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

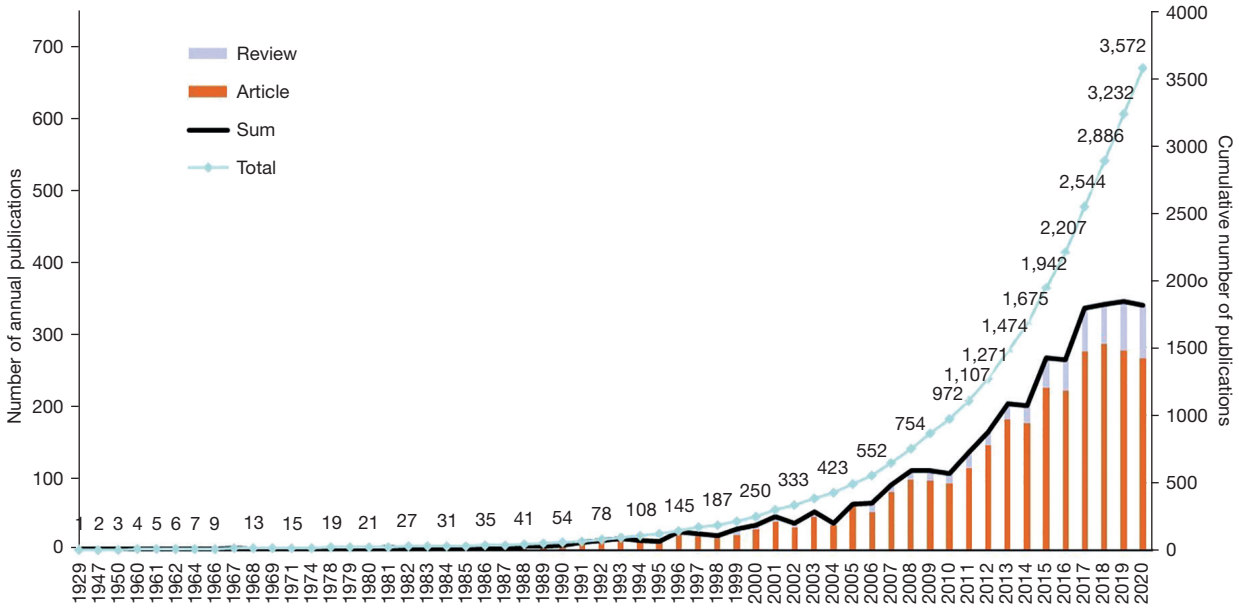

Figure 1 Number of papers published related to diabetes-associated periodontal disease from 1929 to 2020.

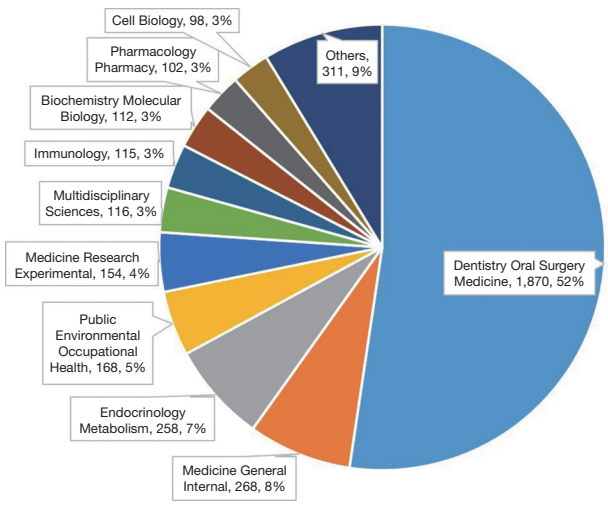

Figure 2 Subject categories of diabetes-associated periodontal disease from 1929 to 2020.

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

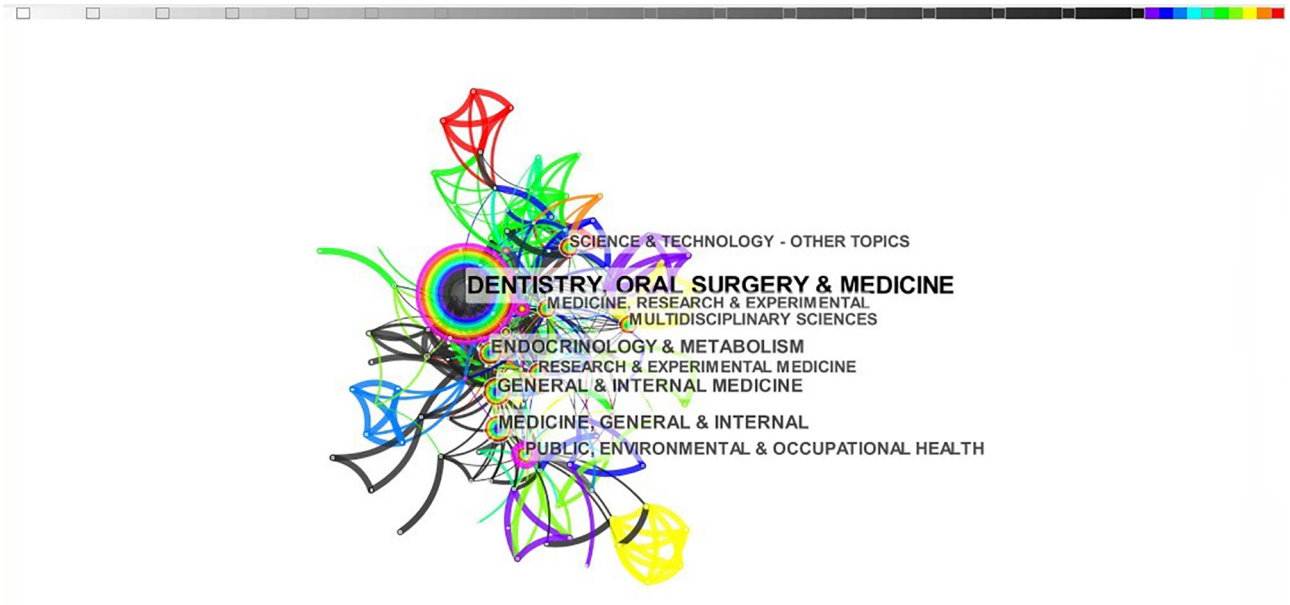

Figure 3 Subject categories in the co-occurrence network of diabetes-associated periodontal disease from 1929 to 2020. The color of the bar, from white to colorful, corresponds with the occurrence frequency. The larger the number of publications includes in the subject category, the warmer the color 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

