Original Article

Visualized analysis of hotspots and frontiers in diabetes-associated periodontal disease research: a bibliometric study

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Background: Diabetes-associated periodontal disease is caused by diabetes-enhanced host immune-inflammatory responses to bacterial insult. An increasing number of papers related to diabetes-associated periodontal disease have been published. This study analyzed research on diabetes-associated periodontal disease with bibliometrics methods. The objective of this study was to identify hotspots and frontiers in the diabetes-associated periodontal disease research field.

Methods: Publications were extracted from the Web of Science core collection database, and the document types included were limited to articles and reviews. The bibliometric analysis software CiteSpace5 was used to analyze the number of articles, research fields, countries/regions, institutions, authors, keywords, and other information. Outcomes were visualized to analyze the hotspots and research frontiers of diabetes-associated periodontal disease.

Results: A total of 3,572 articles were retrieved. Among the research fields, dentistry, oral surgery, and medicine accounted for the highest proportion of publications, and public, environmental, and occupational health had the highest betweenness centrality. The number of publications from the United States ranked first among all the countries, while Columbia University ranked first among all the institutions. Global cooperation was not frequent. Keyword analysis showed that inflammatory pathways were the hotspots. Burst words analysis indicated that early prevention was a research frontier.

Conclusions: The bibliometric method helped identify research hotspots and frontiers. Inflammatory pathways were hotspots, and early prevention was a frontier in diabetes-associated periodontal disease.

Keywords: Bibliometrics; diabetes mellitus; periodontal disease; Web of Science core collection

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Introduction

Periodontal disease is a chronic infectious disease caused by inflammatory reactions to microorganisms in the dental plaque, which results in periodontal support tissue destruction. Diabetes is a metabolic disease characterized by hyperglycemia. In 1998, Lalla *et al.* (1) raised the concept of diabetes-associated periodontal disease. Diabetes-associated periodontal disease usually refers to diabetes-associated periodontitis (DP), a host immune response caused by interaction between periodontopathic bacteria and the host.

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To some degree, it aggravates diabetic complications and increases the course of periodontitis (2).

Advanced glycation end products (AGEs) are stable covalent compounds formed by the spontaneous reaction of macromolecules, such as proteins, lipids, or nucleic acids, with glucose or other reducing monosaccharides without the participation of enzymes. They participate in the pathogenesis of major complications of diabetes, including vascular diseases and immune dysfunction (3). The receptor for AGEs (RAGE) is a receptor membrane protein, which is closely related to diabetes complications (4). Lalla *et al.* (5) used a diabetic mouse model infected by *Porphyromona gingivalis* to verify the role of RAGE in diabetes-associated periodontal disease. With increased awareness of the disease and continuous improvement of research methods, diabetes-related periodontal disease has gradually become a research hotspot.

Many previous studies have explored the interaction mechanism between diabetes and periodontal disease, but there are no specific conclusions. Bibliometric analysis provides an overview of the current state of research and easily identifies new research trends in a visual way. However, to the best of our knowledge, there is no available bibliometric analysis about diabetes-associated periodontal disease, so it is necessary to explore the characteristics of studies conducted in this field of research.

With the combination of CiteSpace software (5.8.R1) and bibliometric methods, we analyzed the data from the Web of Science core collection (WoSCC) database and performed a co-occurrence visualization analysis of the literature. This study aimed to explore the research hotspots and frontiers and provide a scientific basis for research in this field.

Methods

Data collection and processing

CiteSpace is a bibliometric analysis software based on Java developed by Professor Chaomei Chen, a professor at Drexel University in the United States. The burst detection algorithm designed by Kleinberg is used to identify an emerging research frontier. The betweenness centrality proposed by Freeman is adopted to highlight the key points of connecting other points like a bridge (6). Cluster views greatly simplify the steps of bibliometric analysis and effectively visualize the analysis results (7,8).

In this study, data were obtained from the WoSCC. The query keyword search was as follows: (TS = periodont* AND diabet*). All electronic searches were performed on August 20, 2021. The search period was from January 1, 1929, to January 1, 2021. The types of documents included articles and reviews. Full record and cited references for the record content include information on author, title, source, abstract, and references. Every publication was described with the characteristic information mentioned above. Co-occurrence refers to the phenomenon that the characteristics of articles occur together (9).

Statistical analysis

All data were imported into CiteSpace and Microsoft Excel 2019 (Redmond, WA, USA) for subsequent analysis. All data were downloaded from the public database without medical ethics issues. We took January 1929 to January 2021 as the time range and selected the top 50 most cited publications each year. Other settings were the system's default linear interpolation. When analyzing keywords, we used the minimum spanning tree algorithm. Nodes for which betweenness centrality exceeded 0.1 were called key nodes.

Results

Characteristics of publications

With the search strategy, a total of 3572 papers were retrieved. The distribution of publications is shown in *Figure 1* by year. The original data are available in Table S1. As the years passed, the number of papers and the proportion of reviews increased.

From 1929 to 1989, fewer than 10 related studies were published each year. The first article was "Periodontosis and diabetes," published in 1929 (10). In 1961, it was found that genetic diabetes model mice could be afflicted with severe periodontitis (11), which began research on diabetes-related periodontitis. In 1984, Barnett *et al.* (12) suggested that there may be a connection between diabetes and periodontitis. At this stage, most studies were observational studies regarding diabetes as a risk factor for periodontal disease, and researchers paid more attention to type 1 diabetes than to type 2 (13-15).

