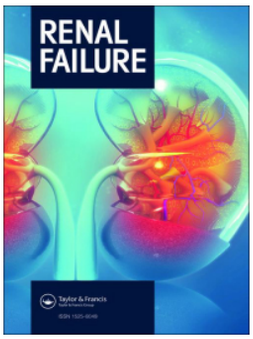

Renal Failure

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Jueyi Mao, Cuifang Li, Feifeng Wu, Yang Wang, Junquan Zhu & Chuan Wen (2024) The relationship between kidney disease and mitochondria: a bibliometric study, Renal Failure, 46:1, 2302963, DOI: 10.1080/0886022X.2024.2302963

To link to this article: https://doi.org/10.1080/0886022X.2024.2302963

Published online: 23 Jan 2024.

RENAL FAILURE
2024, VOL. 46, NO. 1, 2302963
https://doi.org/10.1080/0886022X.2024.2302963

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The relationship between kidney disease and mitochondria: a bibliometric study

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ABSTRACT

Background: Due to its highly reabsorptive function, the kidney is a mitochondria-dependent organ. Research on the association between mitochondria and kidney disease has always been a serious focus of researchers, with many publications. Bibliometrics is a secondary analysis of published literature that extracts relevant information to gain insights into hotspots and trends in the field. Through bibliometric analysis, we aimed to understand the development trends and hotspots in the field of research on the association between kidney disease and mitochondria.

Method: Three bibliometric mapping tools (Biblimetrix R Package, VOS Viewer, CiteSpace) were used to provide an overview of the literature and analyze the co-occurrence of keywords and reference citations.

Results: A total of 2672 relevant research articles were included. The co-occurrence network identified three clusters related to the association between mitochondria and kidney disease, including experimental methods, research mechanisms, and disease phenotypes. We found that research in this field has shifted from disease-level studies to mechanism-based studies, with the most prominent disease being diabetic nephropathy and the most prominent pathogenic mechanism being related to mitochondrial ROS production.

Conclusion: The bibliometric analysis provided a comprehensive understanding of the progress of research on the role of mitochondria in kidney disease, enriching the review literature in this field.

ARTICLE HISTORY
Received 19 June 2023
Revised 13 December 2023
Accepted 3 January 2024

KEYWORDS
Mitochondria; kidney diseases; bibliometrics

1. Introduction

Kidney diseases often appear in the form of syndromes in clinical settings, and there are many different pathological classifications. Common symptoms include abnormal urination, edema, fatigue, etc. Secondary kidney diseases can present as damage related to primary diseases. Kidney disease is classified in various ways, and chronic kidney disease alone affects about 10% of adults worldwide [1]. It is estimated that by 2040, chronic kidney disease will become the fifth leading cause of death globally, and it is also the fastest growing among all causes of death [2]. Kidney disease is a serious health problem in both developed and developing countries, causing a significant economic burden.

The study of kidney disease has advanced, and researchers have observed the role of mitochondria in this field. The kidneys are important organs for metabolism and rely heavily on mitochondria for energy. Mitochondrial abnormalities can affect energy metabolism, mitochondrial DNA leakage, and the release of ROS, which are all involved in the development of kidney disease. Researchers have made significant progress in this field and our bibliometrics analysis provides a visual representation of the research landscape including key terms, authors, countries, and institutions. This analysis aims to advance the research of mitochondrial involvement in kidney disease.

2. Materials and methods

Bibliometrics is a quantitative method used to describe and analyze the dynamics and progress of a discipline or research field. In this study, WOSCC (Web of science core collection) was used as the data source, and articles related to 'kidney disease' and 'mitochondria' were selected as the subject words for retrieval. Considering the different English expressions of subject words, the subject (Topic) retrieval item was used

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with the 'logical' (AND) connection. The retrieval formula was: TS = ('disease, kidney' OR 'kidney diseases' OR 'kidney disorder' OR 'kidney pathology' OR 'nephropathy' OR 'peri-nephritis' OR 'perirenal infection' OR 'renal disease' OR 'renal disorder' OR 'unilateral kidney disease') AND TS = ('mitochondria' OR 'mitochondrial contraction' OR 'mitochondrial property'). The search was limited to articles and reviews, written in English, with no time restrictions. The search result export date was set as January 30, 2023. Bibliometric tools such as VosViewer, Citespace, and the bibliometrix R package were used to visually analyze the articles based on authors, countries, institutions, and keywords. To ensure the reliability of data extraction, two team members collaborated on this task.

The co-citation analysis of literature has been determined through Cite Space 6.1.6 co-occurrence analysis. In the graphics of this software, each point represents an element, which can include authors, countries, institutions, and keywords, indicated by the size of the point.

Moreover, the connections between points represent the appearance or co-citation relationships, and the number of connections seems to increase the closeness of collaboration, representing the co-occurrence or co-citation strength. The parameter settings of Citespace are as follows: time slices (1999–2023), number of years per slice (1), term sources (all selected), selection criteria (top 50%), visualization (cluster view static, show merged network). The size of each point in the figure signifies the frequency of occurrence or citation. The thickness and color of circles around each point indicate the number of occurrences or citations and the corresponding period.

