therapy could reduce nephropathy by 21 % and thus reduce the occurrence of main macrovascular and microvascular complications by 10 % but had no significant effect on DR [59]. These studies suggest that to prevent DR, we need to control risk factors other than hyperglycemia, such as hyperlipidemia.

Cluster #0 (Fenofibrate) also includes a clinical trial compared statin/fibrate combined therapy with statin monotherapy on cardiovascular disease in T2D patients, which concluded Fenofibrate/simvastatin combined therapy had no significant effects on reducing fatal cardiovascular complications and non-fatal heart stroke [60]. Cluster #0 (Fenofibrate) also includes an interesting experimental study [61]. By staining human retinal sections from 4 groups (non-diabetic, T2D without DR, NPDR, and PDR) with apolipoprotein B100, macrophages, and oxidized LDL, they showed that extravasated, modified LDL could promote DR, which supports the idea that dyslipidemia is related to DR development [61].

3.7.4.3. Details of cluster#1 (metabolomics). Cluster#1 (Metabolomics) is the most recent cluster; papers were all published from 2016 to 2021 (Table 10). This cluster includes two studies regarding statin and DR/DME from Korea [30] and Taiwan [31]; both concluded that statin was beneficial to T2D patients regarding retinopathy development. Another important paper is about the PREDIMED study, which revealed that dietary omega-3 PUFA was beneficial to T2D patients regarding retinopathy development [36]. There are also four papers regarding DR prevalence prediction and three reviews on DR mechanism and treatment.

4. Discussions

4.1. DR-related lipid research is a hot spot in DR research

The volume of scientific papers is an essential indicator of academic conduct. As shown in Figs. 2 and 1402 documents were published from 1993 to 2023 regarding DR-related lipid research. Obviously, from 1993 to 2007, the growth was relatively slow, but after 2008, the increase was rapid, likely due to the seminal publication of the FIELD study in 2007 [32]. After 2014, the growth was further speeded up, probably due to the seminal publication of the ACCORD eye study of that year [47].

As shown in Table 1, the high-yield countries are based in North America (USA), Asia (China, Japan, India, and Singapore), Oceania (Australia), and Europe (England, Italy, Spain, and Germany). Any subject with a BC score exceeding 0.1 is believed to be potent in the field. Europe, North America, and Oceania delivered the most impressive DR-related lipid research. Regarding these high-performance institutions, the top 10 were from Australia, Singapore, the USA, and China. Australian and USA institutions were prominent in this research field based on the volume of publications and the BC value. Research capacities in Asian institutes (Japan, China, India, and Singapore) were also strong.

As shown in Fig. 3, the USA, Australia, and European nations, which contributed significantly to DR-related lipids research, developed cooperative partnerships worldwide. Australia, Singapore, and the USA developed a good collaboration network, as shown in Fig. 4. Despite China having contributed substantially to publication counts, Chinese institutes still need to form a robust cooperative network. The productive authors in Table 3 and Fig. 5 were mainly from Singapore, Australia, the USA, and India. Singapore and Australian researchers greatly influenced DR-related lipids research, demonstrating their outstanding performance and leading roles in the field. Dr. Wong TY was the most fruitful and cited scientist in this field. He was previously a professor at the National University of Singapore (NUS), but now he is the founding head of the Medicine College of Tsinghua University in China.