From 1990 to 2009, the number of annual publications on diabetes-associated periodontal disease increased. In 1993, Löe (16) described periodontal disease as the sixth complication of diabetes. AGEs were found to play an

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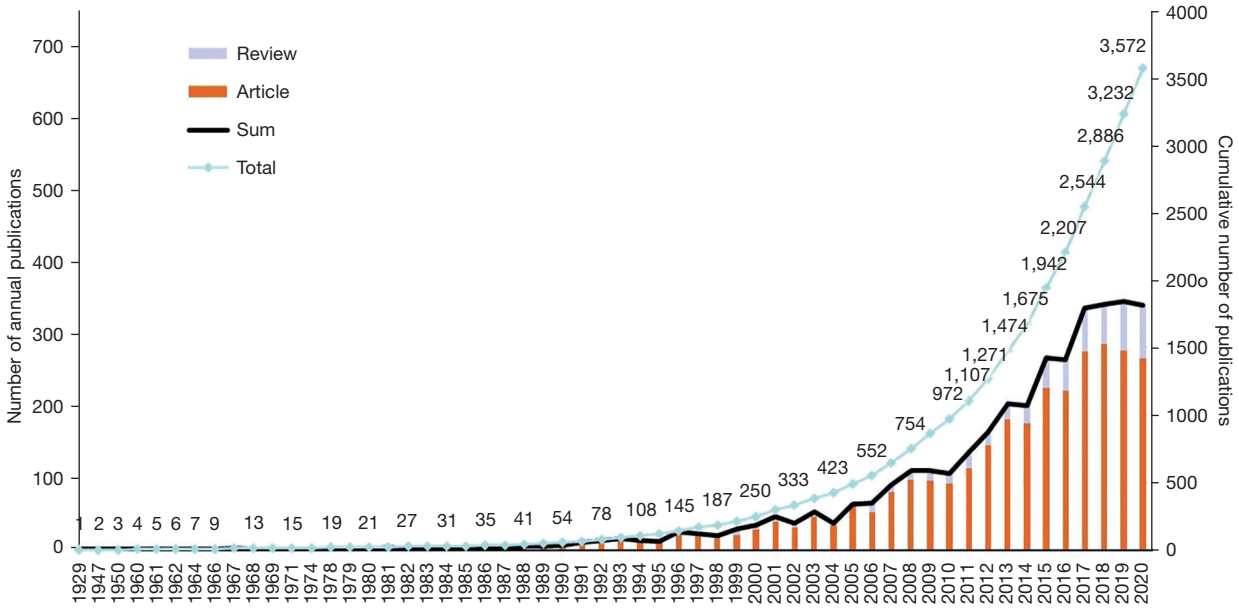

Figure 1 Number of papers published related to diabetes-associated periodontal disease from 1929 to 2020.

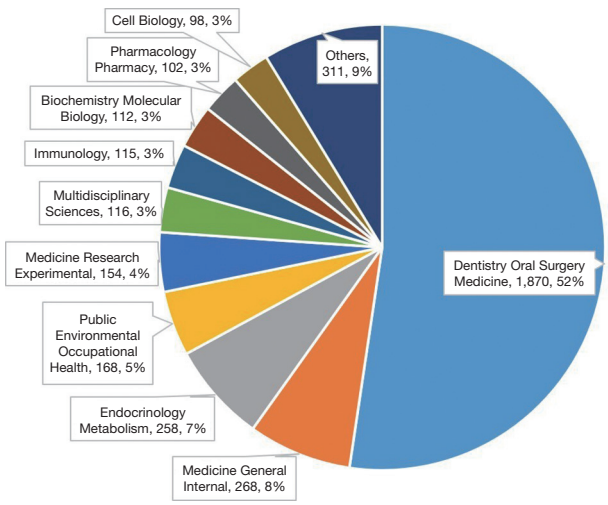

Figure 2 Subject categories of diabetes-associated periodontal disease from 1929 to 2020.

important role in diabetes complications; thus, they were usually involved in diabetes-associated periodontal disease studies (17). With periodontal disease taken as one of the complications of diabetes, there were major studies about the relationship between periodontal disease, diabetes, and other systemic chronic diseases (18-21).

From 2009 to 2020, the number of annual publications exceeded 100. At this stage, high-quality research mostly focused on inflammatory pathways (22-24). Molecular biological techniques were widely used in revealing disease-related pathways and cytokines; however, the specific mechanism was still unknown (25-28). Since 2017, more than 300 papers have been published each year, showing a growing interest in diabetes-associated periodontal disease research.

Subject categories analysis

Based on the field tag from the WoS database, we analyzed the subject categories related to diabetes-associated periodontal disease. *Figure 2* shows the pie chart of all the subject categories, with the top 10 especially labeled. Results showed that "Dentistry, Oral Surgery & Medicine" (n=1,870) was the major research field and had almost 7 times the number of publications as did "General & Internal Medicine" (n=268). The betweenness centrality of "Dentistry, Oral Surgery & Medicine" was 0.29, ranking second. Stomatology was the main focus of the research on diabetes-related periodontal disease. According to data and *Figure 3*, the relationship between different subject categories was complex. "Public, Environmental & Occupational Health" had the highest betweenness centrality, which was 0.44. This suggested that "Public, Environmental & Occupational Health" was the central

