Research article

Bibliometric and visual analysis of ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications from 2000 to 2023

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ABSTRACT

Background: The pathogenesis of diabetes and its microvascular complications are intimately associated with renin angiotensin system dysregulation. Evidence suggests the angiotensin converting enzyme 2 (ACE2)/angiotensin 1-7 (Ang 1–7)/Mas receptor (MasR) axis regulates metabolic imbalances, inflammatory responses, reduces oxidative stress, and sustains microvascular integrity, thereby strengthening defences against diabetic conditions. This study aims to conduct a comprehensive analysis of the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications over the past two decades, focusing on key contributors, research hotspots, and thematic trends.
Methods: This cross-sectional bibliometric analysis of 349 English-language publications was performed using HistCite, VOSviewer, CiteSpace, and Bibliometrix R for visualization and metric analysis. Primary analytical metrics included publication count and keyword trend dynamics.
Results: The United States, contributing 105 articles, emerged as the most productive country, with the University of Florida leading institutions with 18 publications. Benter IF was the most prolific author with 14 publications, and *Clinical Science* was the leading journal with 13 articles. A total of 151 of the 527 author's keywords with two or more occurrences clustered into four major clusters: diabetic microvascular pathogenesis, metabolic systems, type 2 diabetes, and coronavirus infections. Keywords such as "SARS", "ACE2", "coronavirus", "receptor" and "infection" displayed the strongest citation bursts. The thematic evolution in this field expanded from focusing on the renin angiotensin system (2002–2009) to incorporating ACE2 and diabetes metabolism (2010–2016). The latter period (2017–2023) witnessed a significant surge in diabetes research, reflecting the impact of COVID-19 and associated conditions such as diabetic retinopathy and cardiomyopathy.
Conclusions: This scientometric study offers a detailed analysis of the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications, providing valuable insights for future research directions.

1. Introduction

According to the 10th edition of the International Diabetes Federation Diabetes Atlas, an estimated 536.6 million individuals aged

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20–79 were living with diabetes globally in 2021, with projections suggesting a rise to 783.2 million by 2045 [1]. In the modern era, diabetes has become a leading chronic metabolic disorder, significantly endangering individual health and placing considerable pressure on worldwide healthcare systems and economies. Diabetics are at increased risk of microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy—which contribute to higher mortality rates, blindness, kidney failure, and a diminished quality of life [2]. Despite significant progress, the exact mechanisms underlying diabetes and its microvascular complications are still not fully understood. Therefore, keeping abreast of current trends and developments in this filed is crucial to elucidate the precise pathogenesis of these conditions.

The renin angiotensin system, a critical endocrine regulator of haemodynamics, body fluid balance, neuroendocrine functions, inflammation, oxidative stress and tissue fibrosis, is modulated globally by classical circulating elements and locally through tissue specific mechanisms [3]. Activation of the angiotensin converting enzyme/angiotensin II axis and its type 1 receptor forms the classical pathway of renin angiotensin system, implicated in the pathogenesis of several diseases, including diabetes and its microvascular complications. Angiotensin converting enzyme 2 (ACE2), a homolog of angiotensin-converting enzyme and a carboxypeptidase, plays a pivotal role in local and systemic hemodynamics, primarily by lowering blood pressure [4]. The enzyme's primary product, angiotensin 1-7 (Ang 1–7), engages the Mas receptor (MasR), promoting vasodilation, antioxidative effects, anti-inflammation, proliferation inhibition, enhanced glucose tolerance, and improving insulin sensitivity. The ACE2/Ang 1–7/MasR pathway functions as a counter-regulatory mechanism against the angiotensin converting enzyme/angiotensin II axis and its type 1 receptor pathway in various pathological conditions [5]. Although considered the protective arm of the renin angiotensin system, the precise mechanisms underpinning these effects remain poorly understood [6]. Extensive research is currently underway on the ACE2/Ang 1–7/MasR axis in metabolic disorders, including diabetes, which shows great potential as a therapeutic target for managing diabetes and its related microvascular complications [6].

Bibliometrics is a methodological approach that quantifies and analyzes the quantity, quality, and impact of scientific literature, playing a crucial role in assessing research outcomes and academic contributions [7]. Compared to traditional review articles, bibliometrics offers researchers an objective and quantifiable perspective, enabling a more thorough understanding and evaluation of academic research achievements, hotspots, and trends within a specific field or disease, thus establishing a foundation for future research endeavors [8]. However, bibliometric studies on the ACE2/Ang 1–7/MasR axis related to diabetes and its microvascular complications are scarce. Consequently, this study utilizes bibliometric analysis to thoroughly examine academic publications concerning the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications. The primary aim of this research is to elucidate potential directions and trajectories for clinical researchers and practitioners.

2. Methods

2.1. Data sources and search strategy

Data were retrieved from the Web of Science Core Collection (WoSCC, https://webofscience.clarivate.cn/wos/alldb/basic-search) between January 1, 2000, and December 20, 2023, comprising full records and cited references. The search utilised the terms "diabetes and its microvascular complications" AND "ACE2/Ang 1–7/MasR axis" (full search terms listed in the appendix). Searches were completed in a single day (December 22, 2023) to circumvent potential errors from daily database updates. For this study, the inclusion criteria limited to English and excluded specific document types: meeting abstracts (n = 20), editorial materials (n = 3), proceeding papers (n = 5), book chapters (n = 1) and letter (n = 5). Only articles (n = 243) and review articles (n = 106) were included, as other types generally bypass peer review and thus, were excluded from the bibliometric analysis (Fig. S1).

2.2. Data analysis and visualization

HistCite Pro 2.1 was used to calculate the total local citation score (TLCS) and total global citation score (TGCS) for publications, authors, institutions, journals and countries/regions, highlighting citation frequencies within local datasets (finally determined 349 publications) and broader recognition across the Web of Science database, respectively. TLCS values were noted to be significantly lower than TGCS values [8]. Biblioshiny R (version 4.1.4) was utilised to analysis authors' h-index, g-index, m quotient, production over time, adherence to Lotka's law, and journals' compliance with Bradford's law [8,9]. The m-index is determined by calculating the median number of citations that the papers in a scientist's h-core receive, with the h-core being defined by the h-index. The q^2 index of the author was derived manually using the specified formula: $q^2 = \sqrt{(h-\text{index}) \times (m-\text{index})}$ [10]. The calculation and definitions of the h-index, g-index, m-index, m quotient, and q^2-index are listed in Table S1. Core authors were identified in accordance with Price's Law, $M = 0.749\sqrt{N_{\max}}$ (M represents a threshold for defining core authors' publication output, with $N_{\max}$ representing the most productive author's paper count) [11]. Microsoft Excel 2019 facilitated the statistical compilation of publication data. VOSviewer (version 1.6.19) enabled the visualization of collaborations and co-occurrences at various levels, including countries/regions, institutional, and authorial, as well as journals and keywords [12]. Three-field plot and theme evolution were performed using Biblioshiny R. CiteSpace (version 6.2.R5) was used to generate keyword bursts and ridge plots [13] (Fig. S1).

3. Results

3.1. Annual publications and citations

Our study identified 349 publications on the ACE2/Ang 1–7/MasR axis related to diabetes and its microvascular complications indexed in the WoSCC, including 243 articles (69.6 %) and 106 review articles (30.4 %). Curve fitting analysis revealed that since 2002, the cumulative number of publications has shown a consistent upward trend, with an averge annual growth rate of 11.03 %. The fitted curve is described by the equation: $y = 0.9824x^2 - 10.717x + 26.969$ ($R^2 = 0.9835$) (Fig. 1A). Between 2000 and 2011, fewer than 10 publications per year were published in this field, however, since then, the annual output has consistently exceeded 10 publications. Notably, in the past four years, there has been a rapid increase in the number of published articles (Table S2). As of the latest search, these publications have accrued 16504 citations, with an average of 47.29 per publication. The year 2020 recorded the highest TGCS at 5243, signifying substantial research excellence during this period. Other years with notably high citation counts include 2013 (TGCS = 1207), 2014 (TGCS = 1254) and 2021 (TGCS = 1925). Given their proximity to the search date, the citations frequencies for 2022 and 2023 were lower than those of earlier years (Fig. 1B). The continuous increase in annual publications and citations mirrors the rapid advancement in the field.