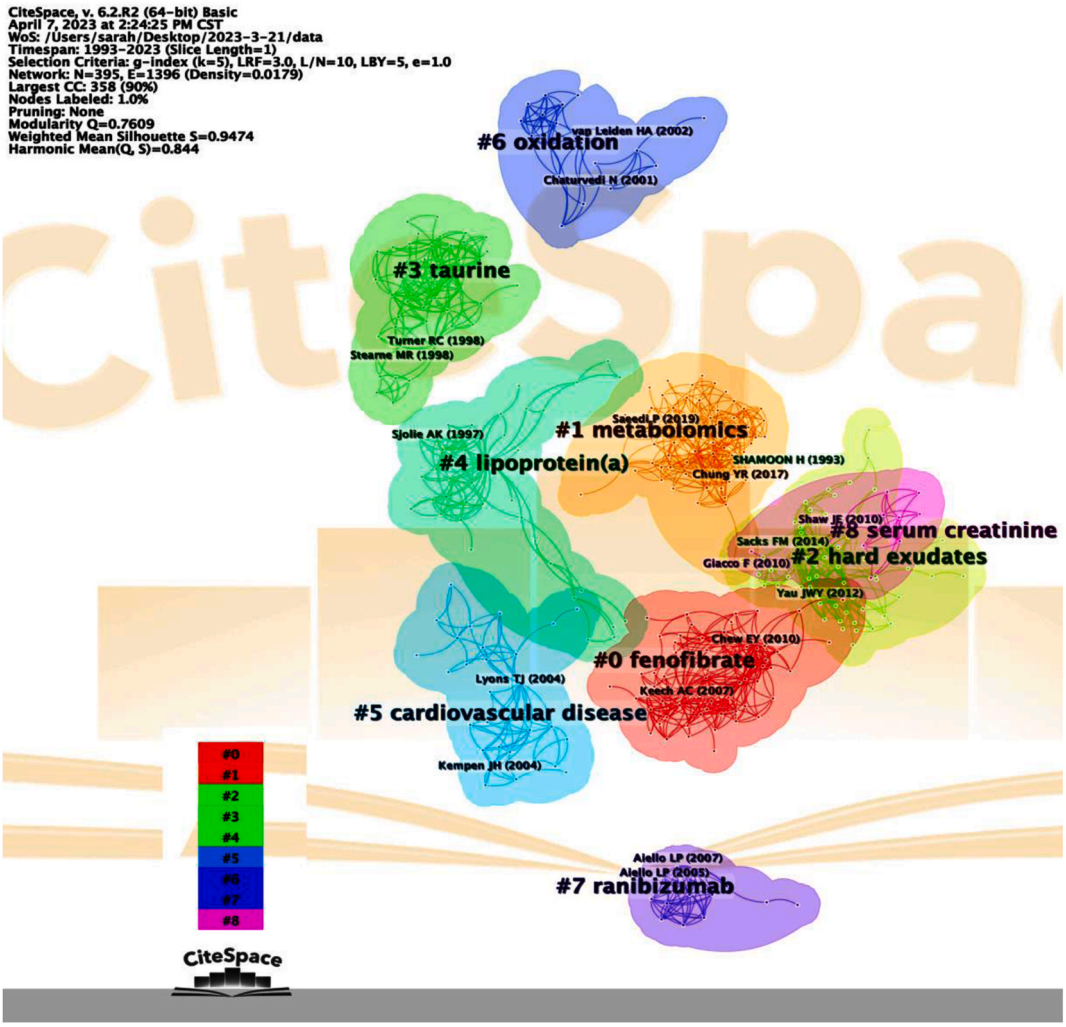

Fig. 9. CiteSpace visualization clusters of co-cited references about DR-related lipid studies.