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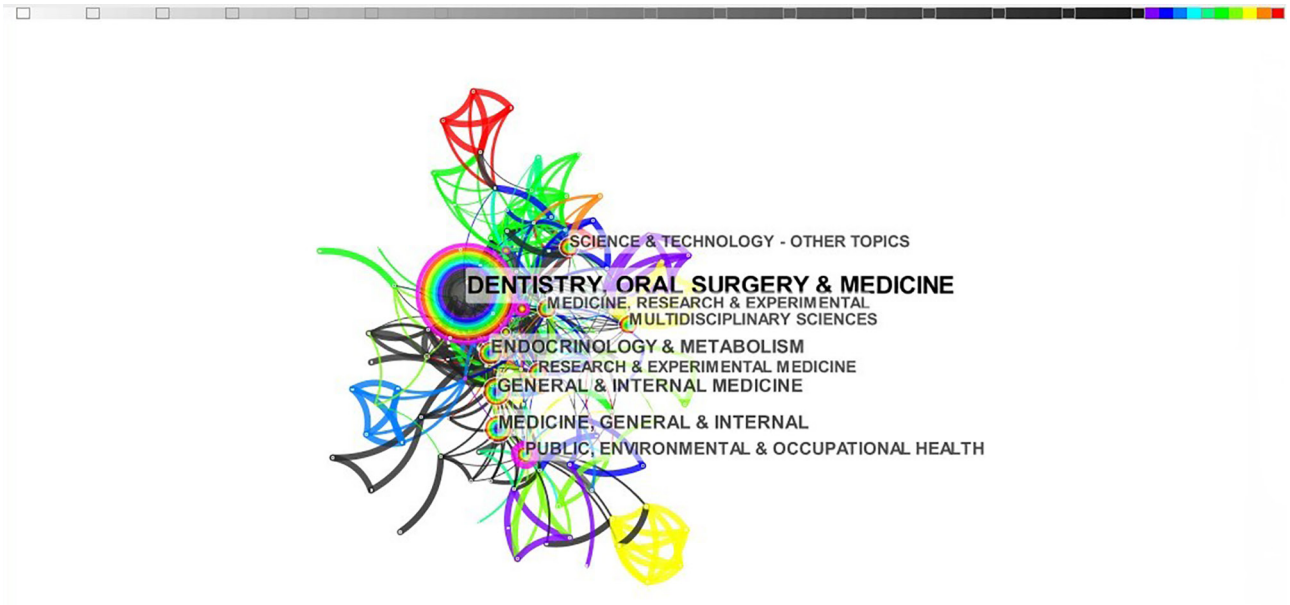

Figure 3 Subject categories in the co-occurrence network of diabetes-associated periodontal disease from 1929 to 2020. The color of the bar, from white to colorful, corresponds with the occurrence frequency. The larger the number of publications includes in the subject category, the warmer the color of the label. A single node represents a subject category. The size of the label and the node represents the number of papers published. The thickness of the purple ring around the node represents the value of betweenness centrality. The line that connects 2 nodes represents the co-occurrence of 2 subject categories.

subject of diabetes-associated periodontal disease research.

Country/region and institution cooperation analysis

In our study, the 50 most commonly reoccurring countries and institutions per year were selected for analysis. The original data are available in Table S2. *Figure 4* shows that the United States ranked first out of the countries that had publications related to diabetes-associated periodontal disease, and the frequency of the United States was more than triple that of China, which ranked second. Apart from the United States, Brazil, and Japan, the betweenness centrality of other countries was below 0.1. The betweenness centrality of the United States was 0.68, and that of Brazil and Japan was 0.12 and 0.10, respectively. Among all the institutions, Columbia University from the United States ranked first, and King Saudi University from Saudi Arabia ranked second (*Figure 5*). The original data are available in Table S3. The institutions from the United States accounted for 60% of the top 20 institutions with relevant research on diabetes-associated periodontal disease. This showed that the United States not only had a large number of studies but also had close cooperation with other countries and regions, which suggested that the United States played an important role in the research field of diabetes-associated periodontal disease.

Author cooperation analysis

A total of 5,672 authors had published papers related to diabetes-associated periodontal disease. The original data about author publications are available in Table S4. Fawad Javed from Rochester University published the largest amount of papers (n=32) as the first author and corresponding author. Among his publications, an article published in *Clinical Oral Implants Research* had the highest number of citations (n=46) and was a clinical trial on the effect of oral hygiene maintenance on hemoglobin A1c levels and peri-implant parameters in patients with type 2 diabetes (29). The publication volume of Fahim Vohra from King Saud University ranked third (n=18), and he had tight cooperation with Fawad Javed. They published 8 articles together, accounting for 44.4% of the papers published by Fahim Vohra.

However, the cooperation between authors was not frequent. As observed in *Figure 6*, an author's cooperative