3.2. Analysis of countries/regions

A total of 52 countries/regions contributed to this research field (Fig. 2A). As shown in Table 1, the United States is the most productive country (n = 105), followed by China (n = 67), and Canada (n = 31). Publications from the United States rank first in both TLCS (424) and TGCS (5953). Although Kuwait, Spain and South Korea are not among top 10 in terms of publications, but their citation score of publications is still considerable. Each circle represents a country/region, with its size indicated the total link strength from that specific location. The thickness of the connecting lines the reflects the intensity of cooperation, and the same color signifies relatively closer collaboration (Fig. 2B). Evidently, the United States, the United Kingdom, Canada, China, Germany and Brazil are prominent in this research field, with closest cooperation observed between the United States and Canada. Some countries/regions do not have academic exchange within this research field, such as Pakistan, Mexico and Ghana. Fig. 2C shows that Kuwait and Brazil were
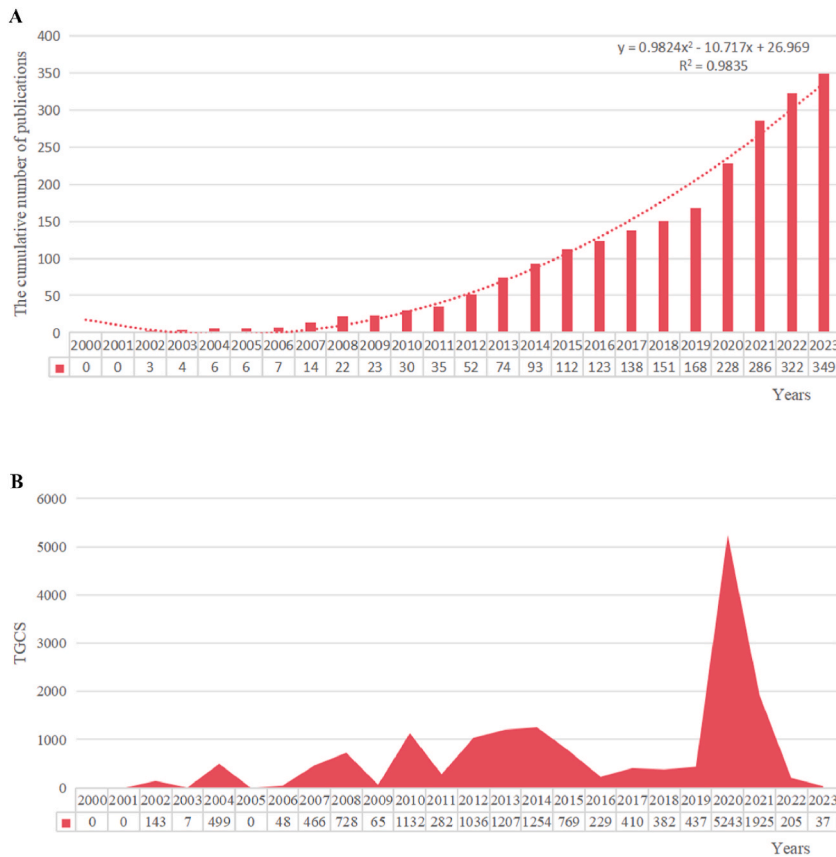

Fig. 1. Analysis of publication outputs and citations. (A) Cumulative number of publications. (B) Annual global citations. TGCS: total global citation score.
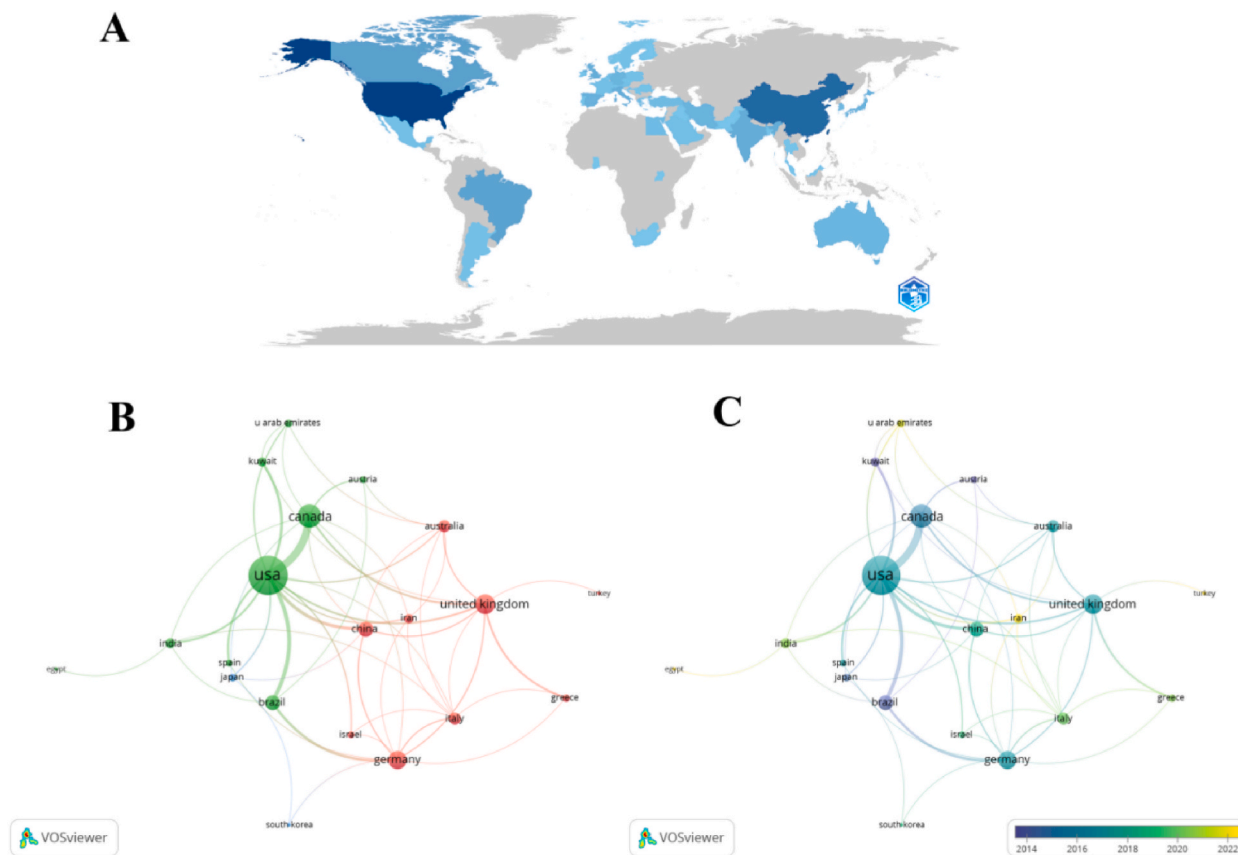
Fig. 2. Visualization analysis of countries/regions involved in research on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications. (A) Global distribution of publications using Biblioshiny R. (B) Network visualization using VOSviewer (minimum number of publications of a country/region is five), the size of each circle represents the total link strength of a country, with more cooperation producing larger circles. The line between the two points in the figure represents those two countries/regions had established a similar relationship. The thicker the line, the closer the link between the two countries/regions. (C) Overlay visualization using VOSviewer (minimum number of publications of a country/region is five), the occurrence of the blue words took place in the early stages, whereas the yellow words emerged more recently. The weights and normalization method for the visual analysis of VOSviewer were set to total link strength and LinLog/modularity, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
The top 10 countries/regions with the most publications or total citation score.

Rank	Publication	Country/region	Rank	TLCS	Country/region	Rank	TGCS	Country/region
1	105	USA	1	424	USA	1	5953	USA
2	67	China	2	213	Canada	2	3775	China
3	31	Canada	3	205	China	3	3416	Canada
4	30	Brazil	4	99	Kuwait	4	2568	UK
5	19	India	5	95	Brazil	5	1531	Brazil
6	19	UK	6	87	UK	6	1108	Germany
7	17	Germany	7	81	Japan	7	1050	Italy
8	17	Italy	8	71	Australia	8	817	Japan
9	15	Japan	9	63	Germany	9	710	South Korea
10	14	Australia	10	57	Spain	10	660	Kuwait

TLCS: total local citation score. TGCS: total global citation score.

the first to begin study in this field, while Iran, Egypt, and the United Arab Emirates were relatively late. The corresponding authors of publications in this field are spread across all five continents, indicating that every region is actively exploring this field of study. In Asia, 22.7 %, Europe 31.7 %, Africa 50 %, Oceania 40 %, North America 27.4 %, and South America 36.7 % of the publications are the result of international collaborations by the corresponding authors (Table S3).