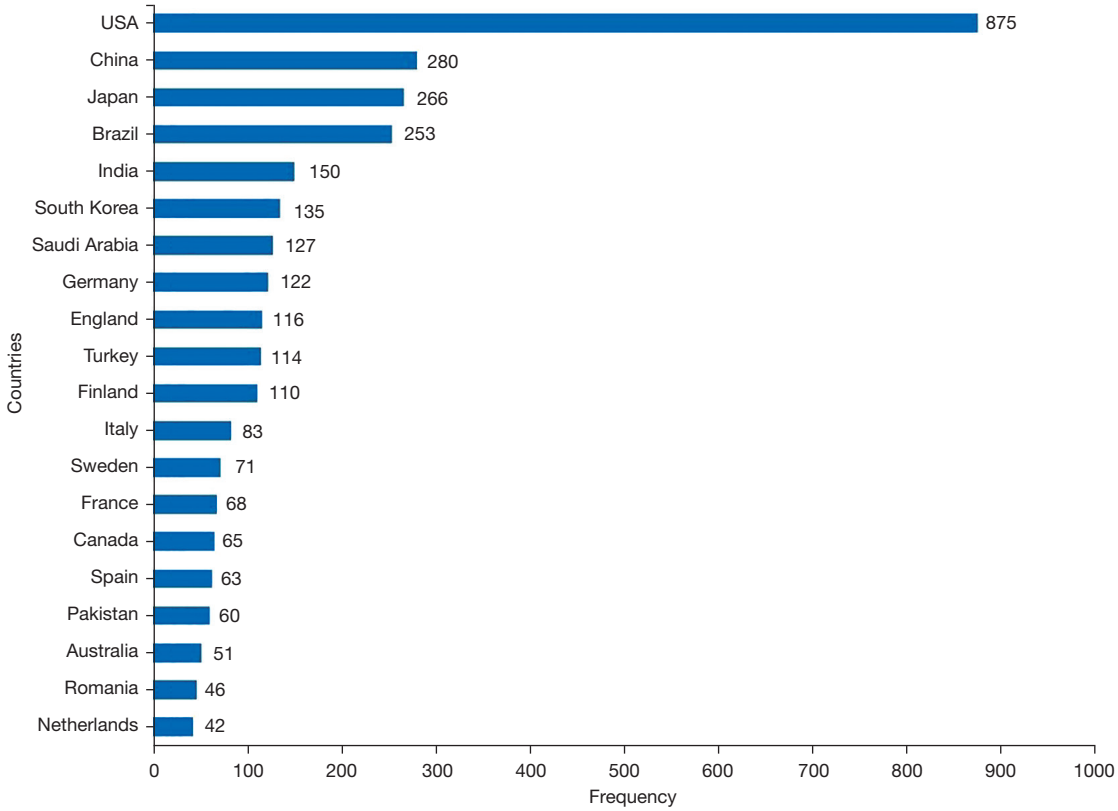

Figure 4 Top 20 countries with relevant research on diabetes-associated periodontal disease from 1929 to 2020.

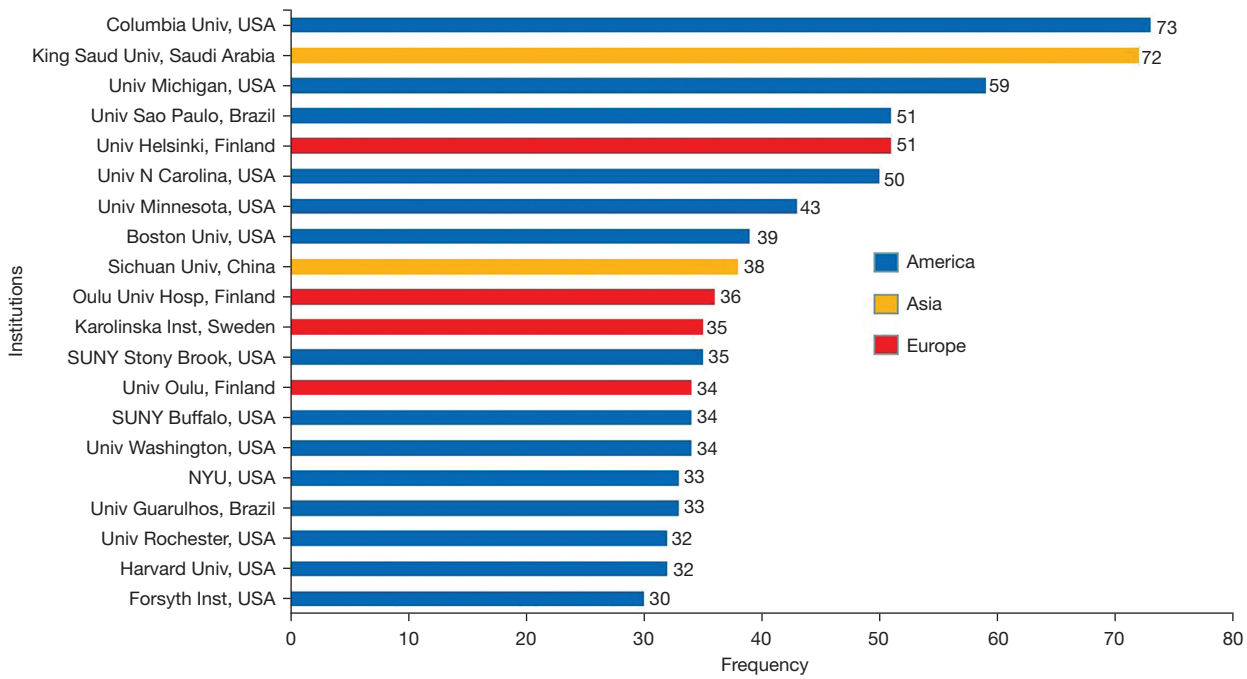

Figure 5 Top 20 institutions with relevant research on diabetes-associated periodontal disease from 1929 to 2020.