The cluster analysis of keywords is visualized using VosViewer 1.6.19. In this visualization, keyword elements are depicted as nodes in space, and the connections between nodes represent co-citation relationships between these elements. The elements are categorized, and their importance is represented by different colors, shapes, and sizes. In the co-citation graph, different points represent different keywords, and the size of the points corresponds to the quantity of those elements. The lines connecting the points signify co-citation relationships. Points and lines of different colors denote various clusters or time periods. The data retrieval process involves importing the data into VosViewer, selecting 'create map based on txt file word,' and then importing the search results from Web of Science (WOS). From the titles and abstracts, terms are extracted, and keywords that appear at least 15 times are retained. Afterward, any irrelevant words are manually removed to obtain co-occurrence results.

In the Bibliometrix R package, the visualization and analysis of literature authors, citation frequency, and countries are conducted. To do this, the necessary commands are run in RStudio after importing the compressed data.

For journal impact factors, the information is obtained from the 2022 Journal Citation Report (JCR). It is important to note that since all this data and information are derived from secondary sources available on the open database (WOSCC), informed consent and ethical approval are not required for this research.

3. Results

A preliminary search of 2746 articles was conducted, and after removing duplicates, 2672 articles were obtained. A total of 2672 papers were analyzed in this article, which came from 919 different journals with a time span from 1999 to present 2023-1-30. A total of 13436 authors participated in writing these papers. According to Figure 1, the literature in this field shows an increasing trend, with the fastest growth rate occurring between 17 and 21 years.

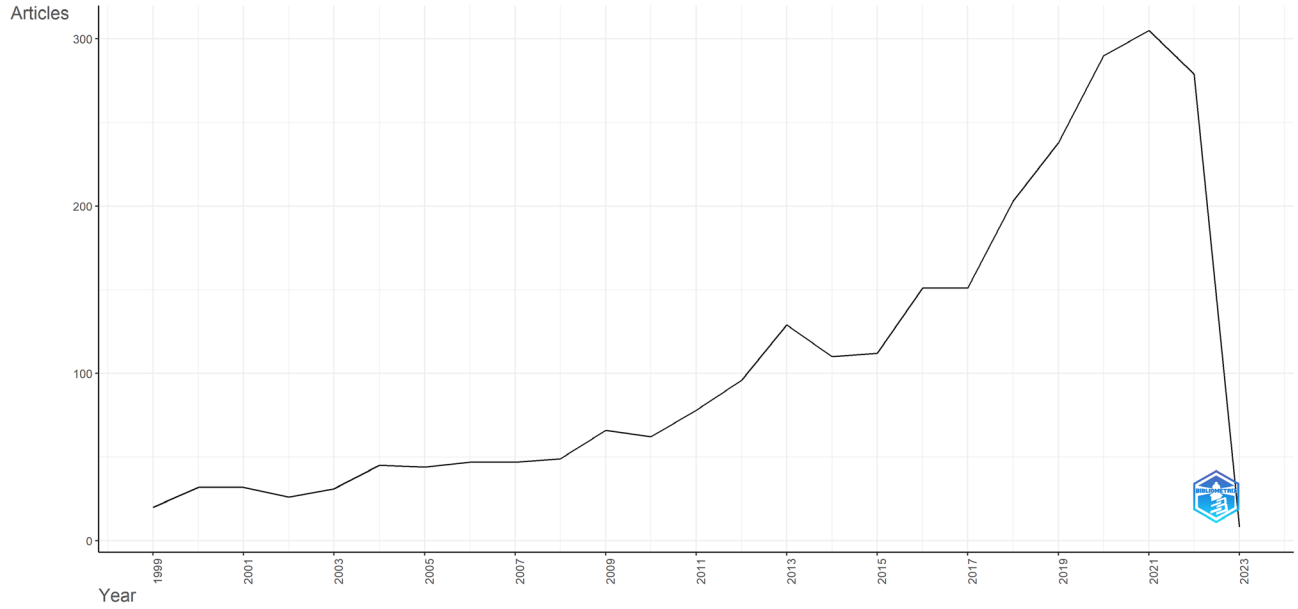

Figure 1. Annual scientific publication.

3.1. Authors, affiliation and countries

Contributions in the field of online mitochondria and kidney are from 67 countries, with the top five countries being China (657 papers, 592 as single country publications, SCP and 83 as multiple country publications, MCP), the United States (639 papers, 478 as SCP and 161 as MCP), Japan (199 papers, 156 as SCP and 43 as MCP), Italy (93 papers, 68 as SCP and 43 as MCP), and the United Kingdom (84 papers, 53 as SCP and 31 as MCP) (Figure 2). The top five publishing institutions are Central South University, Mayo Clinic, Nanjing Medical University, Southern Medical University, and the University of Florida, with three being from China and two from the United States, consistent with the national output (Figure 3).