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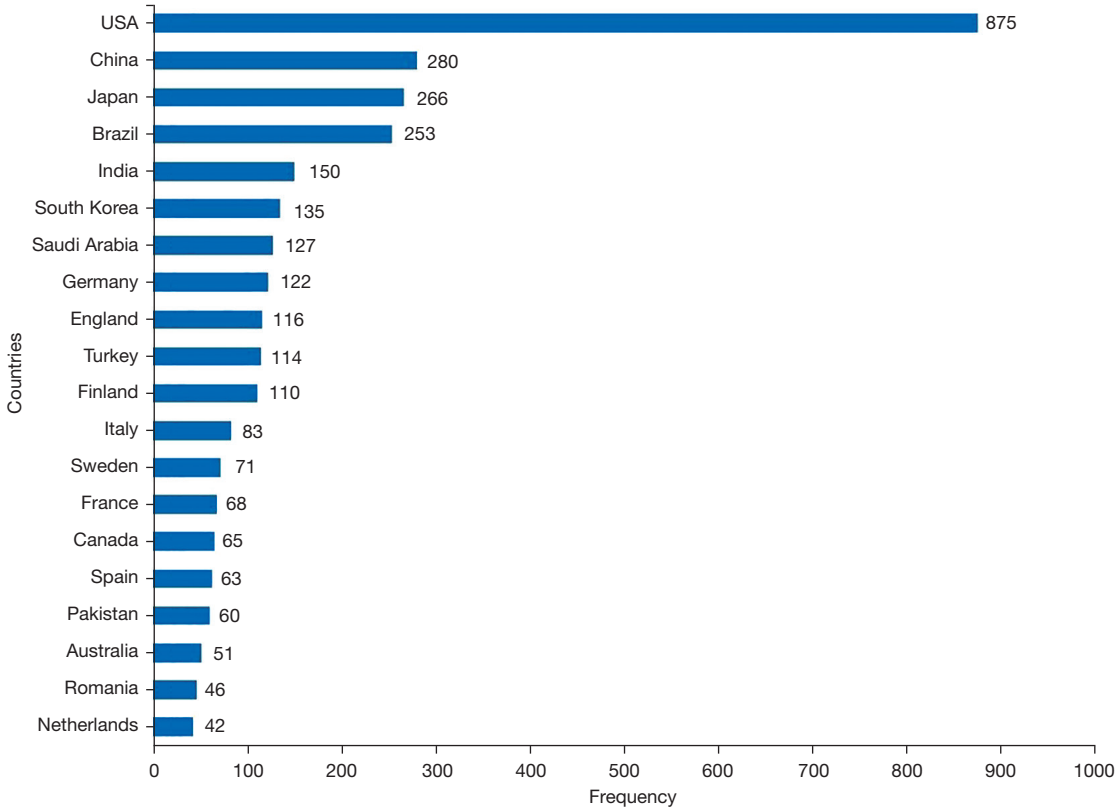

Figure 4 Top 20 countries with relevant research on diabetes-associated periodontal disease from 1929 to 2020.

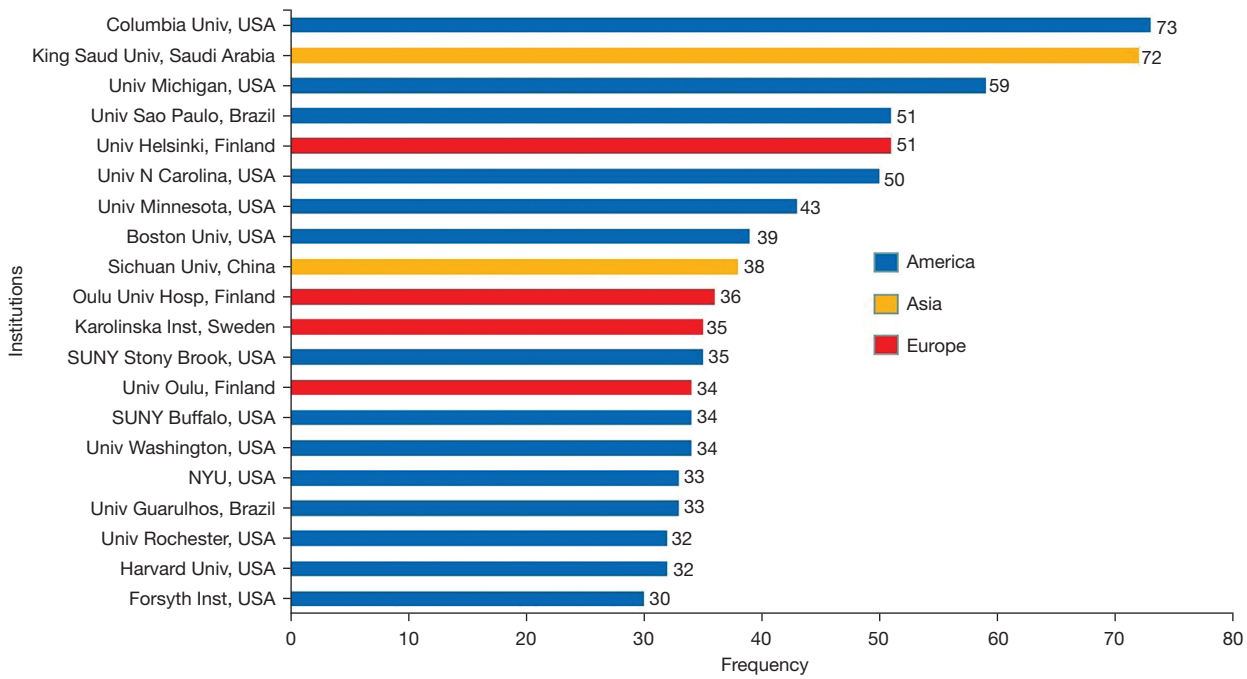

Figure 5 Top 20 institutions with relevant research on diabetes-associated periodontal disease from 1929 to 2020.