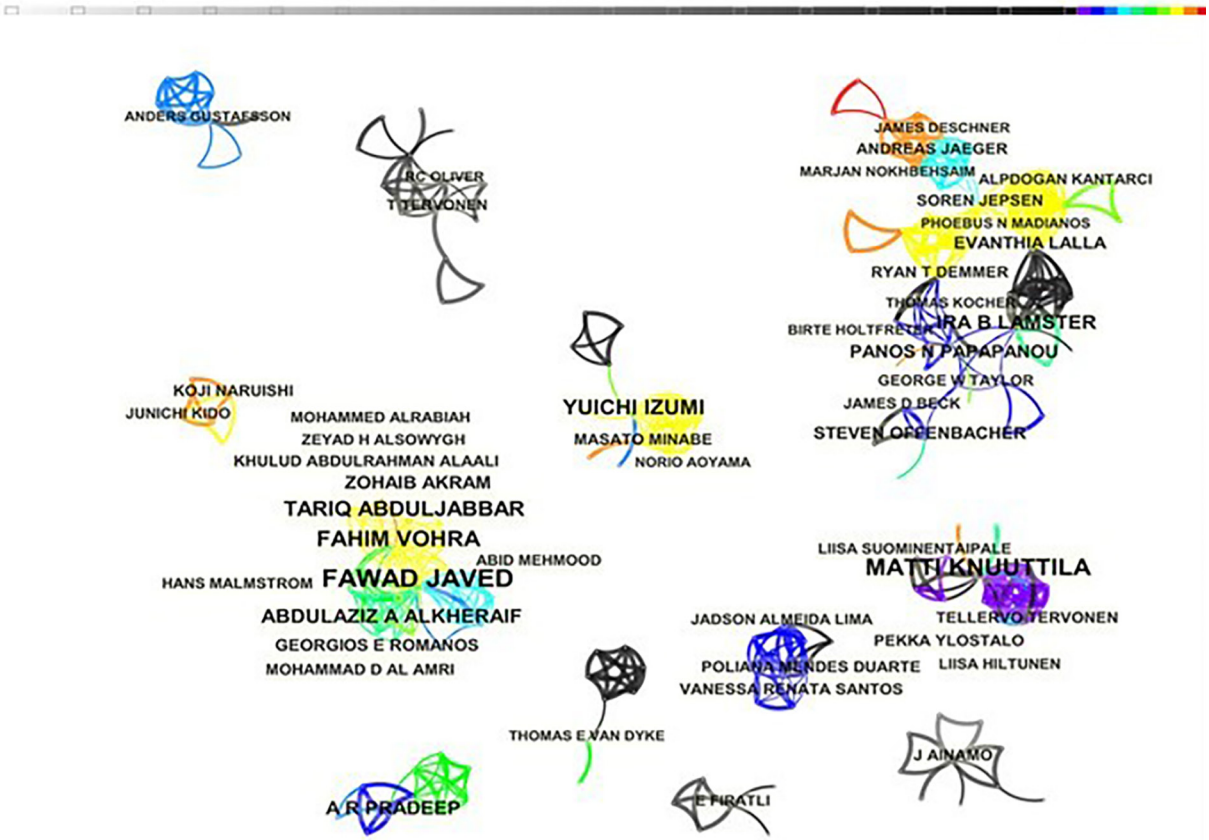

Figure 6 Collaborative network of major authors with relevant research on diabetes-associated periodontal disease from 1929 to 2020. This figure shows the cooperation network of authors who have published more than 8 papers. A single node represents 1 author, and the size of the label represents the 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

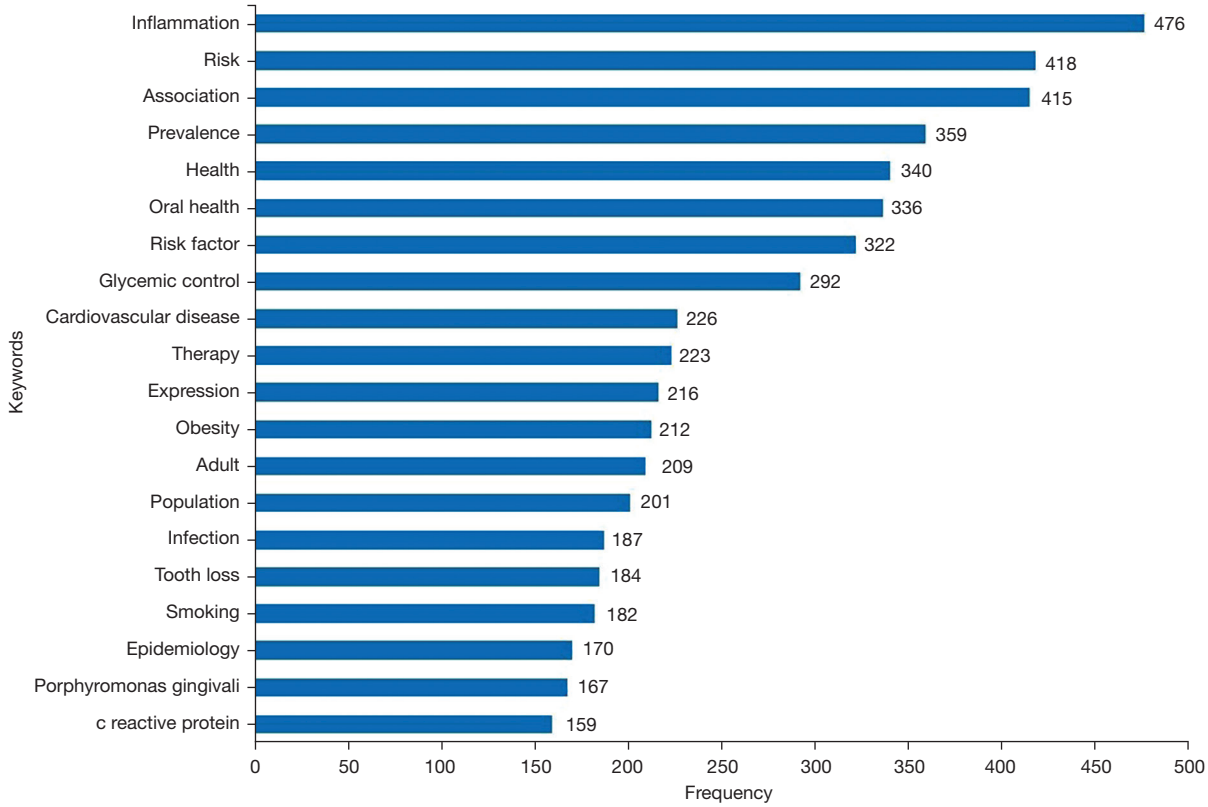

Figure 7 Top 20 keywords of diabetes-associated periodontal disease from 1929 to 2020.