The authors with the highest relevance in this field include Zhang Y, Li Y, Lerman LO, Liu Y, and Eirin A (Figure 4). The cooperation among authors, countries, and institutions is shown in Figure 5. The scholars with higher center degrees in research can be seen in Figure 6. The core journals in the field of mitochondria and kidney disease related to online literature were obtained based on Bradford's law (Figure 7; Table 1).

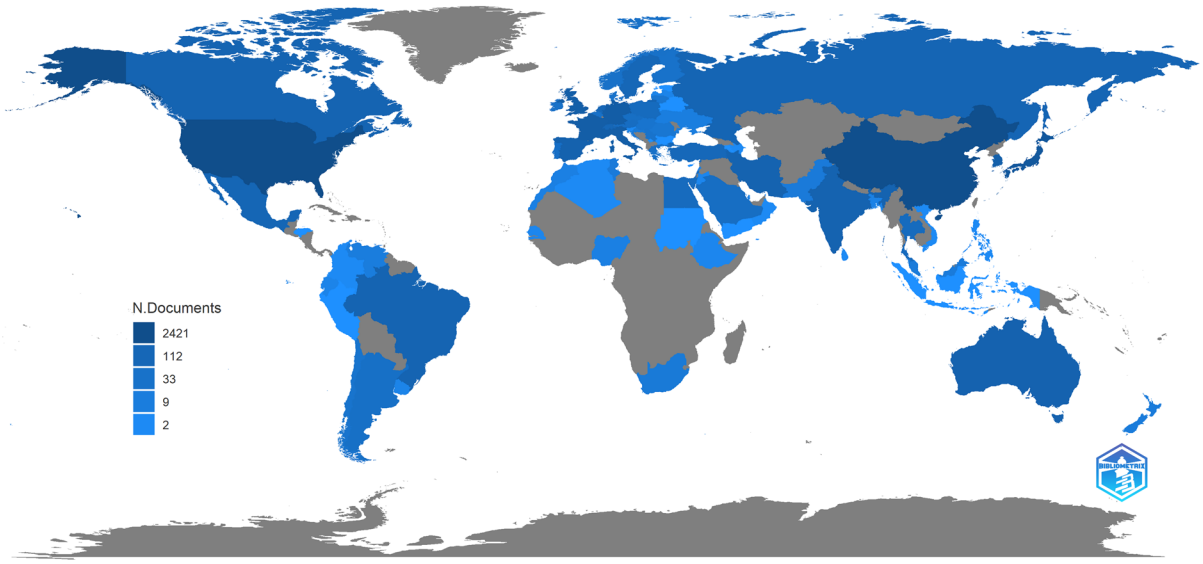

Figure 2. Country scientific production.

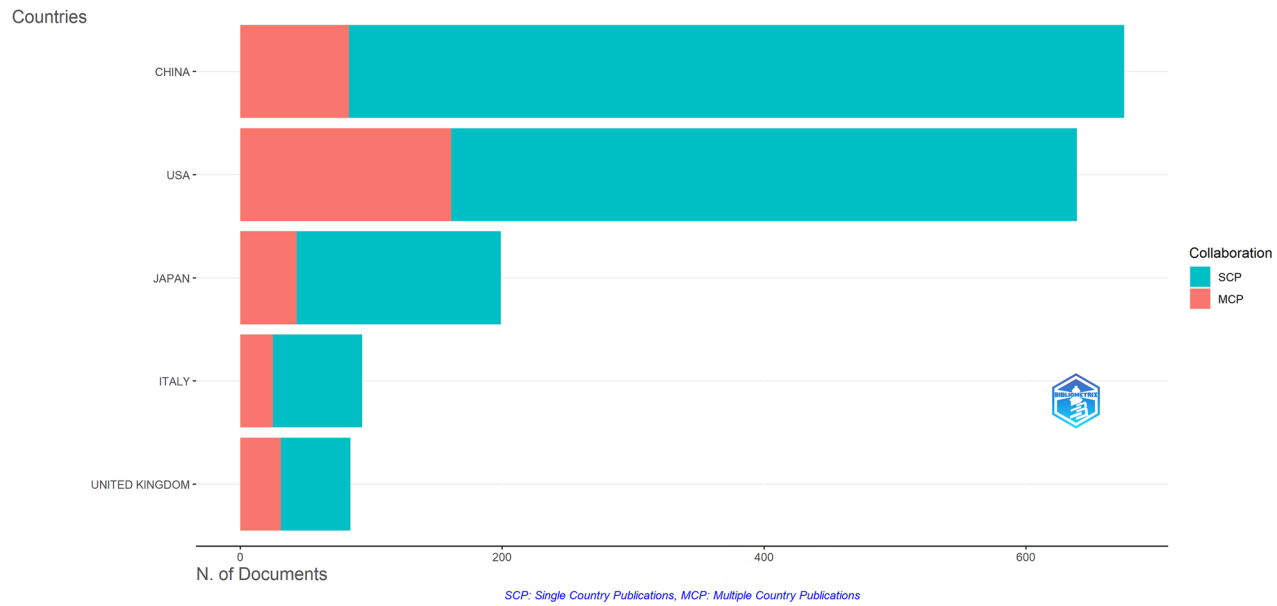

Figure 3. Corresponding authors countries.