Table 2
The top 10 institutions with the most publications or total citation score.

Rank	Publication	Institution	Country/region	Rank	TLCS	Institution	Country/region	Rank	TGCS	Institution	Country/region
1	18	Univ Florida	USA	1	110	Capital Med Univ	China	1	2112	Capital Med Univ	China
2	13	Capital Med Univ	China	2	101	Univ Florida	USA	2	1915	Univ Florida	USA
3	13	Kuwait Univ	Kuwait	3	99	Kuwait Univ	Kuwait	3	1804	Univ Leeds	UK
4	13	Univ Fed Minas Gerais	Brazil	4	85	Univ Toronto	Canada	4	1574	Univ Alberta	Canada
5	10	Univ Sao Paulo	Brazil	5	83	Univ Fed Minas Gerais	Brazil	5	1311	Univ Alabama Birmingham	USA
6	8	Univ Ottawa	Canada	6	76	Univ Alberta	Canada	6	803	Univ Toronto	Canada
7	7	Univ Alberta	Canada	7	70	Austrian Acad Sci	Austria	7	770	IRCCS Tradate VA	Italy
8	7	Univ Toronto	Canada	8	66	Wake Forest Univ	USA	8	770	Univ Insubria	Italy
9	7	Wake Forest Univ	USA	9	56	Northwestern Univ	USA	9	770	Osped S Maria Misericordia	Italy
10	6	Univ Alabama Birmingham	USA	10	47	Louisiana State Univ	USA	10	677	Univ Fed Minas Gerais	Brazil

TLCS: total local citation score. TGCS: total global citation score.

3.3. Analysis of institutions

A total of 554 institution collectives conducted studies on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications. Table 2 shows the top 10 institution collectives (minimum number of documents of a institution: 6) with the most published papers. Among them, the University of Florida (n = 18) had the highest output, followed by Capital Medical University (n = 13) and Kuwait University (n = 13). The 10 most productive institution collectives were located in the United States (n = 3), Canada (n = 3), Brazil (n = 2), China (n = 1) and Kuwait (n = 1). The top 3 institution collectives with the highest local cited were the Capital Medical University (TLCS = 110), University of Florida (TLCS = 101) and Kuwait University (TLCS = 99). The top 3 institution collectives with the highest global cited were the Capital Medical University (TGCS = 2112), University of Florida (TGCS = 1915) and University of Leeds (TGCS = 1804). Moreover, only 520 out of 554 institutional collectives have established academic external exchanges. Fig. 3A shows the collaboration network of institutional collectives with two or more publications, and there is close cooperation between most of them. Kuwait University, University of Sao Paulo and Universidade Federal de Minas Geraiswere the earliest to start this research field (Fig. 3B).

3.4. Analysis of authors

A total of 1820 authors engaged in research and published articles in this field. Of these authors, 87.7 percent published only one paper, and 12.3 percent published multiple papers, fitting with Lotka's law (Fig. S2). In order to identify the core authors among these more precisely, Price's law was used. After calculating the number of papers published by the core authors, the threshold value was 2.803 papers, and this resulted in 85 core authors. The top 10 core authors (minimum number of documents of a author: 7) were shown in Table 3 and author rankings based on the h-index, g-index and m quotient were listed in Table S4. Among the ten most productive authors, Benter IF (n = 14) published the most articles, while Oudit GY (TLCS = 145, TGCS = 1971) was the most cited author. Benter IF had the highest h-index (12) and g-index (14), Pascual J and Riera M had the highest m-quotient (both 0.7) and Oudit GY had the highest q^2-index of 32.496. In addition, potential relationships between top 10 authors and institutions-countries/regions were visualized (Fig. S3). Fig. 4A presents the network of collaboration of authors who published two and more papers, and it is possible to observe multiple author collaborations, such as Raizada MK, Grant MB and Oudit GY, Benter IF and Yousif MHM, Pascual J, Riera M and Gimeno J, Scholey JW and Oudit GY. Among the top 10 most productive authors, both Benter IF, Oudit GY and Yang JK were pioneers in this field and continue to achieve notable advancements in their research over the last 5 years. Moreover, Grant MB, Raizada MK and Oudit GY have shown enhanced activity in this research area over the last 5 years (Fig. 4B and C).

3.5. Analysis of journals

The analysis resulted in 349 publications from 202 journals. Table 4 displays the top 10 most productive or cited journals based on statistical analysis, highlighting their Impact Factor (IF) and ranked in the category quartile of the Journal Citation Reports 2022. The
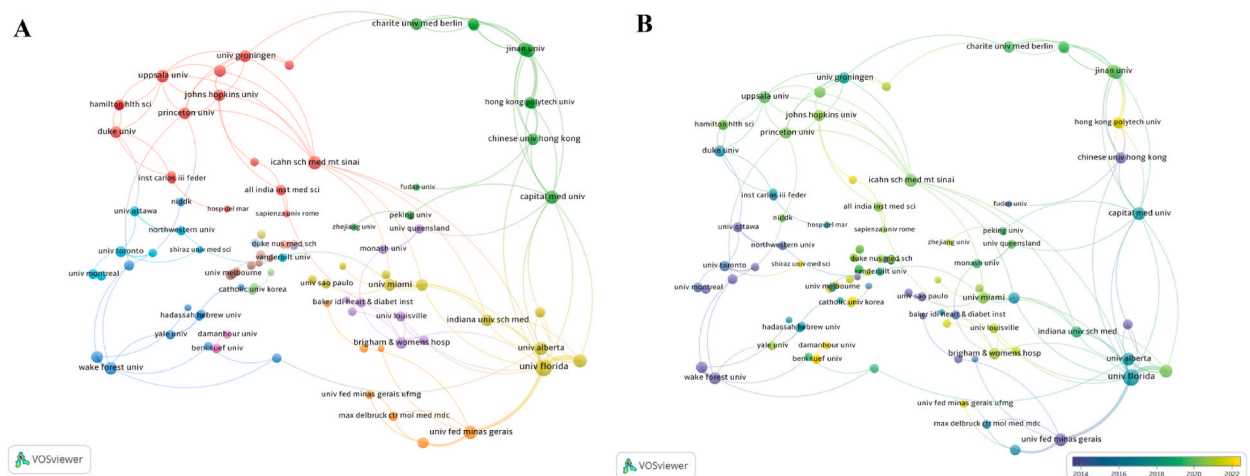

Fig. 3. Visualization analysis of institution collectives involved in research on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications. (A) Network visualization using VOSviewer (minimum number of publications of a institution collective is two), the size of each circle represents the total link strength of a country, with more cooperation producing larger circles. The line between the two points in the figure represents those two institution collectives had established a similar relationship. The thicker the line, the closer the link between the two institution collectives. (B) Overlay visualization using VOSviewer (minimum number of publications of a institution collective is two), the occurrence of the blue words took place in the early stages, whereas the yellow words emerged more recently. The weights and normalization method for the visual analysis of VOSviewer were set to total link strength and LinLog/modularity, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
The top 10 authors with the most publications or total citation score.