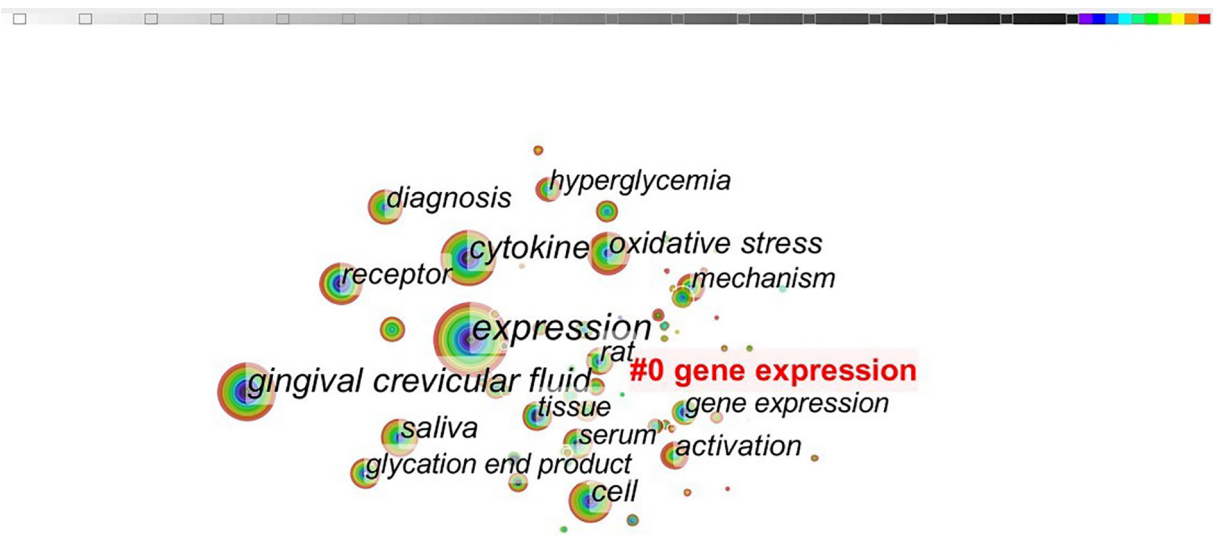

Figure 8 Keyword co-occurrence map of the largest cluster showing the keywords whose frequency was more than 50 in the largest cluster. The size of the node represents the number of publications, and the color of the node represents the publication year. The later the latest publication year of the keyword-related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

(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

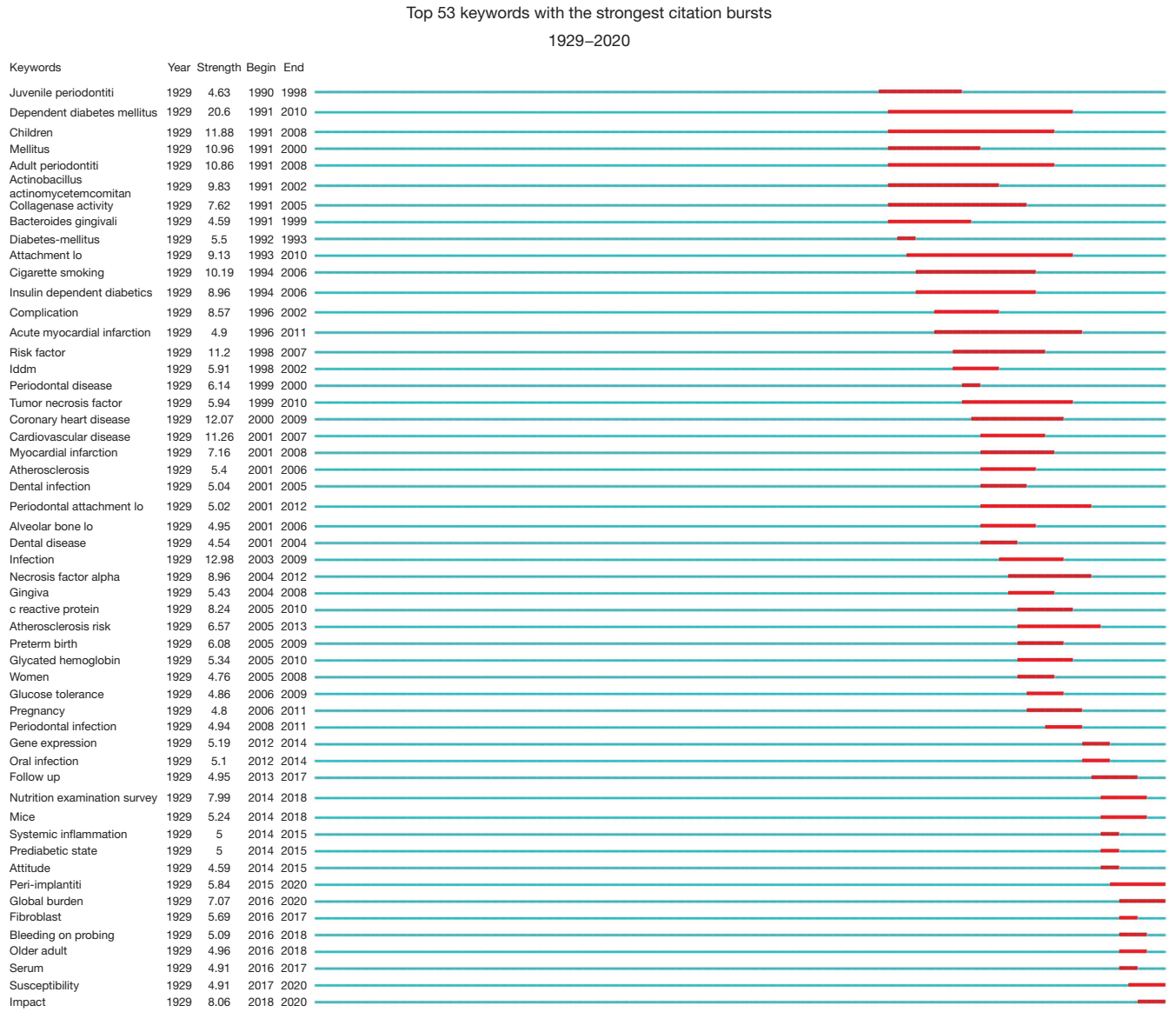

Figure 9 Top 53 keyword burst of relevant research on diabetes-associated periodontal disease. The full length of the blue bars represents the period from 1929 to 2020, and the red bars within it represent the period of each burst.

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

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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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2443/coif). HY reports funding received from the Medical and Health Science and Technology Program of Zhejiang Province (No.