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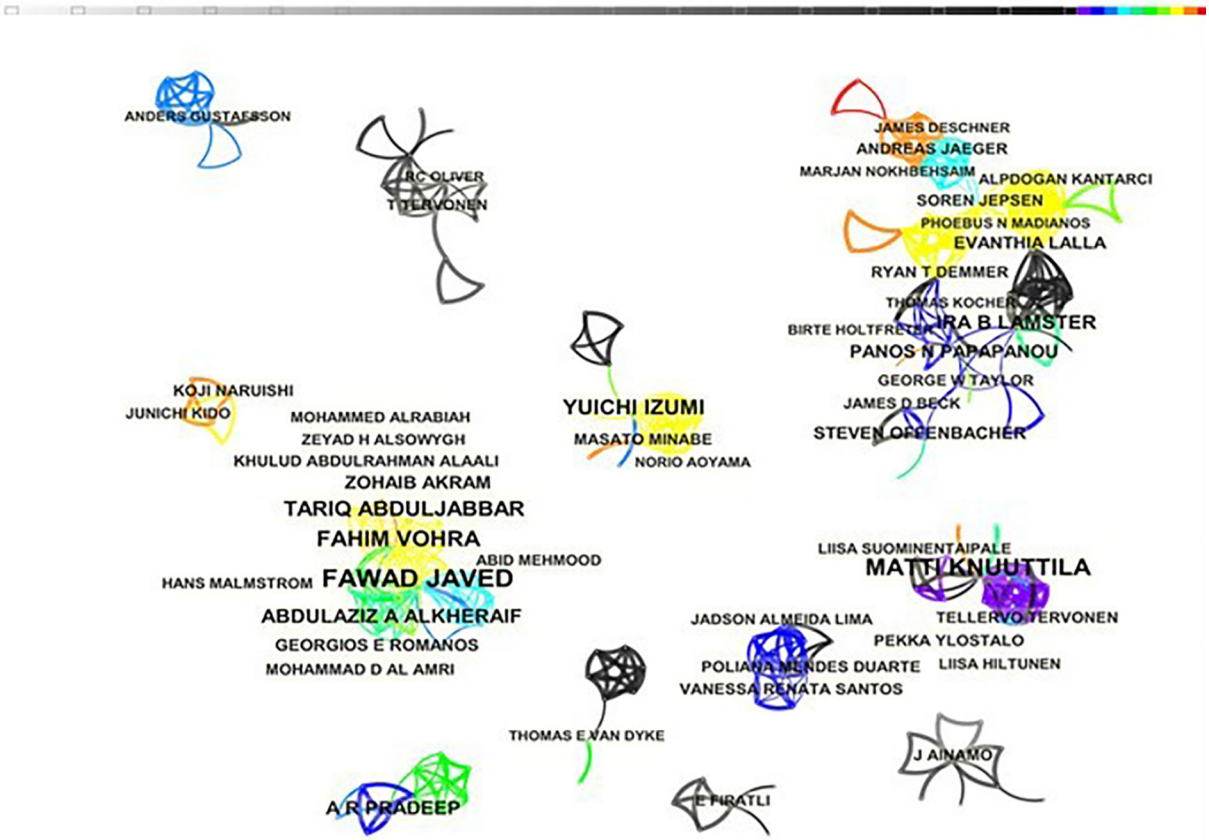

Figure 6 Collaborative network of major authors with relevant research on diabetes-associated periodontal disease from 1929 to 2020. This figure shows the cooperation network of authors who have published more than 8 papers. A single node represents 1 author, and the size of the label represents the number of papers published by the author. The line that connects 2 nodes represents the co-occurrence of the 2 authors. The color of the line represents the year of the authors' cooperation, and the thickness represents the strength of the connection. The later the authors cooperate, the warmer the color of the line.

network was usually small in scale, and there was no direct connection between other small cooperative networks. The authors in the center of cooperative networks preferred to interact with authors in the same institution.

Research hotspots

Excluding the search keywords, *Figure* 7 shows the keywords whose occurrence frequency ranked in the top 20. The original data are available in Table S5. "Inflammation" was the most popular keyword with a frequency of 476. According to the cluster analysis of keywords, 12 clusters were formed. The largest cluster, number zero (*Figure 8*), was labeled as gene expression, containing 145 keywords. The original data are available in Table S6. The term "gene expression" meant the generation of a functional gene product from the information encoded by a gene through the processes of transcription and translation. The top 3 keywords in the largest cluster were "expression", "gingival crevicular fluid", and "cytokine". After organizing papers with these keywords, we found 6 articles in which the top 3 keywords co-occurred (30-35). The main content of these articles was bone resorption–related cytokines and protein expression in serum, saliva, and gingival crevicular fluid of patients with type 2 diabetes mellitus and chronic periodontitis. The involved markers were lymphokines (interleukin-1, interleukin-4, interleukin-6, tumor necrosis factor-α, interferon-γ), chemokines (recombinant regulated on activation in normal T-cell expressed and secreted, macrophage inflammatory protein-1α, granulocyte colony stimulating factor, vascular endothelial growth factor, fibroblast growth factor), the matrix metalloproteinase