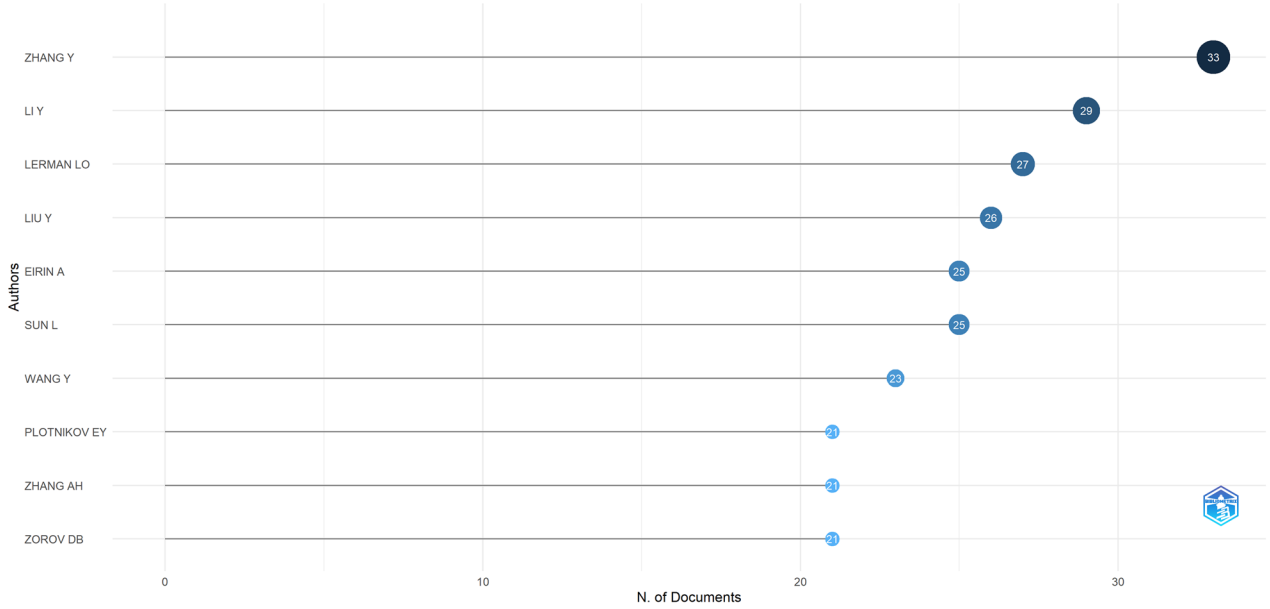

Figure 4. Most relevant authors.