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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Table S1 Number of papers published related to diabetes-associated periodontal disease from 1929 to 2020

Publication years	Record count	% of 3,572
2019	346	9.686
2018	342	9.574
2020	340	9.518
2017	337	9.434
2015	267	7.475
2016	265	7.419
2013	203	5.683
2014	201	5.627
2012	164	4.591
2011	135	3.779
2008	111	3.108
2009	111	3.108
2010	107	2.996
2007	91	2.548
2006	65	1.82
2005	64	1.792
2003	53	1.484
2001	46	1.288
2002	37	1.036
2004	37	1.036
2000	34	0.952
1999	29	0.812
1996	25	0.7
1997	22	0.616
1998	20	0.56
1993	16	0.448
1994	14	0.392
1992	13	0.364
1995	12	0.336
1991	11	0.308
1990	7	0.196
1989	6	0.168
1988	5	0.14
1981	4	0.112
1967	3	0.084
1986	3	0.084
1966	2	0.056
1974	2	0.056
1978	2	0.056
1982	2	0.056
1983	2	0.056
1984	2	0.056
1929	1	0.028
1947	1	0.028
1950	1	0.028
1960	1	0.028
1961	1	0.028
1962	1	0.028
1964	1	0.028
1968	1	0.028
1969	1	0.028
1971	1	0.028
1979	1	0.028
1980	1	0.028
1985	1	0.028
1987	1	0.028

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Table S2 Countries' publication information

Frequency	Centrality	Year of first publication	Country/region
875	0.68	1974	USA
266	0.1	1996	Japan
253	0.12	1991	Brazil
280	0.05	1999	China
150	0.05	1990	India
135	0	1999	South Korea
127	0.06	2002	Saudi Arabia
122	0.08	1991	Germany
116	0.07	1995	England
114	0.07	1993	Turkey
110	0.01	1974	Finland
83	0.09	1995	Italy
71	0.01	1986	Sweden
68	0.08	1992	France
65	0.05	1992	Canada
63	0.05	2003	Spain
60	0	2002	Pakistan
51	0.04	1997	Australia
46	0.04	2008	Romania
42	0.07	1989	Netherlands
37	0.01	1997	Switzerland
36	0.01	2010	Poland
35	0.07	1994	Mexico
32	0	2000	Thailand
30	0.02	2004	Greece
30	0.01	1974	Denmark
30	0	2006	Iran
27	0.03	2000	Norway
27	0	2000	Israel
24	0.01	2001	Chile
21	0.07	1988	Serbia
21	0	1996	Portugal
18	0	2010	Malaysia
16	0.04	2002	Belgium
16	0.01	2002	Egypt

Table S2 (*continued*)

Table S2 (*continued*)

Frequency	Centrality	Year of first publication	Country/region
16	0.01	2008	U Arab Emirates
16	0	1999	Scotland
15	0.01	1999	Austria
15	0	2003	Jordan
15	0	2002	Singapore
13	0	1989	Ireland
11	0	2004	Kuwait
10	0	1998	Colombia
10	0	2004	Hungary
10	0	2011	Indonesia
10	0	2004	New Zealand
10	0	2005	Russia
9	0	1984	Nigeria
8	0.01	2006	North Ireland
8	0	1978	Argentina
7	0.01	2013	Qatar
7	0	1998	Croatia
6	0	2011	Lithuania
6	0	2001	South Africa
5	0	2001	Czech Republic
5	0	2005	Sri Lanka
4	0	2009	Bulgaria
4	0	2017	Iraq
4	0	2008	Lebanon
4	0	2013	Sudan
3	0.01	2006	Slovenia
3	0	2018	Cameroon
3	0	2014	Libya
3	0	2011	Trinidad Tobago
3	0	2014	Tunisia
3	0	2017	Ukraine
3	0	2005	Venezuela
2	0	2020	Albania
2	0	2015	Bangladesh

Table S2 (*continued*)

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Table S2 (*continued*)

Frequency	Centrality	Year of first publication	Country/region
2	0	2010	Herzeg-Bosnia
2	0	2016	Ethiopia
2	0	2014	Ghana
2	0	2017	Nepal
2	0	2013	Peru
2	0	2011	Senegal
2	0	2005	Slovakia
2	0	2018	Vietnam
2	0	2006	Wales
1	0	2019	Bahrain
1	0	2017	Cote Ivoire
1	0	2018	Dominican Rep

Table S3 Institutions' publication information (Frequency >10)

Frequency	Centrality	Year of first publication	Institution
73	0.12	1998	Columbia Univ
72	0.02	2003	King Saud Univ
59	0.13	1998	Univ Michigan
51	0.06	1997	Univ Helsinki
51	0.04	2002	Univ Sao Paulo
50	0.06	1998	Univ N Carolina
43	0.04	1998	Univ Minnesota
39	0.08	2003	Boston Univ
38	0.03	2009	Sichuan Univ
36	0.02	1999	Oulu Univ Hosp
35	0.03	1998	SUNY Stony Brook
35	0.03	2003	Karolinska Inst
34	0.07	2001	Univ Washington
34	0.04	1998	SUNY Buffalo
34	0.01	1999	Univ Oulu
33	0.01	2007	Univ Guarulhos
33	0.01	1979	NYU
32	0.03	1999	Harvard Univ
32	0.01	2005	Univ Rochester
30	0.11	2008	Forsyth Inst
28	0.05	1998	Tokyo Med & Dent Univ
26	0.08	2002	UCL
26	0.04	2004	Niigata Univ
26	0.01	2003	Univ Estadual Campinas
25	0.03	2008	Univ Hong Kong
23	0.03	2000	Okayama Univ
23	0.01	2004	Univ Puerto Rico
22	0.01	2001	Kyushu Univ
21	0.02	2014	Catholic Univ Korea
21	0.01	2006	Univ Fed Minas Gerais

Table S3 (*continued*)

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Table S3 (*continued*)

Frequency	Centrality	Year of first publication	Institution
20	0.03	2003	Aichi Gakuin Univ
20	0.01	2004	Med Univ S Carolina
20	0	2005	King Abdulaziz Univ
19	0.04	2009	Seoul Natl Univ
19	0.02	2001	Univ Bern
18	0.01	2009	Vrije Univ Amsterdam
18	0	2009	Yonsei Univ
17	0.03	2004	Newcastle Univ
17	0.02	1999	Univ Calif San Francisco
17	0.01	2010	Univ Amsterdam
17	0.01	2000	Kuopio Univ Hosp
16	0.05	2004	Univ Bonn
15	0.02	2001	Ege Univ
15	0	2006	Kyungpook Natl Univ
14	0.02	2011	Kings Coll London
14	0.02	2000	Ernst Moritz Arndt Univ Greifswald
14	0.01	2003	Univ Maryland
14	0.01	2000	Univ Florida
14	0	2011	Univ Med & Pharm Craiova
14	0	2013	Univ Eastern Finland
14	0	2017	Princess Nourah Bint Abdulrahman Univ
14	0	2012	Govt Dent Coll & Res Inst