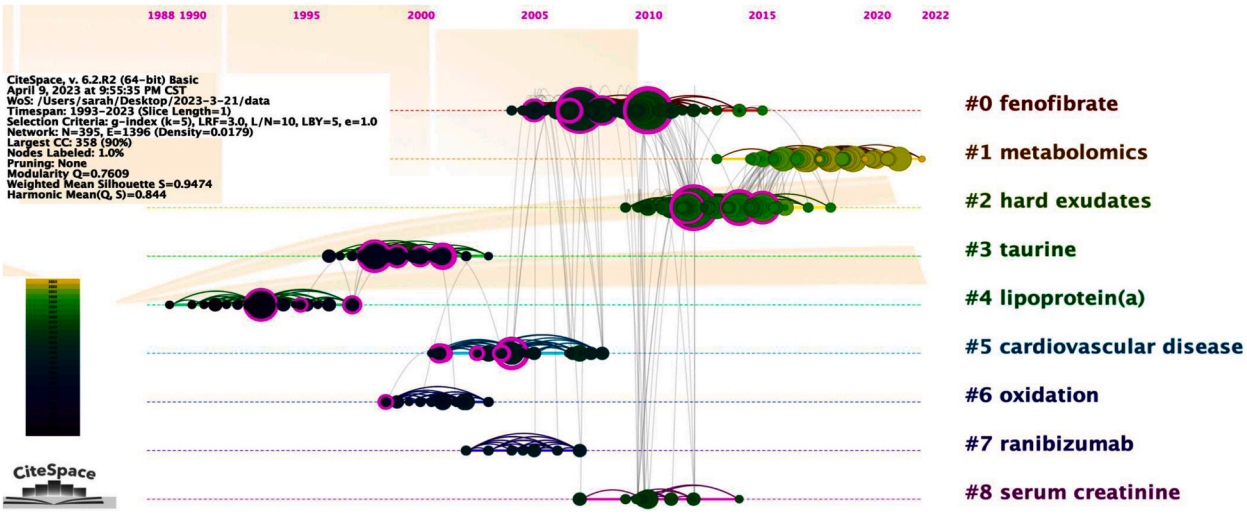

Fig. 10. Timeline views of clusters of co-cited references about DR-related lipid studies.

Table 8
Cited papers with the highest betweenness centrality among the top 9 clusters.

Rank	Centrality	Co-citation	References	Cluster #
1	0.77	14	Lyons TJ (2004): DR in the DCCT/EDIC cohort	5
2	0.55	8	Kim J (2007): Fenofibrate regulates retinal endothelial cell survival	0
3	0.55	11	Kowluru RA (2001): Effect of long-term antioxidants on the development of DR	3
4	0.55	3	Colhoun HM (2004): ARDS study	5
5	0.53	42	Chew EY (2010): Medical therapies and DR	0

Table 9
Cluster#0 fenofibrate.

Citation	Author (Year), Journal, Volume, Page	Contents
44	Keech Ac (2007), Lancet,V370,P1687	FIELD study
42	Chew EY (2010) , New Engl J Med, V363, P233	Medical therapies on DR
25	Cheung N (2010), Lancet, V376,P124	Diabetic retinopathy
19	Gerstein HC (2008), New Engl J Med,V358, P2545	Intensive glucose lowering in TT2D
15	Wong TY (2008), Ophthalmology, V115, P1869	Diabetic retinopathy
14	Zhang XZ (2010), Jama-J Am Med Assoc,V304, P649	Prevalence of DR in the United States, 2005–2008
12	Wu MY (2008), Invest Ophth Vis Sci, V49, P2679	Intraretinal DL in DR
10	Patel A (2008), New Engl J Med, V358, P2560	Intensive blood glucose control and T2D
10	Ginsberg HN (2010), New Engl J Med, V362, P1563	Combined lipid therapy in T2D
10	Mohamed Q (2007), Jama-J Am Med Assoc,V298, P902	DR management

Table 10
Cluster#1 metabolomics.

Citation	Author (Year), Journal, Volume, Page	Contents
20	Chung YR (2017), Cardiovasc Diabetol,V16, P0	Statin and DR/DME
20	Saeedi P (2019), Diabetes Res Clin Pr,V157, P0	Global and regional diabetes prevalence
19	Ogurtsova K (2017), Diabetes Res Clin Pr,V128, P40	Global estimates for the prevalence of diabetes
18	Wang W (2018), Int J Mol Sci,V19, P0	Diabetic Retinopathy
17	Sala-Vila A (2016), Jama Ophthalmol, V134, P1142	Dietary ω-3 Fatty Acids: the PREDIMED Trial
16	Duh EJ (2017), JCI Insight,V2, P0	Diabetic retinopathy
15	Wong TY (2016), Nat Rev Dis Primers,V2, P0	Diabetic Retinopathy
15	Teo Zl (2021), Ophthalmology, V128, P1580	Global Prevalence of DR
14	Cho NH (2018), Diabetes Res Clin Pr,V138, P271	Global estimates of diabetes prevalence
14	Kang EYC (2019), JAMA Ophthalmol,V137, P363	Statin therapy and DR

According to Tables 4–5, DR-related lipid research has been published mainly in diabetic journals such as *Diabetes Research & Clinical Practice, Diabetes Care, Diabetologia, Diabetic Med, Journal of Diabetes & Its Complications*, and *Diabetes*; at the same time, some are also published in ophthalmic journals such as *IOVS, BJO, Ophthalmology*, and *Archives of Ophthalmology*. Notably, some papers in this field were published in top-tier journals such as *NEJM* and *Lancet*, indicating this research field is essential for public health worldwide.