Rank	Publications	Author	h-index[a]	g-index[a]	m quotient[a]	m-index[a]	q^2-index[a]
1	14	Benter IF	12	14	0.667	37.5	21.213
2	10	Akhtar S	9	10	0.6	25	15.000
3	10	Raizada MK	9	10	0.692	65	24.187
4	9	Soler MJ	8	9	0.615	43	18.547
5	9	Yousif MHM	9	9	0.5	47	20.567
6	8	Oudit GY	8	8	0.444	132	32.496
7	8	Santos SHS	8	8	0.533	61	22.091
8	8	Yang JK	8	8	0.471	31.5	15.875
9	7[b]	Burns KD	7	7	0.538	41	16.941
10	7[b]	Grant MB	6	7	0.462	75	21.213
Rank	**TLCS**	**Author**	**h-index[a]**	**g-index[a]**	**m quotient[a]**	**m-index[a]**	**q^2-index[a]**
1	145	Oudit GY	8	8	0.444	132	32.496
2	100	Benter IF	12	14	0.667	37.5	21.213
3	98	Yousif MHM	9	9	0.5	47	20.567
4	86	Yang JK	8	8	0.471	31.5	15.875
5	78	Scholey JW	5	5	0.278	71	18.841
6	75	Raizada MK	9	10	0.692	65	24.187
7	73	Grant MB	6	7	0.462	75	21.213
8	70	Penninger JM	3	3	0.13	189	23.812
9	69	Herzenberg AM	2	2	0.111	198.5	19.925
10	67	Santos SHS	8	8	0.533	61	22.091
Rank	**TGCS**	**Author**	**h-index[a]**	**g-index[a]**	**m quotient[a]**	**m-index[a]**	**q^2-index[a]**
1	1971	Oudit GY	8	8	0.444	132	32.496
2	1804	Turner AJ	4	4	0.19	260	32.249
3	1584	Raizada MK	9	10	0.692	65	24.187
4	1500	Grant MB	6	7	0.462	75	21.213
5	1308	Zhong JC	3	3	0.231	124	19.287
6	1176	Gheblawi M	1	1	0.2	1176	34.293
7	1176	Nguyen Q	1	1	0.2	1176	34.293
8	1176	Viveiros A	1	1	0.2	1176	34.293
9	1176	Wang KM	1	1	0.2	1176	34.293
10	921	Yang JK	8	8	0.471	31.5	15.875

TLCS: total local citation score. TGCS: total global citation score.

[a] The calculation of the h-index, g-index, m quotient, m-index and q^2-index was based on the literature data collected in this study, and not on all scientific publications of a particular scholar.

[b] Seven authors each have a publication tally of seven, including Burns KD, Grant MB, Li QH, Pascual J, Riera M, Santos RAS, and Wang Y. Based on the alphabetical ordering of the authors' surnames, only Burns KD and Grant MB are listed in the table.

highest publication counts were in *Clinical Science* (n = 13, 2022IF = 6, Q1), *Peptides* (n = 11, 2022IF = 3, Q3), and *American Journal of Physiology-Renal Physiology* (n = 9, 2022IF = 4.2, Q1). Notably, the most cited journals were *Circulation Research* (TGCS = 1300, 2022IF = 20.1, Q1), *European Journal of Internal Medicine* (TGCS = 710, 2022IF = 8, Q1), and *Acta Diabetologica* (TGCS = 707, 2022IF = 3.8, Q2). The core journals of this research field by Bradford's Law [9] was also analyzed (Fig. S4). The top 59 most productive journals (minimum number of documents of a journal: 2) were visualized in Fig. 5A. 349 publications have cited 15,278 references from 2820 journals. The most cited reference journals include *Hypertension*, *Diabetes*, *The New England Journal of Medicine*, *Circulation Research*, *Nature*, and *The Journal of Biological Chemistry*. Fig. 5B presents a network visualization of journals cited 20 and above times.

3.6. Keywords co-occurrence and clustering analysis

Keywords serve as concise descriptors used in indexing or cataloguing to provide a brief and precise summary of an article. In this study, a total of 527 author's keywords were identified across 349 documents, with 151 satisfied the criterion (minimum number of occurrences of a keyword: 2). Through co-occurrence visualization of these keywords using VOSviewer, it was not difficult to identify four main clusters (Fig.6A and Table S5). The cluster 1 (red) encompasses keywords such as "diabetes", "angiotensin 1-7", "oxidative stress", "apoptosis", "diabetic nephropathy" and "diabetic retinopathy", primarily related to the pathological mechanism of the ACE2/Ang 1–7/MasR axis in diabetic microvascular complications. The cluster 2 (blue) predominantly studies the targets and pathways of the renin angiotensin system in the metabolism system associated with diabetes, with keywords such as "insulin", "glucose", "adipose tissue", "lipid metabolism" and "hypertension". The cluster 3 (green), including "type 2 diabetes", "chronic kidney disease", "SGLT2 inhibitor", "biomarkers", "olmesartan", and "metformin", represents the relationship between this axis and type 2 diabetes. The cluster 4 (yellow) includes terms like "ACE2", "COVID-19", "SARS-COV-2", "lung", and "ARDS", focusing on the role of ACE2/Ang 1–7/MasR axis in diabetes and coronavirus interaction. VOSviewer also color-coded the keywords according to the average appearing year (Fig. 6B), where blue represents earlier appearances and yellow signifies more recent ones. These keywords were published sequentially from 2014 to 2022 in this field.
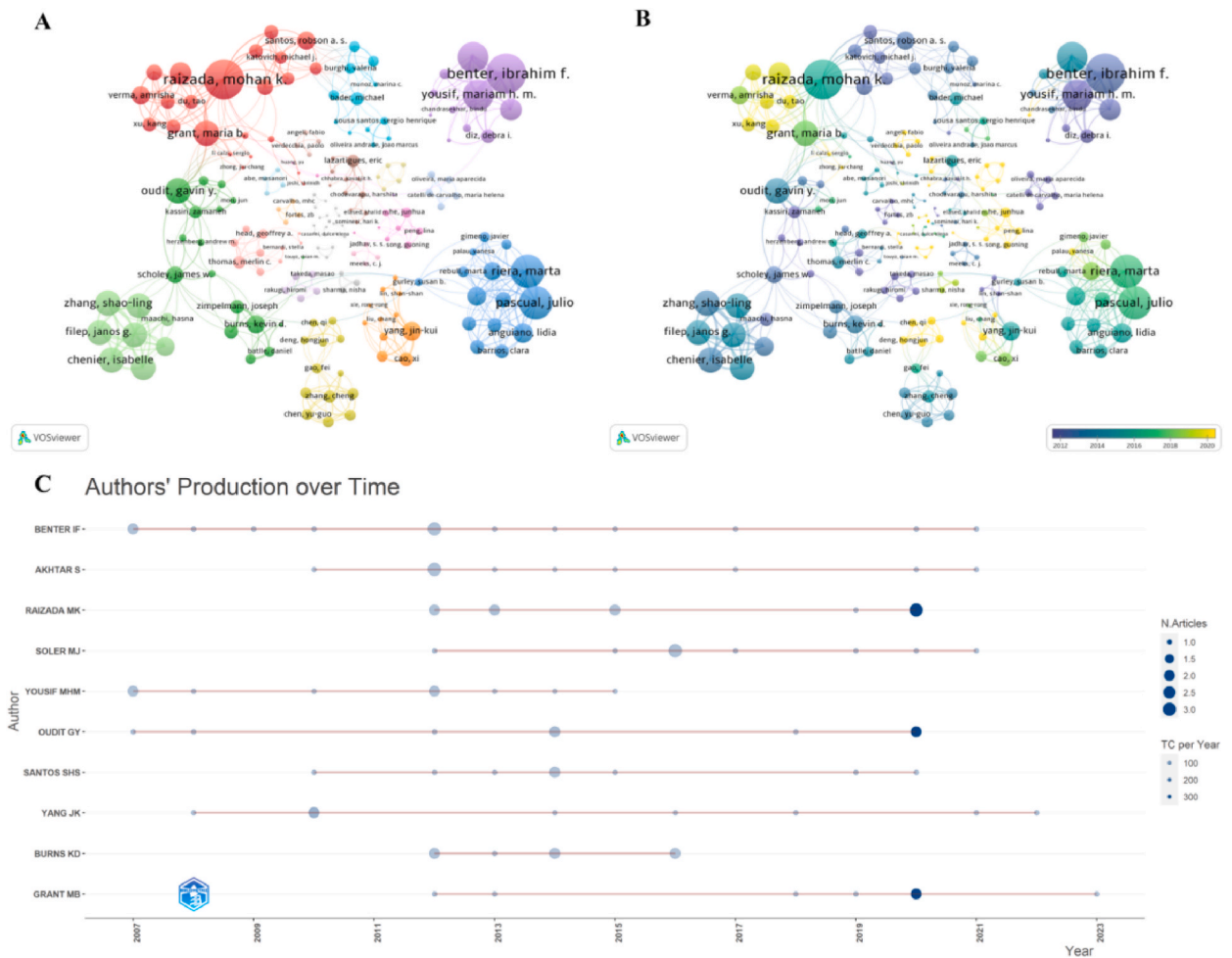
Fig. 4. Visualization analysis of authors involved in research on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications. (A) Network visualization using VOSviewer (minimum number of publications of a author is two), the size of each circle represents the total link strength of a country, with more cooperation producing larger circles. The line between the two points in the figure represents those two authors had established a similar relationship. The thicker the line, the closer the link between the two authors. (B) Overlay visualization using VOSviewer (minimum number of publications of a author is two), the occurrence of the blue words took place in the early stages, whereas the yellow words emerged more recently. The weights and normalization method for the visual analysis of VOSviewer were set to total link strength and LinLog/modularity, respectively. (C) The top 10 authors' production overtime using Biblioshiny R. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.7. Keyword burst detection and theme evolution