Table S3 (*continued*)

Table S3 (*continued*)

Frequency	Centrality	Year of first publication	Institution
13	0.03	2002	Natl Univ Singapore
13	0.02	1998	Univ Calif Los Angeles
13	0.02	2011	Shandong Univ
13	0.01	2011	Univ Estadual Paulista
13	0.01	2003	Tulane Univ
13	0.01	2007	Natl Yang Ming Univ
13	0.01	2008	INSERM
13	0	2017	Ziauddin Univ
12	0.02	2006	Univ Illinois
12	0.01	2004	Univ Oslo
12	0	2004	Univ Athens
12	0	2018	Tokushima Univ
12	0	2016	Kanagawa Dent Univ
12	0	2003	Brigham & Womens Hosp
11	0.03	2007	Univ Birmingham
11	0.02	2006	Natl Taiwan Univ
11	0.01	2005	Univ Toronto
11	0.01	2006	Univ Copenhagen
11	0.01	2002	Univ Chile
11	0.01	2005	Osaka Univ
11	0.01	1998	Hiroshima Univ
11	0	2013	Wuhan Univ
11	0	2001	Univ Adelaide
11	0	2002	Case Western Reserve Univ

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Table S4 Authors' publication information (Frequency >5)

Frequency	Centrality	Year of first publication	Author
32	0	2013	Fawad Javed
25	0	2008	Matti Knuuttila
18	0	2016	Fahim Vohra
17	0	2012	Yuichi Izumi
17	0	2017	Tariq Abduljabbar
16	0	2014	Kyungdo Han
14	0	2016	Junbeom Park
13	0	2007	Ira B Lamster
13	0	2012	Bruno G Loos
13	0	2015	Abdulaziz A Alkheraif
11	0	1996	F Nishimura
11	0	2007	A R Pradeep
10	0	2018	Zohaib Akram
10	0	2006	Kaumudi J Joshipura
10	0	2012	Panos N Papapanou
9	0	2007	Steven Offenbacher
9	0	2006	Evanthia Lalla
9	0	2007	Robert J Genco
8	0	1981	Rj Genco
8	0	1999	Amh Syrjala
8	0	2013	Qi Wang
8	0	2015	Georgios E Romanos
7	0	2018	Khulud Abdulrahman Alaali
7	0	2010	Vanessa Renata Santos
7	0	2009	Andreas Jaeger
7	0	2014	Soren Jepsen
7	0	2009	Pekka Ylostalo
7	0	1974	J Ainamo
7	0	2013	Luciano Tavares Angelo Cintra

Table S4 (*continued*)

Table S4 (*continued*)

Frequency	Centrality	Year of first publication	Author
7	0	2015	Mohammad D Al Amri
7	0	2009	Tellervo Tervonen
7	0	2010	Ryan T Demmer
7	0	2018	Koji Naruishi
7	0	2006	Anwar T Merchant
7	0	1996	E Lalla
7	0	2010	Poliana Mendes Duarte
7	0	2018	Masato Minabe
6	0	2019	Ahmad Zare Javid
6	0	2018	Junichi Kido
6	0	2014	Abid Mehmood
6	0	2011	Fernando Oliveira Costa
6	0	2008	Liisa Suominentaipale
6	0	2018	Mohammed Alrabiah
6	0	1993	E Firatli
6	0	2000	Ib Lamster
6	0	2013	Doris Hissako Sumida
6	0	2018	Zeyad H Alsowygh
6	0	2010	Jadson Almeida Lima
6	0	2008	Lijian Jin
6	0	2015	Hans Malmstrom
6	0	2008	George W Taylor
6	0	2017	Jaehong Lee
6	0	1990	Lm Golub
6	0	2007	James D Beck
6	0	1998	Gw Taylor
6	0	2009	Liisa Hiltunen
6	0	2006	Alpdogan Kantarci
6	0	1986	T Tervonen

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Table S5 Keywords' information (Frequency >5)

Frequency	Burst	Degree	Betweenness Centrality	Sigma	Keyword
982		22	0.02	1	Periodontal disease
873		24	0.03	1	Disease
836		31	0.08	1	Periodontiti
778		36	0.15	1	Diabetes mellitus
532		31	0.06	1	Mellitus
476		37	0.14	1	Inflammation
418		25	0.02	1	Risk
415	7.31	26	0.07	1.66	Association
388		25	0.08	1	Diabete
359		23	0.04	1	Prevalence
340		34	0.05	1	Health
336		31	0.07	1	Oral health
322		31	0.07	1	Risk factor
292		22	0.02	1	Glycemic control
226	5.98	24	0.04	1.28	Cardiovascular disease
223		37	0.09	1	Therapy
216		19	0.02	1	Expression
212		22	0.01	1	Obesity
209	4.72	26	0.06	1.32	Adult
201		23	0.03	1	Population
187	9.82	26	0.04	1.53	Infection
184		32	0.04	1	Tooth lo
182		45	0.13	1	Smoking
170	7.18	24	0.02	1.18	Epidemiology
167	6.49	24	0.05	1.36	Porphyromonas gingivali
165	13.24	15	0.01	1.11	Chronic periodontiti
159	13.96	18	0.02	1.27	C reactive protein
159	6.74	20	0.01	1.07	Coronary heart disease
155	9.39	18	0.03	1.34	Insulin resistance
147		26	0.11	1	Gingival crevicular fluid
145	5.23	23	0.04	1.2	Metabolic control
121	14.36	24	0.05	1.95	Type 2 diabetes mellitus
115	8.59	15	0.01	1.06	Metaanalysis
110	4.56	22	0.05	1.27	Complication
104	5.42	21	0.07	1.45	Cytokine
102	4.74	18	0.02	1.1	Atherosclerosis

Table S5 (*continued*)

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Table S5 (*continued*)