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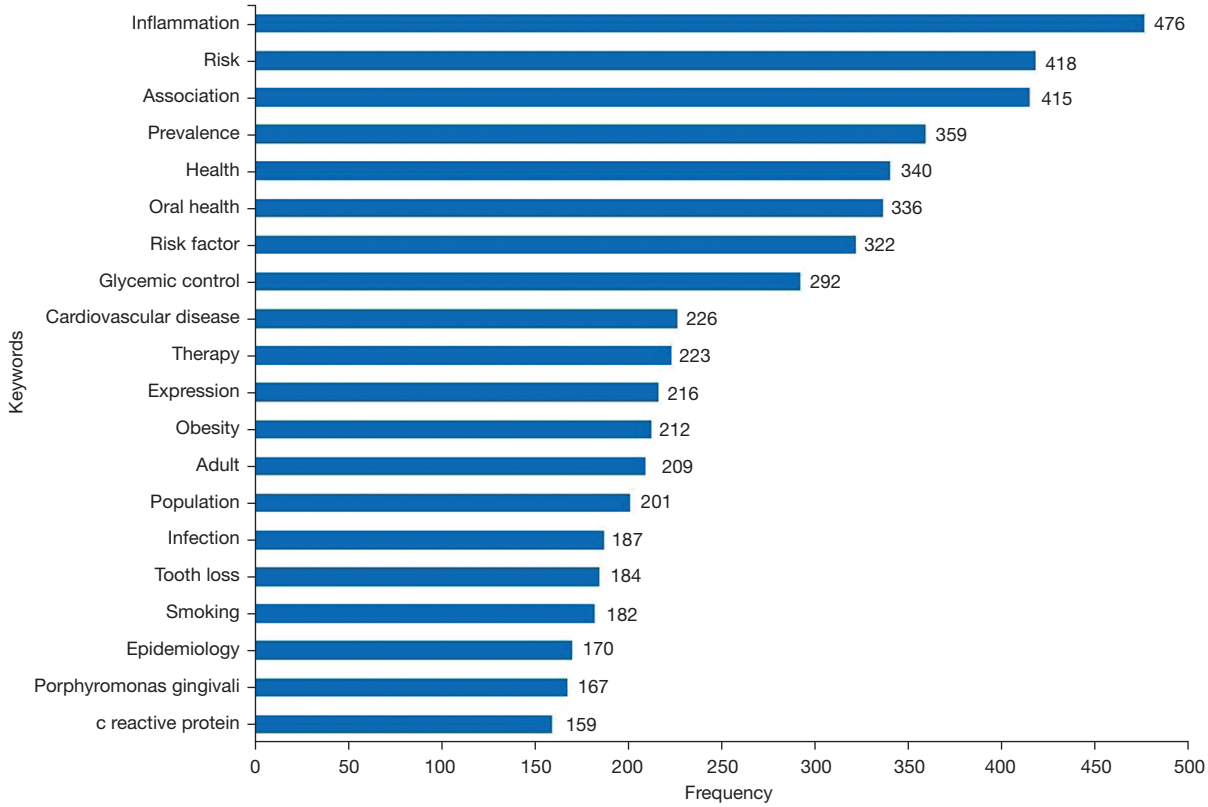

Figure 7 Top 20 keywords of diabetes-associated periodontal disease from 1929 to 2020.

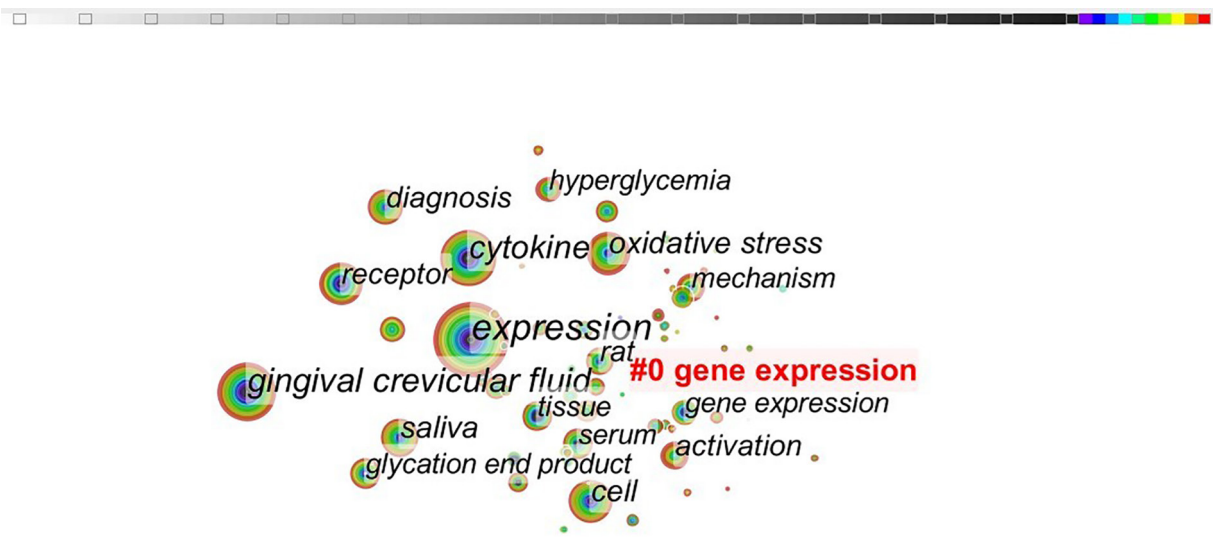

Figure 8 Keyword co-occurrence map of the largest cluster showing the keywords whose frequency was more than 50 in the largest cluster. The size of the node represents the number of publications, and the color of the node represents the publication year. The later the latest publication year of the keyword-related articles is, the more the outermost circle color becomes warm. The red text is the cluster label, and the black text is the keyword.

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(MMP) family (MMP- 2. MMP-8, MMP-9), and C-reactive protein (a protein present in blood serum in various abnormal states, such as inflammation or neoplasia). After combining the information on the clusters and inflammation, we concluded that inflammatory pathway research was a research hotspot in diabetes-associated periodontal disease research.

"Risk" ranked second by frequency. After reviewing articles with this keyword, we concluded that "risk" had 2 meanings. On the one hand, chronic diseases of older adults, such as cardiovascular disease, rheumatoid disease, and hyperlipidemia, increase the risk of diabetes and periodontitis. On the other hand, diabetes-associated periodontal disease also had an impact on other chronic diseases of older adults (36).