Compared to analyzing high-frequency keywords, identifying burst keywords (i.e., frequently cited keywords within a defined period) until December 20, 2023 offers deeper insight into cutting-edge themes and developing trends. The top 55 keywords were selected based on their burst intensity and arranged chronologically according to their burst time, as illustrated in Fig. 7A. The results indicated that "SARS", "ACE2", "coronavirus", "receptor" and "infection" were the top five keywords with the strongest citation bursts. The earliest burst keywords of ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications include "renin angiotensin", "carboxypeptidase", "diabetes", "homolog" and "angiotensin II type 1 receptor". Moreover, fourteen keywords burst continue to last until the end of 2023, including "obesity", "inflammation", "receptor", "infection", "COVID-19", "mortality", "spike protein", "risk", "pathogenesis", "cells", "axis", "dipeptidyl peptidase 4", "tmprss2", "type 2 diabetes". In the analyzed period from 2002 to 2023, research themes transitioned from the renin-angiotensin system (RAS) to emerging intersections between diabetes, its complications, and COVID-19. The thematic evolution in this field expanded from focusing on the renin angiotensin system (2002–2009) to incorporating ACE2 and diabetes metabolism (2010–2016). The latter period (2017–2023) witnessed a significant surge in diabetes research, reflecting the impact of COVID-19 and associated conditions such as diabetic retinopathy and cardiomyopathy (Fig. 7B). Additionally, we utilised CiteSpace to further explore research topics of persistent interest, those with fluctuating attention, as well as emerging or declining themes (Fig. 7C).

Table 4
The top 10 most productive or cited journals.

Rank	Most productive journals	Publication	TLCS	TGCS	Quartile (Q)	2022IF
1	Clinical Science	13	49	462	Q1	6
2	Peptides	11	35	364	Q3	3
3	American Journal of Physiology-Renal Physiology	9	68	433	Q1	4.2
4	European Journal of Pharmacology	7	21	174	Q1	5
5	Frontiers in Endocrinology	7	0	78	Q1	5.2
6	Plos One	7	0	250	Q2	3.7
7	Diabetes	6	99	427	Q1	7.7
8	Endocrinology	6	19	443	Q2	4.9
9	Kidney International	6	88	499	Q1	19.6
10	American Journal of Physiology-Endocrinology and Metabolism	5	27	148	Q2	5.1

Rank	Most cited journals	Publication	TLCS	TGCS	Quartile (Q)	2022IF
1	Circulation Research	2	44	1300	Q1	20.1
2	European Journal of Internal Medicine	1	11	710	Q1	8
3	Acta Diabetologica	2	32	707	Q2	3.8
4	Nature Reviews Endocrinology	1	5	520	Q1	40.5
5	Kidney International	6	88	499	Q1	19.6
6	Clinical Science	13	49	462	Q1	6
7	Endocrinology	6	19	443	Q2	4.9
8	American Journal of Physiology-Renal Physiology	9	68	433	Q1	4.2
9	Diabetes	6	99	427	Q1	7.7
10	Cell Metabolism	3	3	403	Q1	29

TLCS: total local citation score. TGCS: total global citation score. Q: a journal that is ranked in the quartile of the Journal Citation Reports. IF: impact factor.
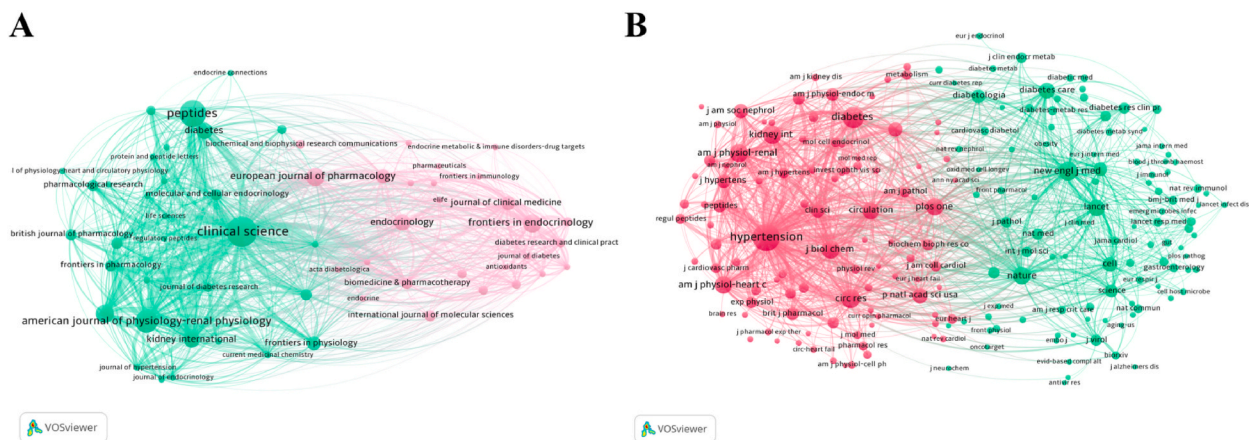

Fig. 5. Analysis of journals from publications and references using VOSviewer. (A) Network visualization (minimum number of publications of a journal is two), the size of each circle represents the number publication of a journal, with more production producing larger circles. The weights and normalization method for the visual analysis of VOSviewer were set to documents and LinLog/modularity, respectively. (B) Network visualization (minimum number of cited of a journal is twenty), the size of each circle represents the number publication of a journal, with more citation producing larger circles. The weights and normalization method for the visual analysis of VOSviewer were set to citations and LinLog/modularity, respectively. The line between the two points in the figure represents those two journals had established a similar relationship. The thicker the line, the closer the link between the two journals.