Frequency	Burst	Degree	Betweenness Centrality	Sigma	Keyword
101		20	0.03	1	Alveolar bone lo
100	6.41	12	0	1.02	Metabolic syndrome
80	4.72	17	0.04	1.19	Children
78		23	0.04	1	United states
77	13.72	15	0.01	1.11	Necrosis factor alpha
76		19	0.03	1	Saliva
74		13	0.01	1	Gingiviti
69	5.72	20	0.07	1.45	Glucose
66	4.85	14	0.05	1.26	Cell
66	7.92	9	0.01	1.07	Oxidative stress
64	6.41	20	0.02	1.15	Marker
61	6.3	20	0.04	1.26	Receptor
55	10.89	19	0.04	1.5	Cigarette smoking
54	8.37	12	0.04	1.33	Diagnosis
53	10.25	13	0.02	1.23	Bone lo
51	13.84	10	0.04	1.75	Dental implant
51	15.3	7	0.01	1.2	Impact
46	6.55	10	0.01	1.07	Dental cary
42		11	0.02	1	Activation
42		11	0.01	1	Mortality
41	17.05	9	0.02	1.29	Dependent diabetes mellitus
41	9.24	21	0.05	1.53	Serum
40	7.47	11	0.01	1.07	Progression
39	5.38	8	0.01	1.07	Mechanism
36	9.69	11	0.02	1.2	Actinobacillus actinomycetemcomitan
35	5.56	8	0.02	1.09	Bacteria
34	10.43	11	0.01	1.06	Women
33	11.43	19	0.04	1.63	Attachment lo
33		20	0.08	1	Rat
32	8.25	10	0.02	1.13	Adolescent
32	7.93	12	0.04	1.33	Gene expression
32	5.67	6	0	1.02	Hypertension
32	7.17	17	0.04	1.34	Oral hygiene
32	6.34	24	0.05	1.37	Tnf alpha
30	11.72	30	0.07	2.31	Tumor necrosis factor

Table S5 (*continued*)

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Table S5 (*continued*)

Frequency	Burst	Degree	Betweenness Centrality	Sigma	Keyword
28		4	0	1	Consensus report
27	6.38	26	0.08	1.66	Pathogenesis
27		10	0.01	1	Type 2 diabete
24		9	0	1	Model
24		10	0.03	1	Protein
24	7.74	16	0.04	1.39	Rheumatoid arthriti
22	5.42	7	0	1.02	Glycation end product
22		4	0	1	Update
21	4.8	16	0.04	1.19	Plaque
21	8.44	9	0.01	1.12	Risk indicator
20		6	0.02	1	Hyperglycemia
20	9.75	11	0.02	1.2	Insulin dependent diabetics
20	4.7	8	0.01	1.03	Periodontaldisease
19	9.3	4	0	1.02	Adult periodontiti
19	10.02	2	0	1	Nutrition examination survey
19	8.11	17	0.04	1.39	Tissue
18	4.61	12	0.04	1.17	Matrix metalloproteinase
18	8.45	20	0.03	1.27	Myocardial infarction
17		2	0	1	Care
17		4	0	1	Classification
17	4.83	16	0.04	1.2	Insulin
17		8	0.01	1	Workshop
16	7.26	7	0	1.03	Hba1c
15		4	0	1	National health
14	6.85	6	0.02	1.11	Collagenase activity
14	5.92	9	0.01	1.08	Crevicular fluid
14	5.82	4	0	1.03	Follow up
14	6.13	6	0.01	1.05	Gingiva
14		5	0.03	1	Identification
14	7.64	8	0.01	1.05	Preterm birth
13	4.58	6	0.01	1.03	Age
13		5	0.01	1	Cary
13	5.96	8	0	1.02	Glycated hemoglobin
13	5.16	8	0.02	1.12	In vitro
12	5.4	1	0	1	Parameter

Table S5 (*continued*)

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Table S5 (*continued*)

Frequency	Burst	Degree	Betweenness Centrality	Sigma	Keyword
12		8	0.01	1	Periodontal therapy
11		2	0.02	1	Apical periodontiti
11	5.27	6	0	1	Body mass index
11	4.75	4	0	1.01	C-reactive protein
11		4	0.01	1	Differentiation
11		10	0.02	1	Polymorphism
11	5.47	6	0.02	1.09	Severity
11	5.54	13	0.03	1.18	Systemic disease
10		5	0	1	Efficacy
10		5	0	1	Factor alpha
10		1	0	1	Global burden
10	6.11	3	0	1	IDDM
10	6.11	19	0.07	1.55	Juvenile periodontiti
10	4.74	5	0.01	1.06	Maintenance
10	5.71	7	0.01	1.03	Microbiology
10		1	0	1	Peri-implantiti
10		17	0.02	1	Prevention
10		2	0	1	Quality of life
10		8	0.02	1	Stress
10		2	0	1	Systemic inflammation
9		6	0.01	1	Antibody
9		4	0	1	Behavior
9	4.76	5	0	1	Dental infection
9		9	0.03	1	Interleukin 6
9		6	0.01	1	Lipopolysaccharide
9	4.68	11	0.03	1.15	Oxidant stress
9		4	0	1	Pregnancy
9		7	0.01	1	Teeth
8		3	0.01	1	Antioxidant
8		2	0	1	Biomarker
8		7	0.01	1	Bone
8		5	0.03	1	Collagenase
8	5.04	6	0	1.01	Dental disease
8	5.42	0	0	1	Diabetes-mellitus
8		6	0.01	1	Experience
8		11	0.02	1	Individual

Table S5 (*continued*)

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Table S5 (*continued*)

Frequency	Burst	Degree	Betweenness Centrality	Sigma	Keyword
8		7	0.03	1	Juvenile
8		7	0.01	1	Neutrophil
8		5	0	1	Older
8		2	0	1	Proliferation
8		9	0.03	1	Response
8		17	0.04	1	Tetracycline
7		5	0	1	Acute myocardial infarction
7		4	0	1	Atherosclerosis risk
7		4	0	1	Bacteroides gingivali
7		4	0	1	Blood
7		3	0	1	Early onset periodontiti
7		6	0.01	1	Follow-up study
7		2	0	1	Leukocyte
7		7	0.02	1	Neutrophil chemotaxi
7		7	0	1	Pathogen
7		6	0.02	1	Periodontal diseases/epidemiology
7		2	0	1	Periodontal infection
7		2	0	1	Type 2
6		2	0	1	Adipose tissue
6		3	0	1	Alpha
6		2	0	1	Diabetes mellitus insulin-dependent
6		4	0	1	Diabetic rat
6		5	0.01	1	Glycation
6		5	0.01	1	Growth factor
6		2	0	1	Hygiene
6		6	0.01	1	Insulin-dependent diabetes mellitus
6		4	0.01	1	Knowledge
6		2	0	1	Low birth weight
6		6	0	1	Macrophage
6		7	0	1	Manifestation
6		7	0	1	Periodontal attachment lo
6		1	0	1	Prediabetic state
6		13	0.04	1	Riskfactor
6		3	0	1	Socioeconomic status
6		7	0	1	Type 1

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Table S6 Keywords of Cluster 0