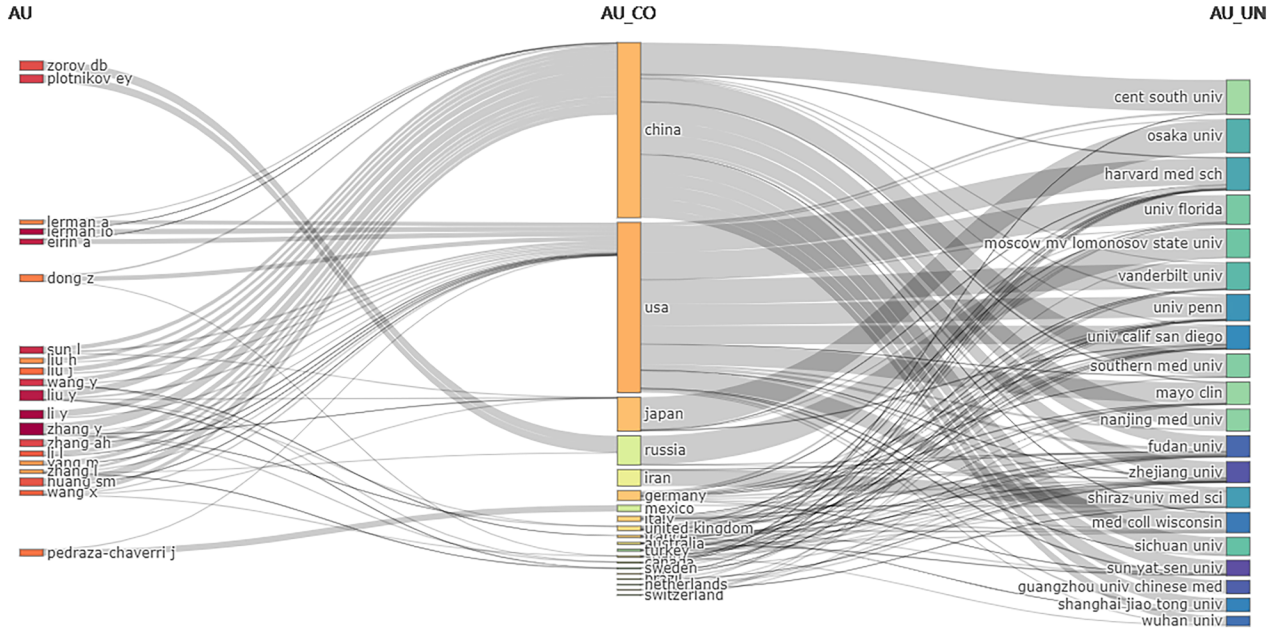

Figure 5. Author country and institution.

The top ten journals with the highest publication rate in the core area of the field are: AMERICAN JOURNAL OF PHYSIOLOGY-RENAL PHYSIOLOGY (4.091)/international journal of MOLECULAR SCIENCES (6.208)/kidney international (18.9)/plos one (3.75)/JASN (14.978)/OXIDATIVE MEDICINE AND CELLULAR LONGEVITY (7.31)/FREE RADICAL BIOLOGY AND MEDICINE (8.101)/SCIENTIFIC REPORTS (4.996)/BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (3.322)/FRONTIERS IN PHYSIOLOGY (4.755). Only two of these journals have an IF factor greater than 10, which indicates that the field has not received widespread attention and there are still many problems for us to explore. Among the 2672 references, the top ten most cited papers worldwide are listed in Table 2. It can be seen that in the study of the relationship between mitochondria and kidney disease, most of the background information comes from authoritative journals with high IF values.

3.2. Co-citation

Co-cited references refer to the references that are cited by two or more publications at the same time. Among the

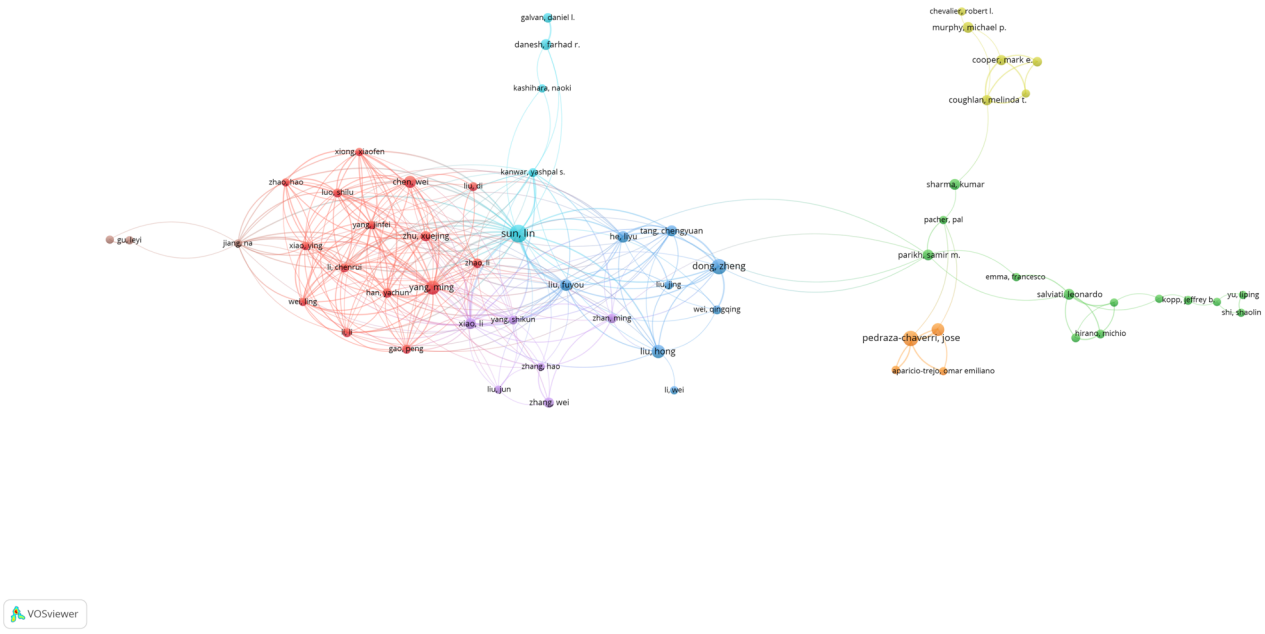

Figure 6. Collaborative connections among authors.