3.8. Analysis of co-cited publications and co-cited references

We performed a statistical analysis of 349 publications and found that 37 documents had more than 100 citations. The top 10 most global cited publications were shown in Table 5. The most cited publication was a review written by Gheblawi, M et al. [3] in *Circulation Research* titled Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System (TGCS = 1176), followed by Verdecchia P (TGCS = 710) and Yang JK (TGCS = 688). The top 11 most co-cited references was listed in Table 6, and the results illustrated that the document published by Donoghue M [4] had the highest record of co-cited references followed by Tipnis SR [14] and Santos RAS [15].
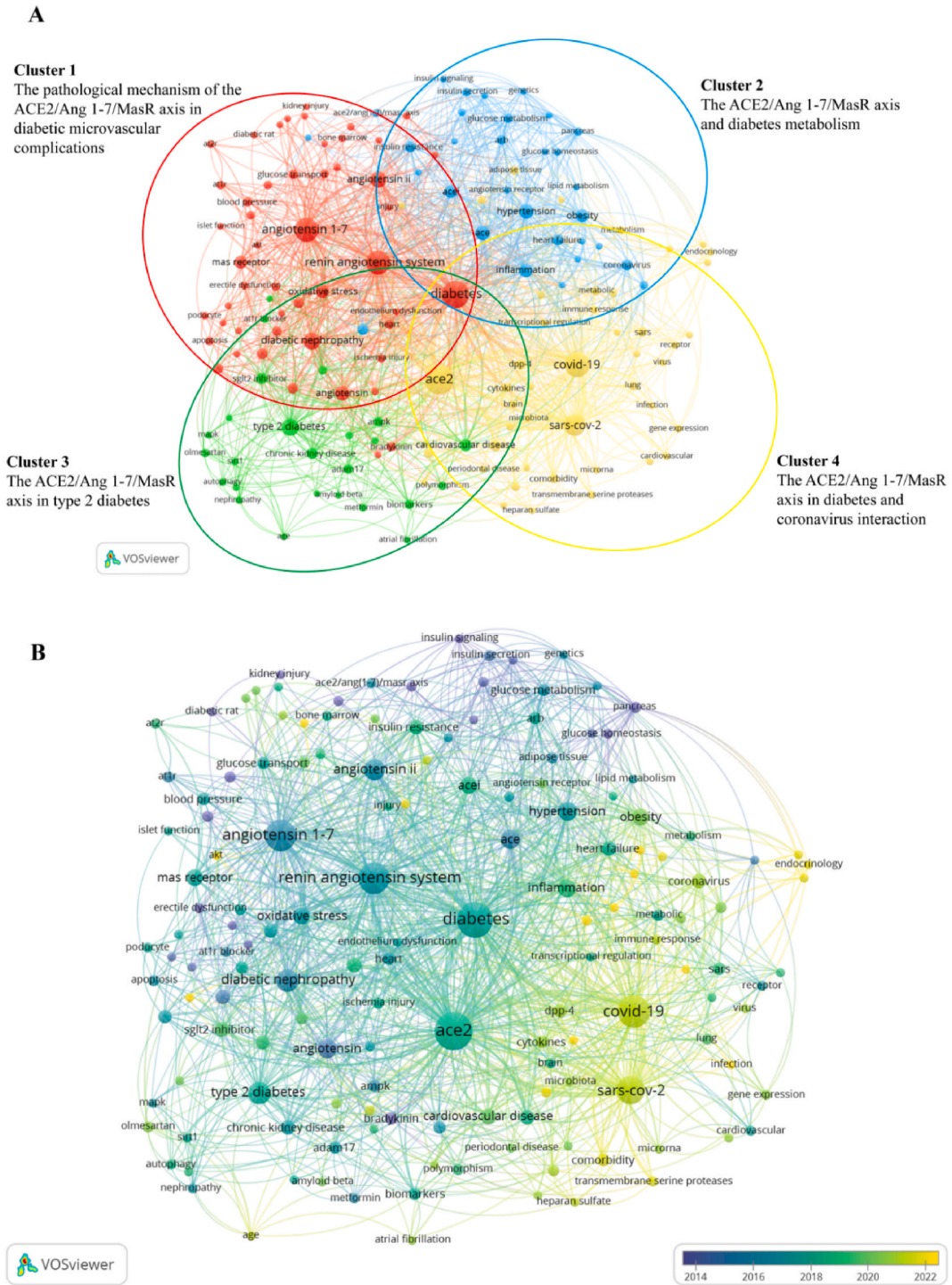
Fig. 6. Visual analysis of author keywords co-occurrence on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications research using VOSviewer. (A) Network visualization, each node represents a keyword, and more frequent keywords occurrence, the larger the node. The line between nodes represents the extent of keywords co-occurrence. (B) Overlay visualization, the occurrence of the blue words took place in the early stages, whereas the yellow words emerged more recently. The weights and normalization method for the visual analysis of VOSviewer were set to occurrences and LinLog/modularity, respectively. The minimum cluster size set at 20. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
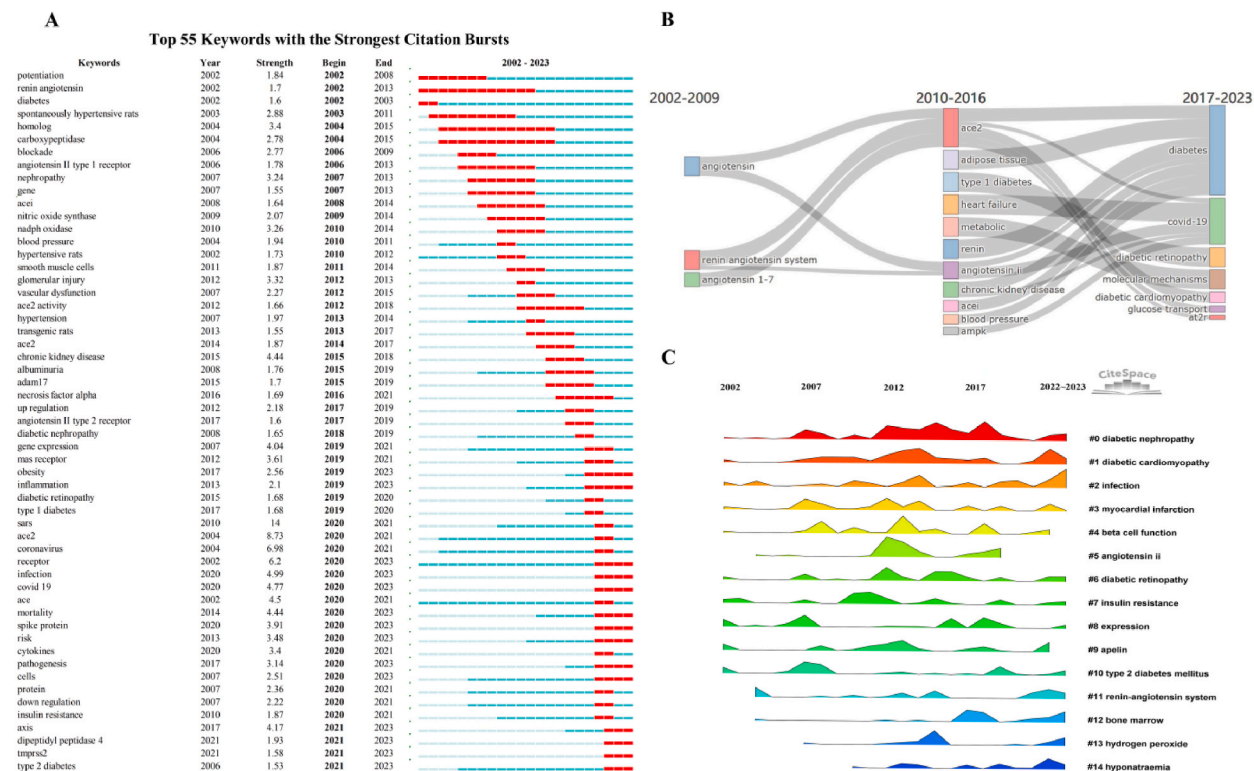
Fig. 7. Keyword burst detection and theme evolution on the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications research. (A) Detect the top 55 keywords with the strongest citation bursts using CiteSpace. (B) Visualization of theme evolution using Biblioshiny R, analysis field set as all author's keyword, weight index set as inclusion index weighted by word occurrences, time slices set as 2 cutting points (2009 and 2016). (C) Ridge plot of theme using CiteSpace, timespan set as 2002–2023 (slice length = 1), selection criteria set as top 50 per slice, LRF = 3.0, L/N = 10, LBY = 5, e = 1.0.

Table 5
The top 10 most cited publications in research of ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications from 2000 to 2023.

Rank	Publication Title (*review and #article)	Corresponding author	Year	Journal	TGCS	DOI
1	Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator ofthe Renin-Angiotensin System Celebrating the 20th Anniversary of the Discovery of ACE2*	Gavin Y. Oudit	2020	Circulation Research	1176	10.1161/circresaha.120.317015
2	The pivotal link between ACE2 deficiency and SARS-CoV-2 infection*	Paolo Verdecchia	2020	European Journal of Internal Medicine	710	10.1016/j.ejim.2020.04.037
3	Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes#	Jin-Kui Yang	2010	Acta Diabetologica	688	10.1007/s00592-009-0109-4
4	COVID-19 and diabetes mellitus: from pathophysiology to clinical management*	Michael A. Nauck	2020	Nature Reviews Endocrinology	520	10.1038/s41574-020-00435-4
5	ACE2: from vasopeptidase to SARS virus receptor#	Anthony J. Turner	2004	Trends in Pharmacological Sciences	391	10.1016/j.tips.2004.04.001
6	COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection*	Érika Bevilaqua Rangel	2021	European Journal of Clinical Microbiology & Infectious Diseases	322	10.1007/s10096-020-04138-6
7	Organ-specific manifestations of COVID-19 infection*	Meletios A. Dimopoulos	2020	Clinical and Experimental Medicine	284	10.1007/s10238-020-00648-x
8	Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets*	Cheng Zhang	2014	Nature Reviews Cardiology	278	10.1038/nrcardio.2014.59
9	Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19*	Gui-Qiang Wang	2020	Journal of Medical Virology	274	10.1002/jmv.25785
10	Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications*	Daniel J. Drucker	2020	Endocrine Reviews	272	10.1210/endrev/bnaa011

TGCS: total global citation score.