4.2. Trends in DR-related lipid research

Publications and keywords that are cited frequently have a critical academic impact. Based on co-citation references and keyword analysis, we predict that the following four topics will be the focus of future study in this field.

4.2.1. The lipid biomarker for DR (lipid aldehydes, ALEs, and cholesterol crystals)

While several studies, such as WESDR, ETDRS, CHS, SMES, and CURES, reveal that higher levels of circulating LDL-C, but not HDL-C, were correlated to DR/DME [13,14,16], UKPDS find that higher HDL-C is linked to more advanced DR [20]. SRT, AusDiab, and MESA studies find no correlation of DR/DME with HDL-C, LDL-C, and TG [5,22,34]. Thus, the associations of individual lipid classes (such as TG, total cholesterol, HDL-C, and LDL-C) with DR are inconsistent and weak [25]. One possible reason for this inconsistency is that we use the wrong lipid biomarker for these studies, as blood levels of individual lipids do not manifest leaky lipids and chemical modifications of lipids in the retina nor the status of the intra-retinal lipid metabolism.

As shown in Fig. 7, lipid peroxidation was the keyword with the most robust citation strength. The fundamental mechanisms underlying DR development are hyperglycemia-induced oxidative stress and increased ROS levels [62]. Lipids can undergo modification (such as lipid peroxidation) which promotes the oxidative degradation of lipids to form lipid aldehydes, including malondialdehyde (MDA), glyoxal (GO), 4-hydroxynonenal (4-HNE), and acrolein (ACR) [63,64]. Lipid aldehydes interact with DNA, protein, and phospholipids to produce advanced lipoxidation end products (ALEs) [65].

Both lipid aldehydes and ALEs are crucial for DR pathogenesis [64,66]. For example, MDA is a commonly used biomarker of lipid peroxidation. MDA increased substantially in blood samples of DR patients in a recent meta-analysis [67]. Blood MDA was also correlated with DR severity [68]. Glyoxal (GO) is the simplest dialdehyde that reacts with proteins to form Nepsilon-(carboxymethyl) lysine (CML) [69]. CML was upregulated in the blood and aqueous samples of DR patients and increased along with the progression of DR, correlated to both the onset and severity of DR [70].

4-HNE is the product of the peroxidation of omega-6 PUFAs [71] and one of the most toxic lipid aldehydes [72]. The level of 4-HNE increased in DR patient blood samples [63] and diabetic rat retinas [73]. In vitro exposure of 4-HNE to cultured RPE cells and retinal capillary endothelial cells activated the canonical Wnt pathway by stabilizing the LDL receptor-related protein 6 (LRP6) [73]. 4-HNE can impair the activity of the BK channel in rat retinal arterioles, thus causing vasoconstriction [74], an early phenotype of DR [75]. 4-HNE can also impair Kir4.1 and AQP4 channels of cultured retinal Müller glia, which may be related to DME [76].

In STZ-induced diabetic rat models, ACR-protein adducts FDP-Lys gathered mainly within the Müller and retinal ganglion cells [77]. Immunostaining of retinal fibrovascular tissue from PDR patients demonstrated the presence of FDP-Lys in Müller glial cells, endothelial cells, and pericytes [78]. FDP-Lys level also increased in the vitreous of PDR patients [79]. In vitro, exposure to FDP-Lys to cultured MIO-M1 human Müller cells induced oxidative stress, impaired K^+ ion channel function, and expression of VEGF and pro-inflammatory cytokines [77], while exposure ACR to human endothelial cells induced oxidative stress and cellular toxicity [79]. All these results indicate that FDP-Lys contribute to DR development.

In conclusion, these lipid-derived toxic biomolecules contribute to the pathogenesis and severity of DR. Thus, they are good candidates as lipid biomarkers for DR. However, measuring lipid aldehydes and ALEs is not as easy as serum lipids. The methods to measure lipid aldehydes include some complicated technologies [80]; to measure ALEs, proteomic and antibody-dependent approaches are required [81]. Thus, this field will aim to establish an easy way to measure lipid aldehydes and ALEs accurately.