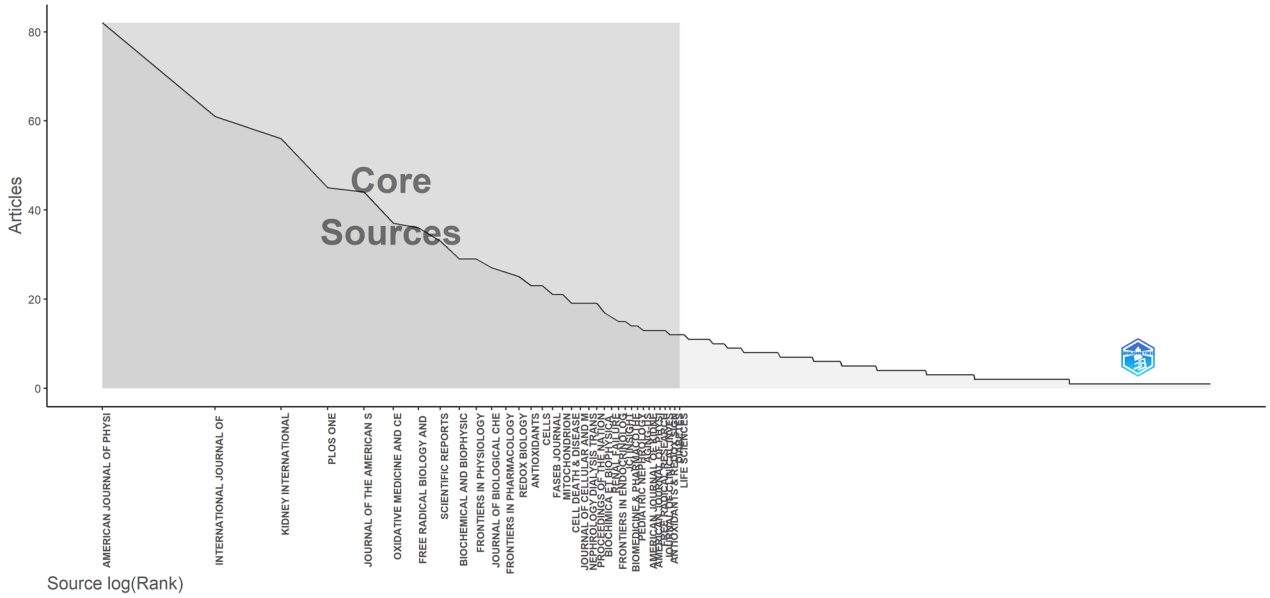

Figure 7. Core sources by Bradfords Law.

references cited in 2,672 literature, the top ten most cited references globally in relation to mitochondria and kidney disease are shown in Tables 2 and 3.

This indicates the main background and supplementation in research related to mitochondria and kidney disease.

According to the keyword clustering obtained by CiteSpace, the most prominent keywords in research related to mitochondria and kidney disease are 'oxidative stress', while the most prominent disease models are DN, AKI, and CKD models. From the graph, we can see the changes in the focus of this field. The earliest focus in this field was the peroxidation of kidney lipids and the release of oxygen free radicals in the physiological process of mitochondrial oxidative reactions. Subsequently, the role of the electron transfer system in mitochondrial respiration chains in kidney disease began to receive attention. In recent years, the roles of mitochondrial genes, mitochondrial function, and mitochondrial dynamics have gradually been recognized.

From changes in the keywords, we can see that most research in this field is done using *in vivo* experiments in

Table 1. The top ten journals with the highest publication rate.

	Sources	Articles
1	AMERICAN JOURNAL OF PHYSIOLOGY-RENAL PHYSIOLOGY	82
2	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	61
3	KIDNEY INTERNATIONAL	56
4	PLOS ONE	45
5	JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY	44
6	OXIDATIVE MEDICINE AND CELLULAR LONGEVITY	37
7	FREE RADICAL BIOLOGY AND MEDICINE	36
8	SCIENTIFIC REPORTS	33
9	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS	29
10	FRONTIERS IN PHYSIOLOGY	29

Table 2. The top ten most cited references.

	Paper	DOI	Total citations	TC per year
1	GIACCO F, 2010, CIRC RES	10.1161/CIRCRESAHA.110.223545	3144	224.57
2	WALLACE DC, 2005, ANNU REV GENET	10.1146/annurev.genet.39.110304.095751	2352	123.79
3	XIE Y, 2016, CELL DEATH DIFFER	10.1038/cdd.2015.158	1432	179.00
4	VIOLLET B, 2012, CLIN SCI	10.1042/CS20110386	1131	94.25
5	FERRUCCI L, 2018, NAT REV CARDIOL	10.1038/s41569-018-0064-2	972	162.00
6	FLIEGAUF M, 2007, NAT REV MOL CELL BIO	10.1038/nrm2278	854	50.24
7	JOMOVA K, 2011, J APPL TOXICOL	10.1002/jat.1649	813	62.54
8	SANDRI M, 2006, P NATL ACAD SCI USA	10.1073/pnas.0607795103	703	39.06
9	MOOTHA VK, 2003, CELL	10.1016/S0092-8674(03)00926-7	683	32.52
10	PEROCCHI F, 2010, NATURE	10.1038/nature09358	621	44.36

Table 3. Abbreviation table.