Frequency	Burst	Degree	Betweenness centrality	Sigma	keywords
218		32	0.04	1	Expression
142		22	0.02	1	Gingival crevicular fluid
119		25	0.02	1	Cytokine
86		19	0.02	1	Cell
85		18	0.02	1	Oxidative stress
82		22	0.02	1	Saliva
73		20	0.02	1	Receptor
72		18	0.02	1	Diagnosis
69		22	0.02	1	Activation
65		27	0.04	1	Rat
59	4.91	17	0.02	1.08	Serum
59		20	0.02	1	Glycation end product
57		12	0.01	1	Mechanism
53		18	0.02	1	Tissue
52	5.19	15	0.02	1.08	Gene expression
51		12	0.01	1	Hyperglycemia
49		22	0.03	1	Protein
47		22	0.03	1	Model
46		16	0.01	1	Biomarker
44		17	0.02	1	Lipopolysaccharide
41		24	0.04	1	Pathogenesis
40		23	0.03	1	Bone
35		22	0.02	1	Antioxidant
34		11	0.01	1	In vitro
33		20	0.03	1	Alveolar bone
32		20	0.03	1	Identification
30		12	0.01	1	Stress
25		11	0.01	1	High glucose
24		7	0	1	Differentiation
23		11	0	1	Apoptosis
22		19	0.02	1	Polymorphism
22		13	0.02	1	Proliferation
21		11	0.01	1	Matrix metalloproteinase
21		14	0.01	1	Alpha
20		10	0	1	Macrophage
19	5.24	7	0	1.02	Mice

Table S6 (*continued*)

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Table S6 (*continued*)

Frequency	Burst	Degree	Betweenness centrality	Sigma	keywords
16		11	0.01	1	Adipokine
16		12	0.01	1	Secretion
15	5.69	8	0.01	1.03	Fibroblast
15	4.91	6	0	1.01	Susceptibility
15		5	0	1	Diabetes mellitus type 2
14		9	0	1	Inflammatory cytokine
14		12	0.01	1	Destruction
14		5	0	1	Gingival
13		9	0	1	Nf kappa b
13		7	0	1	Type 1 diabetes mellitus
13		8	0	1	Chemokine
12		9	0.01	1	Rage
12		15	0.01	1	Endothelial cell
12		13	0.02	1	In vivo
11		12	0.01	1	Growth factor
11		3	0	1	Inhibition
11		5	0	1	Type 1 diabete
11		8	0	1	Factor kappa b
11		10	0.01	1	Pathway
10		7	0	1	Interleukin 1 beta
10		9	0.01	1	Epithelial cell
10		9	0	1	Osteoblast
10		7	0.01	1	Toll like receptor
10		4	0	1	Metformin
9		3	0	1	Dysfunction
9		12	0.01	1	Advanced glycation end product
8		8	0	1	Collagen
8		5	0	1	Interleukin-6
8		4	0	1	Nitric oxide
8		6	0	1	Bone formation
7		3	0	1	Rankl
7		4	0	1	Stem cell
7		3	0	1	Induction
6		5	0	1	Oxidant stress
6		16	0.02	1	Attachment

Table S6 (*continued*)

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Table S6 (*continued*)

Frequency	Burst	Degree	Betweenness centrality	Sigma	keywords
6		3	0	1	Angiogenesis
6		5	0	1	Periodontal ligament
6		10	0	1	Advanced glycation end-product
6		6	0	1	Resorption
5		3	0	1	Patient
5		4	0	1	Inflammatory mediator
5		4	0	1	Lymphocyte
4		3	0	1	Involvement
4		2	0	1	Receptor activator
4		5	0	1	Brain
4		10	0.01	1	Death
4		10	0.01	1	Adipocyte
4		8	0	1	Antioxidant status
4		3	0	1	Melatonin
4		3	0	1	Ligand
4		5	0	1	Antioxidant enzyme
4		1	0	1	Osteogenic differentiation
4		6	0.01	1	Dubliniensis
4		5	0	1	Modulation
4		5	0	1	Autophagy
3		1	0	1	Defect
3		1	0	1	Cytokine level
3		1	0	1	Yeast
3		1	0	1	Nitric oxide synthase
3		1	0	1	Virulence factor
3		4	0	1	Osteogenesis
3		2	0	1	Signaling pathway
3		2	0	1	End product
3		3	0	1	Glucose metabolism
3		1	0	1	Vitamin e
3		2	0	1	Innate
3		3	0	1	Periodontal ligament cell
3		3	0	1	Sclerostin
2		3	0	1	Bone morphogenetic protein 2
2		3	0	1	Breaker

Table S6 (*continued*)

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Table S6 (*continued*)

Frequency	Burst	Degree	Betweenness centrality	Sigma	keywords
2		2	0	1	Alveolar bone resorption
2		3	0	1	T cell
2		4	0	1	Cytokine production
2		1	0	1	Anaerobic bacteria
2		5	0	1	Human
2		5	0	1	Epithelium
2		3	0	1	Prostaglandin e 2
2		1	0	1	Aging
2		4	0	1	Colony enhancing factor
2		6	0	1	Exposure
2		1	0	1	Fibronectin
2		4	0	1	Oral cancer
2		2	0	1	Experimental periodontal disease
2		2	0	1	Cytokine profile
2		3	0	1	Glycosylation end products advanced
2		1	0	1	Caspase-3
2		1	0	1	Interleukin-1
2		1	0	1	Diabetes mellitus type 1
2		1	0	1	Capillary
2		3	0	1	Beta
2		4	0	1	Potential mechanism
2		4	0	1	Abnormality
2		2	0	1	Adherence
2		2	0	1	Monocyte chemoattractant protein 1
2		1	0	1	Candidiasis
2		4	0	1	Advanced
2		2	0	1	25-hydroxyvitamin d-3
2		4	0	1	Antimicrobial peptide
2		3	0	1	Kinase
2		1	0	1	Dna damage
1		1	0	1	Cathepsin
1		6	0	1	Activated protein kinase
1		1	0	1	3t3 l1preadipocyte
1		1	0	1	Bacterial plaque implant
1		3	0	1	Connective tissue

Table S6 (*continued*)

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Table S6 (*continued*)

Frequency	Burst	Degree	Betweenness centrality	Sigma	keywords
1		4	0.01	1	Adipogenesis
1		7	0	1	Accelerated periodontal disease
1		2	0	1	Accessory canal
1		2	0	1	Branemark(r) system
1		1	0	1	Alkaline phosphatase activity
1		1	0	1	Activated receptor gamma

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