Another candidate is cholesterol crystals (CCs). Cholesterol was the top keyword cited in this research field (Table 6). Accumulation of free, unesterified cholesterol can form monohydrate cholesterol crystals inside the cells, such as macrophage foam cells and endothelial cells [82,83]. CCs can activate the NLRP3 inflammasome and induce pro-inflammatory interleukin-1 family cytokines [84]. SD-OCT can identify the retina's cholesterol crystal structures as hyperreflective crystalline deposits (HCDs) or the onion sign [85–87]. Horizontal HCDs in diabetic patients suggest cholesterol crystals in retinal hard exudates [88]. Thus, HCDs or CCs can be a biomarker for imbalanced cholesterol metabolism and DR [88,89]. Future studies will determine the role of CCs in DR pathogenesis [90].

4.2.2. The effects of lipid-lowering drugs on DR

As shown in Table 7, The ACCORD study paper [34] is the most impactful paper, with the highest BC score of 0.53. The ACCORD study revealed that fibrate prevents DR development in T2D patients. Using fibrate and statin together had an even better effect [34, 47].

These two papers are cited more than 800 times and 190 times, respectively (even though co-citation is only 42 or 22). The second most co-cited paper is about the FIELD study, which confirmed the beneficial effect of fibrate on preventing DR progress in T2D patients [32,33]. This paper is cited more than 700 times (even though the co-citation is only 44). These early randomized controlled trials (RCTs) results were confirmed in a large group of Japanese T2D patients; lipid-reducing agents (statin or fibrate) could suppress DR and DME [37]. Thus, using lipid-reducing medication to prevent or treat DR is a significant research focus. Based on these data, Fenofibrate is approved in many countries for T2D patients with DR but has not been supported by Europe and the USA [90,91]. Thus, fibrate RCT trials with primary endpoints related to DR in T1D or T2D are merited.

Similarly, the paper on the PREDIMED study was one of the top co-cited documents in Cluster#1 Metabolomics (Table 10), revealing that omega-3 PUFAs can reduce the risk for vision-threatening DR among T2D patients [36]. Nevertheless, these results are observational, and RCTs with omega-3 PUFAs with primary DR endpoints are required.

The paper reported statin effects on DR/DME [30] was one of the top 10 co-cited papers (Table 7); its citation burst ended in 2023 (Fig. 8), indicating statin deserves special consideration in this field. Together with the data from a cohort of Taiwan patients with DR (NPDR, PDR) and vitreous hemorrhage [31], this paper confirmed the beneficial effects of statin on DR revealed by the Steno-2 Study [29]. However, statins can substantially raise the incidence of new-onset T2D [92], and some studies failed to disclose any benefit of stain on DR [93]. Thus, RCTs using statin with primary DR endpoints are still merited.

4.2.3. The mechanism of lipid-lowering drugs preventing or curing DR

Surprisingly, in both FIELD and ACCORD trials, the beneficial results of fibrates on the DR course were unrelated to blood lipid levels [32,34,47,90]. As we discussed above, these lipid markers may not be suitable to monitor the DR progression; however, another possibility is that fibrate and statin have some retinal-specific or lipids-independent effects.

For instance, the paper reported the anti-apoptosis effects of Fenofibrate on human retinal endothelial cells (HRECs), which is one of the top 5 papers with the highest betweenness centrality (Table 8) [54]. It is well known that Fenofibrate is a PPARα agonist, but this effect is PAR-independent and thus lipid-independent) but AMPK-dependent [54]. Fenofibric acid also seems to have a similar PPARα-independent but AMPK-mediated function to reduce the damage of modified lipoproteins on RPE cells [94]. These off-target effects of fibrate are intriguing and need to be further investigated.

PPARα is predominantly expressed in the liver and is essential for fatty acid and lipoprotein metabolism [95]. PPARα is also expressed in multiple retinal cells. Retinal expression of PPARα decreased in both T1D and T2D animals [96]. Diabetic PPARα$^{-/-}$ mice developed more severe signs of DR, such as vascular leakage and leukocytosis, whereas PPARα overexpression alleviated phenotypes of a rat DR model [96]. Similarly, Fenofibrate has anti-inflammatory and anti-apoptotic functions in vivo and in vitro that do not depend

on its effects on lipids [97,98]. The mechanism of these PPARα-mediated but lipids-independent effects of fibrate need to be further elucidated.