There was an association between diabetes and periodontal disease. Articles related to the keyword "association" included several consensus reports. The most commonly cited article in this cluster was a review published in 1996, which suggested that smoking and diabetes were the 2 main risk factors of periodontitis (37). The consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions concluded that diabetes-associated periodontal disease should not be considered a definitive diagnosis. It suggested that diabetes should be considered an important risk factor and a descriptor term for periodontitis in clinical diagnosis (38). The 2018 Consensus Report and Guidelines of the Joint Workshop on Periodontal Diseases and Diabetes by the International Diabetes Federation and the European Federation of Periodontology suggested that patients with periodontitis had a higher risk of dysglycemia and insulin resistance (39).

Research frontiers

Burst words are keywords emerging suddenly or at a more-than-normal rate in a given period. They can represent a research frontier, while the burst value represents the strength of the trend. There were 53 burst words with the strongest citation burst value from 1929 to 2020 (*Figure 9*). Among the burst words, "peri-implantitis," "global burden," "susceptibility," and "impact" were the most current burst words. These keywords are likely to become new hotspots in the next period.

"Peri-implantitis" refers to inflammation of the soft and hard tissues around implants. With the development of implant technology, scholars began to pay attention to the impact of diabetes on both the soft and hard tissue around implants. There was strong evidence that patients with a history of chronic periodontitis and poor oral hygiene without regular implant maintenance are at a high risk of peri-implantitis. Research showed that hyperglycemia could accelerate the progress of peri-implant inflammation, similar to periodontitis. However, there was no consensus to identify diabetes as a risk factor for peri-implantitis (40).

"Global burden" relates to the global burden of disease, refers to the loss of health due to all causes of disease and death in the world, and can also describe the global health situation. The Global Burden of Disease Study of 2019, published by *The Lancet* in 2020, showed that diabetes was one of the key diseases affecting global disability adjusted life years and that periodontitis was an important nonfatal disease (41). There was a potential link between periodontal disease and other chronic diseases, so preventing and treating periodontal disease could help reduce the risk of adverse events such as death (42,43). Therefore, promoting public oral health programs will help reduce the global disease burden.

"Susceptibility" refers to the risk of humans acquiring diabetes-related periodontal disease, essentially due to genetic factors. The major content of the keyword-related articles related mainly to the effect of gene polymorphisms on diabetes-associated periodontal disease, and the research was evaluated through biochemical studies of human blood or gingival crevicular fluid (25,44).

Articles related to the keyword "impact" illustrated the influence between glycemic control and oral hygiene maintenance. The literature outlines how, first, the level of blood glucose affects the inflammation in the periodontal tissue. Thus, patients with poor glycemic control have more severe periodontitis. Therefore, periodontal status could be one of the items of the diabetes screening chart to identify people who are at high risk of diabetes (45,46). Second, oral hygiene maintenance can help with glycemic control. It was reported that periodontal disease can cause insulin resistance but oral hygiene maintenance can relieve it in patients with type 2 diabetes (39). Therefore, periodontal treatment was expected to become one of the measures of glycemic control (47).

Discussion

The study represents the first visualized analysis on diabetes-associated periodontal disease and has identified several characteristic qualities of this research field. We

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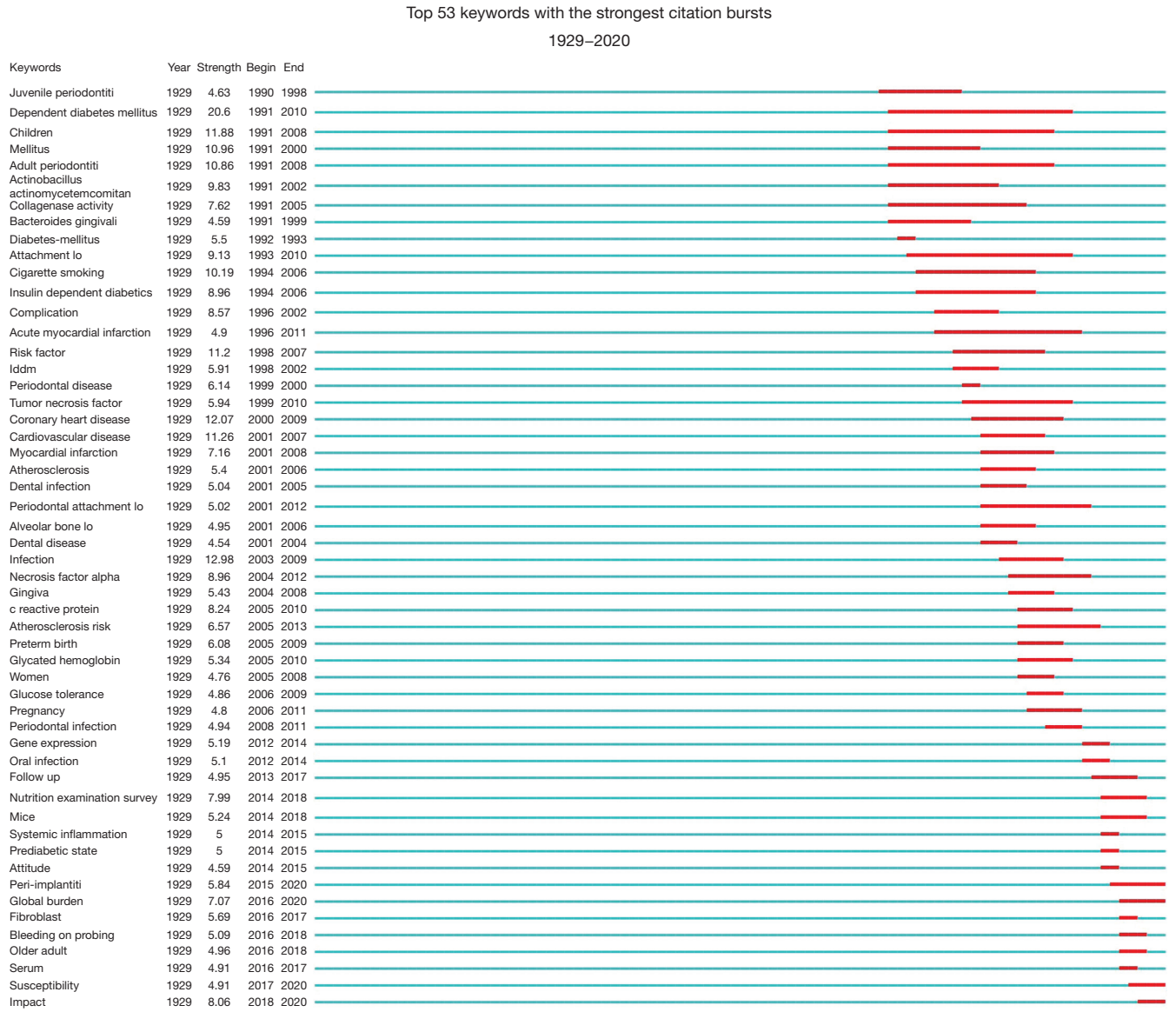