Table 6

The top 11 most co-cited references in research of ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications from 2000 to 2023.

Rank	Reference Title (*review and #article)	Corresponding author	Year	Journal	Citations	DOI
1	A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9#	Susan Acton	2000	Circulation Research	89	10.1161/01.res.87.5.e1
2	A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase#	Sarah R. Tipnis	2000	The Journal of Biological Chemistry	88	10.1074/jbc.M002615200
3	Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas#	Thomas Walther	2003	Proceedings of The National Academy of Sciences of The United States of America	69	10.1073/pnas.1432869100
4	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor#	Stefan Pöhlmann	2020	Cell	68	10.1016/j.cell.2020.02.052
5	Angiotensin-converting enzyme 2 is an essential regulator of heart function#	Josef M. Penninger	2002	Nature	62	10.1038/nature00786
6	Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase#	Peter Tummino	2002	The Journal of Biological Chemistry	52	10.1074/jbc.M200581200
7	Human recombinant ACE2 reduces the progression of diabetic nephropathy#	Gavin Y. Oudit	2010	Diabetes	46	10.2337/db09-1218
8	Glomerular localization and expression of Angiotensin-converting enzyme 2 and Angiotensin-converting enzyme: implications for albuminuria in diabetes#	Daniel Batlle	2006	Journal of The American Society of Nephrology	46	10.1681/ASN.2006050423
9	Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis#	W Timens	2004	Journal of Pathology	43	10.1002/path.1570
10	Angiotensin I-converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice#	Eric Lazartigues	2010	Diabetes	42	10.2337/db09-0782
11	Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease#	Andrew M. Herzenberg	2008	Kidney International	42	10.1038/ki.2008.497

4. Discussion

This study represents the first global bibliometric analysis focus on the ACE2/Ang 1–7/MasR axis in diabetes and its related microvascular complications, where invaluable insights are provided. Through bibliometric assessments and network visualizations, research trends over the last two decades have been explored, with significant engagement from journals, contributions by author, collaborations between institutions, involvement across countries/regions, and keywords dynamics. A notable increase in publications and TGCS was observed in 2020 and 2021, likely attributed to the heightened interest in ACE2 as a potential receptor for severe acute respiratory syndrome coronavirus during the COVID-19 pandemic [3,16]. An ongoing increase in both publications and citations annually has been recorded, reflecting a growing interest in this research filed, thereby suggesting its sustained importance and the potential for further studies. Notably, the highest citation papers are predominantly review articles, while research articles are most frequently cited references, indicating the field's substantial potential for further research advancements.

Research within this domain is globally dispersed, with publication output and citation metrics predominantly led by the United States, China, Canada and Brazil. Contributions are notably made by their respective institutions such as the University of Florida, Wake Forest University, and the University of Alabama at Birmingham in the United States; the University of Ottawa, the University of Alberta, and the University of Toronto in Canada; and Capital Medical University in China. Despite Kuwait not ranking within the top ten for publication volume, significant impact is imparts by their research, as evidenced by the meticulous scholarship of Professors Benter IF, Akhtar S, and Yousif MHM. At the core of the collaboration network, countries such as the United States, Italy, Germany, the United Kingdom, Canada, Brazil, China, and India are seen, each having collaborated on publications with at least six other countries/regions, thereby underscoring their considerable influence in this field. Collaborative relationship have been established by the United States with 22 countries/regions, most frequently with Canada (12 times), followed by Brazil (6 times), China (5 times), and Kuwait (4 times). European countries like Germany and Italy have also engaged in cross-continental collaborations, notably with Argentina, South Africa, and Australia respectively. Moreover, Egypt, located on the African continent, has been involved in collaborations with India, Portugal, Saudi Arabia and Iraq [17,18]. These findings highlight the establishment of an initial collaborative network across the five continents within this research field.

The analysis of authors demonstrated that significant progress in this research field has been driven by a select few, consistent with Lotka's law [11]. As per Price's law, those with more than two publications have been identified as core authors. In the collaboration network analysis of the ten most productive authors, it was found that various relationships exist, notably excluding Yang JK. These include links among Benter IF, Akhtar S and Yousif MHM; Raizada MK, Oudit GY, Grant MB and Santos SHS; as well as Soler MJ and

Burns KD. This indicates that these prolific authors recognise and collaborate with each other to further the field. The h-index, g-index, m quotient, m-index, and q^2 index are widely accepted indicators used to assess author productivity [10]. Benter IF, with the highest h-index, g-index, and the fourth highest m quotient, is characterised by a substantial publication volume and extensive citation reach, demonstrating the profound impact and quality of his research. The pathological and pharmacological mechanisms of Ang 1–7 in diabetic cardiovascular and erectile dysfunction have been extensively investigated by Benter IF et al. [19–30]. Raizada MK and Akhtar S, with g-index exceeding their h-index, highlight the significant citation of key papers, despite fewer publications. Yousif MHM consistently deliver balanced research output and paper quality. Pascual J and Riera M, with lower h-index and g-index but highest m quotient, produce high-quality, impactful work within shorter academic careers. In collaboration with Soler MJ, Pascual J and Riera M have extensively studied ACE2 and ADAM17's role in diabetic kidney disease [31–33]. Additionally, Raizada MK, ranked second in m quotient, has actively collaborated with Grant MB and Oudit GY in recent research, garnering significant attention. Furthermore, the author with the highest citation count, Oudit GY, possesses a significantly high m-index and q2 index, indicating that his papers garner above-average citations, thus exerting a greater impact compared to those of his peers. Collaborating with Reich HN, Patel VB, and Grant MB, Oudit GY investigated the effects of ACE2 gene intervention on diabetic nephropathy, retinopathy, and cardiovascular complications [34–40].

In the sphere of core journals within this field, minimal variation is observed in the publications they publish, highlighting the significant influence these journals have in their domain. A distinct preference for papers focusing on the journals focusing on the ACE2/Ang 1–7/MasR axis is demonstrated by journals specializing in diabetes, endocrinology, and broader interdisciplinary research. This axis is acknowledged as a critical protective factor in the development of diabetes and its microvascular complications [41]. It is anticipated that such journals will maintain a focus on research concerning advancements related to the ACE2/Ang 1–7/MasR axis, especially regarding diabetes and its microvascular complications.

Publications garnering the most citations typically represent the most pivotal research outcomes within a research field, serving to identify the hotspots or key developments therein. Among the top 10 screened publications, the highest global citation count is attributed to a review authored by Gheblawi M et al. [3], published in 2020 in *Circulation Research,* elucidating ACE2's role. Marking the 20th anniversary of ACE2's discovery, this review extensively discusses its discovery, biochemical actions, and essential role in cardiovascular disease, including its recent identification as the receptor for SARS-CoV-2. Remarkably, nine of the top 10 cited publications explore the link between coronavirus receptors and diabetes [3,16,42–48].

In identifying the most cited references, researchers are enabled to swiftly establish the theoretical background and empirical analysis of their papers. This study has identified the top 10 references, with the two most cited being seminal original articles. The first, "A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9" was published by Donoghue M et al. [4] in *Circulation Research* in 2000. The second, "A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase" published by Tipnis SR et al. [14] in *The Journal of Biological Chemistry* in the same year. These studies have been pivotal in elucidating the organismal characterization of ACE2 and have laid a crucial foundation for further research into the ACE2/Ang 1–7/MasR axis, particularly regarding diabetes and its microvascular complications.

Keyword co-occurrence analysis is employed to discern the principal themes and trends within a research field by examining how frequently keywords co-appear in the literature. When two or more keywords are often found together in one or several documents, a potential relationship or dependency between these themes is indicated. VOSviewer is used to automatically categorize keywords into clusters, guided by the strength and frequency of their co-occurrences. Each cluster's keywords are shown to co-occur frequently, suggesting their association with similar or interconnected research topics. In this study, VOSviewer analyzed author keywords appearing more than once, revealing four primary aspects of this research: the pathomechanisms of diabetic microvascular complications, the metabolic system, type 2 diabetes, and coronavirus infections.