SCP	Single country publication
MCP	Multiple country publications
EVs	Extracellular vesicles
DN	Diabetic nephropathy
AKI	Acute kidney injury
CKD	Chronic kidney disease
ROS	Reactive oxygen species
SCP	Single country publication
mtDNA	Mitochondrial DNA
TFAM	Transferring mitochondrial-related proteins

mice. Currently, DN is the most studied disease in this field. The timeline and clustering of keywords can be seen in Figures 8–11.

4. Discussion

This study conducts a bibliometric analysis on existing research with keywords 'mitochondria' and 'kidney disease', aiming to explore the relevant information in this field. According to the results, most of the contributions to the research on the correlation between mitochondria and kidney disease come from developed countries, and it is encouraging to see that China, as a developing country, is included in the list as well. The relevant research is mainly concentrated in Europe, America, and East Asian countries. The field started in European and American countries and slowly, more and more developing countries are actively participating in the research of this field.

Keywords reveal the core theme and main content of an article, and the analysis of these keywords can reasonably describe research hotspots. In the results, we can see that 'reactive oxygen species, (ROS)' is a keyword that cannot be ignored. ROS is a byproduct of mitochondrial glycolysis, which is mainly produced by complex I and complex III in the respiratory chain [4]. When the activity of ROS is upregulated, it can further cause DNA (including nuclear and mitochondrial DNA) damage, lipid peroxidation, protein oxidation modification, cell aging, and eventually lead to inflammatory responses [5]. The upregulation of ROS activity has been observed in a series of kidney diseases (such as AKI, CKD, DN). Similarly, the production of ROS can be observed in ischemia–reperfusion injury of other organs (such as the liver, brain, etc.), and mitochondria may play a similar pathological role as in kidney diseases.

From a clustering perspective, mitochondria, as cell organelles, are involved in a wide and systematic range of pathophysiological processes. Although kidney diseases have been a focal point in the context of mitochondrial research, it's worth noting that other organs are mentioned in the keywords. This suggests that in diseases, mitochondrial abnormalities have a broad impact on high-energy-demanding organs like the brain, heart, liver, rather than being limited solely to the kidneys. Diabetes Nephropathy, as an endocrine system disorder, entails systemic and systematic pathophysiological changes throughout the body.

In the case of DN, mitochondrial research has garnered significant attention. This suggests that in systemic diseases characterized by kidney damage, mitochondria may play a vital and non-negligible role. Looking at the timeline, the focus of research on the relationship between the kidneys and mitochondria initially centered around patient-specific characteristics and the macroscopic concept of specific organs. With the advancement of experimental techniques, the focus shifted toward the microscopic level, with more research grounded in animal models, especially mice, to explore specific mechanistic actions.

In the field of molecular biology, specific functional proteins have received more attention than genetic material and mitochondria-related metabolic products. Research into how mitochondria specifically participate in the progression of kidney diseases has generated widespread interest. Based on the keywords clustering results, current research suggests two main aspects: the energy metabolism function of mitochondria and their involvement in nonspecific and specific immune regulation in inflammation. The former includes topics such as mitochondrial calcium metabolism, lipid metabolism, and fibrosis, while the latter encompasses the generation of reactive oxygen species and the leakage of mitochondrial