Figure 9 Top 53 keyword burst of relevant research on diabetes-associated periodontal disease. The full length of the blue bars represents the period from 1929 to 2020, and the red bars within it represent the period of each burst.

investigated all research on diabetes-associated periodontal disease published until December 31, 2020. We obtained data from the WoSCC and used CiteSpace to analyze the current research situation and developing trends. The publication results showed that diabetes-associated periodontal disease was receiving increased attention and that dentistry was the main research field. According to the analysis of countries, institutions, and authors, global cooperation was not frequent, and scholars from the United States had published more research than had those in other countries. Inflammatory pathways was a research hotspot, and early prevention was at the frontier of research on diabetes-associated periodontal disease.

Inflammatory pathways was the research hotspots of diabetes-associated periodontal disease. We discovered that the total number of relevant research on diabetes-associated periodontal disease has been increasing, but the annual research quantity of the past 3 years did not seem to rise. This might be because there have not been any groundbreaking discoveries in pathogenesis in

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recent years. Particularly, the mechanism of the AGE-RAGE axis influencing inflammatory response remains unclear (48,49). The results showed that inflammation is the key connection between periodontitis and diabetes. The inflammatory products of periodontitis may induce insulin resistance and then affect the metabolic process of diabetes. The dysfunction of immune cells in diabetes also aggravates periodontal tissue inflammation (50). Oxidative stress, inflammation-related receptors activation, and mitochondria-dependent apoptosis are possible mechanisms (9,51-53). Considering the possible effect of AGEs, some research hypothesizes that the combination of AGEs and RAGE activates protein kinase C (PKC) and influences the p38/MAPK signaling pathway or the NF-κB pathway (54,55). The products involve C-reactive protein (CRP), chemokines, lymphokines, MMPs, and growth factors related to angiogenesis (56). All in all, molecular markers and inflammatory pathways are primary topics of this research field.

What can we learn from the inflammatory mechanism? With the in-depth study of the interaction mechanism between periodontitis and diabetes, some scholars have tried to investigate the association between periodontitis and other systemic diseases, such as cardiovascular disease and obesity, through the host inflammatory response mechanism (57,58). These studies remind us of the possibility of using periodontitis as a clue to the occurrence of other chronic diseases related to immune disorders.

From the burst words analysis, we concluded that early prevention of diabetes-associated periodontal disease was a research frontier. The burst words and their related articles were centered around investigations on the early stage of diabetes using testing biomarkers for periodontal inflammation from gingival crevicular fluid and serum (59). The most cited article of the author with the most publications discussed the relationship between the prediabetic state and periodontal disease and the importance of oral hygiene maintenance (29). Other experts also highlighted the importance of oral management in patients with diabetes-associated periodontal disease (60,61). Preventive and noninvasive treatment, supportive periodontal therapy, and patient - specific maintenance plans are critical to maintaining oral health and helping with general condition maintenance in the older population (62).

The literature also described new techniques used to further study gene–environment interaction, which can help predict individual morbidity of periodontitis and diabetes. There were some interesting findings of single-nucleotide polymorphisms (SNPs) demonstrating that polymorphisms in lipid metabolism genes may be associated with susceptibility to diabetes-associated periodontitis (63). The TNF-α rs1800629 polymorphism might affect the risk of diabetes-associated periodontitis, particularly in individuals of Asian descent (28). Research on different functions of SNPs showed that oral health may have an inextricable connection to systemic health, such as with obesity and rheumatoid arthritis (64). The SNPs studies indicate that early prevention, especially individual prevention, is at the frontier of research in this field.

There were some limitations in our study. First, the results of our study were only based on WoSCC. Publications not indexed in WoSCC were neglected, and publications in languages other than English were excluded. Second, the results provided by CiteSpace were calculated with built-in functions, so the analysis might not have identified all meaningful connections. There might have been a subjective selection in the process of sorting.

In conclusion, using bibliometric analysis, we discovered that inflammatory pathways were the hotspots and early prevention was the frontier of the research on diabetes-associated periodontal disease. Although our cluster approach did not allow for a truly comprehensive analysis, it enabled us to discern the most important knowledge from a massive set of data. Our study may help scholars in adjusting their research direction and may ultimately benefit those patients with diabetes-associated periodontal disease through improved disease prevention and treatment.

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Footnote

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2021PY007). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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