To further explore the hotspots and trends in ACE2/Ang1-7/MasR axis research in diabetes and its microvascular complications, keyword bursts and theme evolution were analyzed. From 2002 to 2009, research literature frequently mentioned the renin-angiotensin system and Ang 1–7, especially in cardiovascular protection, were highlighted. Between 2010 and 2016, a marked increase in attention to ACE2 was observed, indicating a deeper understanding of its role in diabetes, particularly its critical function in generating Ang 1–7. The actions of angiotensin II, exploring its role in diabetes-related cardiovascular pathologies, were also extensively studied, signifying a refined focus from the overall renin-angiotensin system system to specific components. From 2017 to 2023, literature focus broadened to encompsss diabetes as a critical global healh issue. The emergence of COVID-19 during this period was link with diabetes research themes, examining the pandemic's impact on diabetic patients. Furthermore, there was a rise in studies on diabetic complications, notably retinopathy and cardiomyopathy, suggesting a growing interest in the disease's deeper mechanistic studies. The bibliometric analysis reveals an evolution in ACE2/Ang 1–7/MasR axis research, from initial broad discussions on angiotensins and the renin system to detailed investigations of ACE2 and Ang 1–7, and now to studies connecting it with diabetic complications and COVID-19. This evolution not only highlights a deepening scientific understanding but also reflects shifts in research interests and foci in response to global health changes.

Ridges plot of research themes can clearly show dynamic changes in thematic research over time, as illustrated by the 14 thematic clusters presented in Fig. 7C. Continued interest in Islet cell function (cluster#4) and insulin resistance (cluster#7), pivotal pathogenic mechanisms in diabetic microvascular complications, has been well documented. It has been shown that activation of the ACE2/Ang 1–7 axis enhances glucose metabolism and ameliorates insulin resistance [49–51]. Compared to wild type mice, ACE2-knockout mice exhibit greater vulnerability to pancreatic β-cell dysfunction induced by high-fat diets [52]. Furthermore, the ACE2/Ang 1–7/MasR axis contributes to improved glucose tolerance and insulin sensitivity by safeguarding pancreatic β cells, augmenting insulin secretion, optimizing glucose metabolism in adipose tissue, facilitating glucose uptake in skeletal muscle, and reducing hepatic gluconeogenesis

[6]. The expression (cluster#8) of ACE2/Ang 1–7/MasR axis components was frequently highlighted, underscoring the need for enhanced mechanistic studies in diabetes. Utilizing a variety of complementary techniques, the presence of ACE2, Ang 1–7, and MasR in both human and animal retinas has been established, primarily localizing in the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, and photoreceptor outer segments [53–56]. In individuals diagnosed with type 2 diabetes, an increase in ACE2 expression in the pancreas, liver, and adipose tissue has been observed [57]. Additionally, clinical and experimental studies have indicated that diminished ACE2 expression may contribute to the progression of diabetic renal injury [39,58,59]. Diabetic nephropathy (cluster#0), commonly leading to severe end-stage renal disease, is influenced by oxidative stress and pro-inflammatory pathways within the angiotensin II and its type 1 receptor axis. Research in the diabetic Akita mouse indicates that human recombinant ACE2 administration mitigates kidney injury, lowers blood pressure, and decreases NADPH oxidase activity. In vitro studies show human recombinant ACE2 enhances Ang 1–7 signaling, reducing angiotensin II levels [60]. Resistance training alters the renal renin-angiotensin system in diabetes, reducing inflammatory markers such as interleukins and cytokine-induced neutrophil chemoattractant-1 [51]. Olmesartan treatment in type 2 diabetes patients decreased urinary albumin excretion, linked to increased serum Ang 1–7 and ACE2 levels, suggesting their therapeutic potential in diabetic nephropathy [61]. However, Ang 1–7's short plasma half-life limits its clinical application, leading to the exploration of the lanthionine-stabilized Ang 1–7 (cyclic Ang 1–7) in experimental studies [62]. Cyclic Ang 1–7, used with lisinopril, shows superior antiproteinuric effects, reduces glomerular fibrosis and inflammation, and enhanced capillary density compared to lisinopril alone [62]. Retinopathy (cluster#6), a severe microvascular complication of diabetes leading to blindness, remains a significant concern. It has been shown that activating the ACE2/Ang 1–7/MasR axis may decrease the risk of retinopathy in diabetic patients [63]. Intravitreal injections of adeno-associated virus-ACE2 or Ang 1–7 have reduced retinal vascular leakage and inflammation triggered by diabetes, effectively preventing retinopathy [64]. Additionally, diabetes-induced gut bacterial dysregulation increases the synthesis of microbial peptides, which enter the bloodstream, reach the retina, and damage retinal vascular endothelial cells via the Toll-like receptor 2-mediated MyD88-ARNO-ARF6 signalling pathway, thereby exacerbating diabetic retinopathy [36]. ACE2, abundantly expressed in the gut and crucial for maintaining gut barrier integrity, has been the foucus of recent studies. Elevating enteral ACE2 to enhance gut barrier integrity has been shown to prevent retinopathy in type 1 diabetes [65]. Furthermore, O-GlcNAcylation modifications regulated by the ACE2/Ang1-7/MasR axis are believed to ameliorate diabetic retinopathy [66]. Bone marrow (cluster#12) dysfunction significantly influences diabetic retionpathy pathogenesis by impairing hematopoietic stem/progenitor cells, marked by increased proinflammatory cytokines secretion and reduced vascular reparative and circulating angiogenic cells (CD34$^+$ cells) populations [36]. Treating diabetic CD34$^+$ cells with Ang1-7 activates the renin-angiotensin system's protective mechanism, restoring their functionality through enhance nitric oxide levels, reduced reactive oxygen species, and improved mobility, thereby aiding retinal vascular repair [40,63]. A recent study has reported, intrathecal administration of Ang 1–7 attenuates streptozotocin-induced diabetic neuropathic pain, and this occurs through a mechanism involving spinal MasR and the inhibition of p38 MAPK phosphorylation [67].

ACE2 was identified in 2003 as a critical receptor for severe acute respiratory syndrome coronavirus [68]. With the emergence of the COVID-19 pandemic, interest in ACE2, especially its pivotal role in viral cell entry, was reignited (cluster#2). This receptor's significance is particularly notable in diabetic individuals, who are believed to have increased vulnerability to the virus. Research efforts have predominantly been directed towards adjusting the ACE2/Ang 1–7 axis to reduce cardiovascular risk in diabetic patients post-infection. Noteworthy is the surge in studies within the fields of diabetic nephropathy, diabetic cardiomyopathy (cluster#1 and #3), the adrenergic-angiotensin system (cluster#11), and hydponatraemia (cluster#14), highlighting the escalated awareness of these complications. Moreover, pandemic-era research has elucidated the intricate interactions between chronic conditions and disease challenges. These studies collectively enhance our understanding of the interplay between diabetes and coronaviruses, forming a solid foundation for the formulation of comprehensive public health strategies.

Several limitations inherent in this study must be acknowledged. Firstly, as a bibliometric analysis, the collection and processing of data heavily depended on software. Although not a substitute for systematic reviews, this approach offers valuable insights through syntheis of extensive data and visual perspectives. Secondly, the study focused exclusively on English-language publication from WoSCC database, potentially omitting valuable research. Given WoSCC's extensive coverage, this oversight is unlikely to significantly affect the overall trends. Lastly, due to the time lag in citation impact, some recent high-quality studies might be underestimated in their influence, necessitating future tracking and updates.

5. Conclusion

To summarize, this study highlights the growing importance of the ACE2/Ang 1–7/MasR axis in diabetes and its microvascular complications through comprehensive bibliometric analysis. It emphasizes the superiority of bibliometric techniques over traditional reviews and underscores the need for more advanced software tools for deeper and more accurate visual investigations. Ongoing research in this research field is crucial for furthering our understanding and driving scientific progress.

Declarations

Ethical statement

As there are no animal or human studies presented in this manuscript, including any potentially identifiable human images or data, ethical approval for this work is not required.

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Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

CRediT authorship contribution statement

Weiwen Hu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jian Tan:** Validation, Formal analysis, Data curation. **Yeting Lin:** Validation, Formal analysis, Data curation. **Yulin Tao:** Validation, Formal analysis, Data curation. **Qiong Zhou:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Abbreviations

ACE2: Angiotensin-converting enzyme 2
Ang 1–7: Angiotensin 1-7
MasR: Mas receptor
TLCS: Total local citation score
TGCS: Total global citation score
IF: Impact factor
WoSCC: Web of science core collection
COVID-19: Corona virus disease 2019
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2