The retina has lots of lipids; about 50 % of its dry weight is lipid [99], and 40 % of the retinal lipids are PUFAs [100]. The retina has membrane phospholipids, sphingolipids, and cholesterol [101]. Docosahexaenoic acid (DHA) makes up about half the fatty acids in the photoreceptors [102]. Notably, the retinal lipid levels are controlled independently of the blood lipid levels [103].

Fibrate, omega-3 PUFAs, and statin can likely regulate the retinal lipid metabolism independent of systemic lipid levels, thus explaining their benefits to DR progression without affecting the serum lipid levels. Indeed, statins have pleiotropic effects regulating immuno-inflammatory processes independent of LDL-cholesterol levels [104,105]. Omega-3 fatty acids can also affect inflammatory pathways in many cell types [28,106]. However, these effects still need to be investigated in the retina and deserve further study.

4.2.4. Ocular delivery of lipid-lowering drugs to diabetic patients

If fibrate and statin can benefit DR patients independent of their lipids-lowering activity, ocular delivery may be the next step for these drugs to reduce toxic systemic side effects. This idea has been evaluated in vivo using animal models of ocular diseases; for instance, intravitreal injection of Fenofibrate reduced retinal vascular permeability and white blood cell migration in diabetic rodent models [107] and inhibited laser-induced CNV model in BN rats [108]. An atorvastatin-solid lipid nanoparticle eye drop has been tested in rat eyes and ARPE-19 cells [109]. Ocular delivery of simvastatin by polymeric micelles has been tested ex vivo in porcine ocular tissues [110], and local delivery of pravastatin by contact lenses has also been tested in rabbits [111]. All results are promising, but more studies targeting DR patients are merited.

4.3. Limitations of this study

Although the predicted trends of this analysis can be helpful for researchers in this field, this study has some limitations. One limitation lies in the restriction to one scientific database (the WoS Core Collection database). Thus, bibliometric studies based on other databases can be carried out and provide more extensive literature exposure in the future. The second limitation of the current bibliometric method is that it mainly relies on computer programs (CiteSpace and VOSviewer). The program calculation may have some biases. The third limitation of bibliometric analysis is that these quantitative indices do not reflect the context and the intention of why researchers refer to other studies.

5. Conclusions

In the current study, according to 1402 papers on DR-related lipid studies acquired from the WOSCC from 1993 to 2023, we performed a bibliometric analysis of the knowledge organization, hotspots, and tendencies in this field. Academic output had an ascending movement. The USA, Singapore, and Australia are leading in the DR-related lipid research field, with many publications, significant scientific influence, and a broad cooperation network about authorship on a national and institutional scale. Wong TY was the paramount scientist in the field with a high scientific impact. Diabetic journals such as *Diabetes Research & Clinical Practice, Diabetes Care, Diabetologia, Diabetic Med, Journal of Diabetes & Its Complications,* and *Diabetes*; and ophthalmic journals such as *IOVS, BJO, Ophthalmology,* and *Archives of Ophthalmology* were considered core journals in the field. All these studies strongly support lipid-lowering drugs (fenofibrate, omega-3 PUFAs, and statins), combined with anti-hyperglycemia and hypertension therapies, to prevent and treat DR. In addition, this study identified the lipid biomarker for DR (lipid aldehydes, ALEs, and cholesterol crystals), the beneficial effects of lipid-reducing medication on DR, the mechanism of lipid-lowering medicines preventing or curing DR, and ocular delivery of lipid-lowering drugs to diabetic patients as the research focus in the future in this field.

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Data availability statement

The original data associated with this study has not been deposited into any publicly available repository, as they are all included in the article. Other Data will be made available on request to the corresponding authors.

CRediT authorship contribution statement

Haishan Tan: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Xiangyu Fu:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Yongjiang Chen:** Writing – review & editing, Writing – original draft, Resources, Formal analysis. **Yujiao Wang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Funding acquisition, Formal analysis. **Danian Chen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Danian Chen reports financial support was provided by National Natural Science Foundation of China. Yujiao Wang reports financial support was provided by National Natural Science Foundation of China.

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