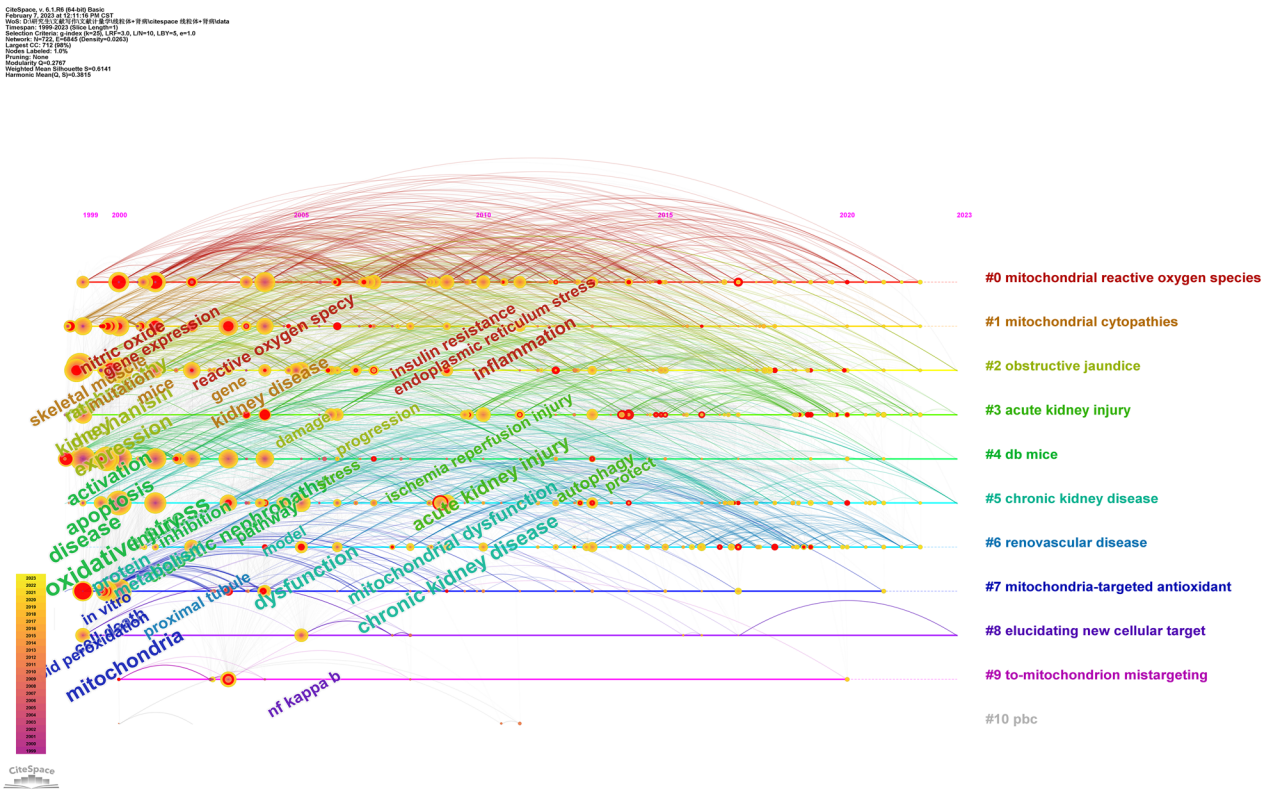

Figure 8. Keyword timezone map.

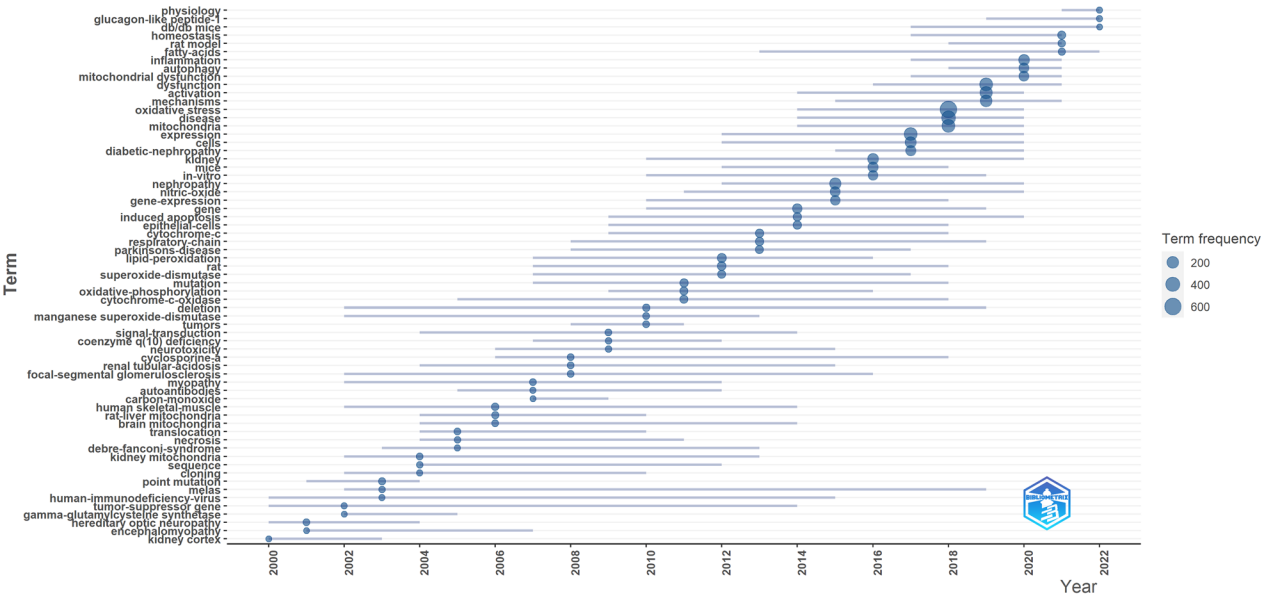

Figure 9. Trend topics.

DNA, which has attracted more research attention compared to the former.

'Diabetic nephropathy' is the most concerned disease, mainly because mitochondria are important sites for glucose metabolism, and the occurrence of diabetic nephropathy is closely related to abnormal glucose metabolism, making its correlation with mitochondria even higher. The intra-body environment of diabetic patients contains a single process induced by high blood sugar, which leads to abnormal NADH/NAD + ratio, and subsequently excessive production of superoxide (i.e. ROS) through the mitochondrial electron transport chain [6]. In addition, there are not many related keywords for emerging research directions in recent years, such as mitochondrial DNA (mtDNA) leakage [7–9],

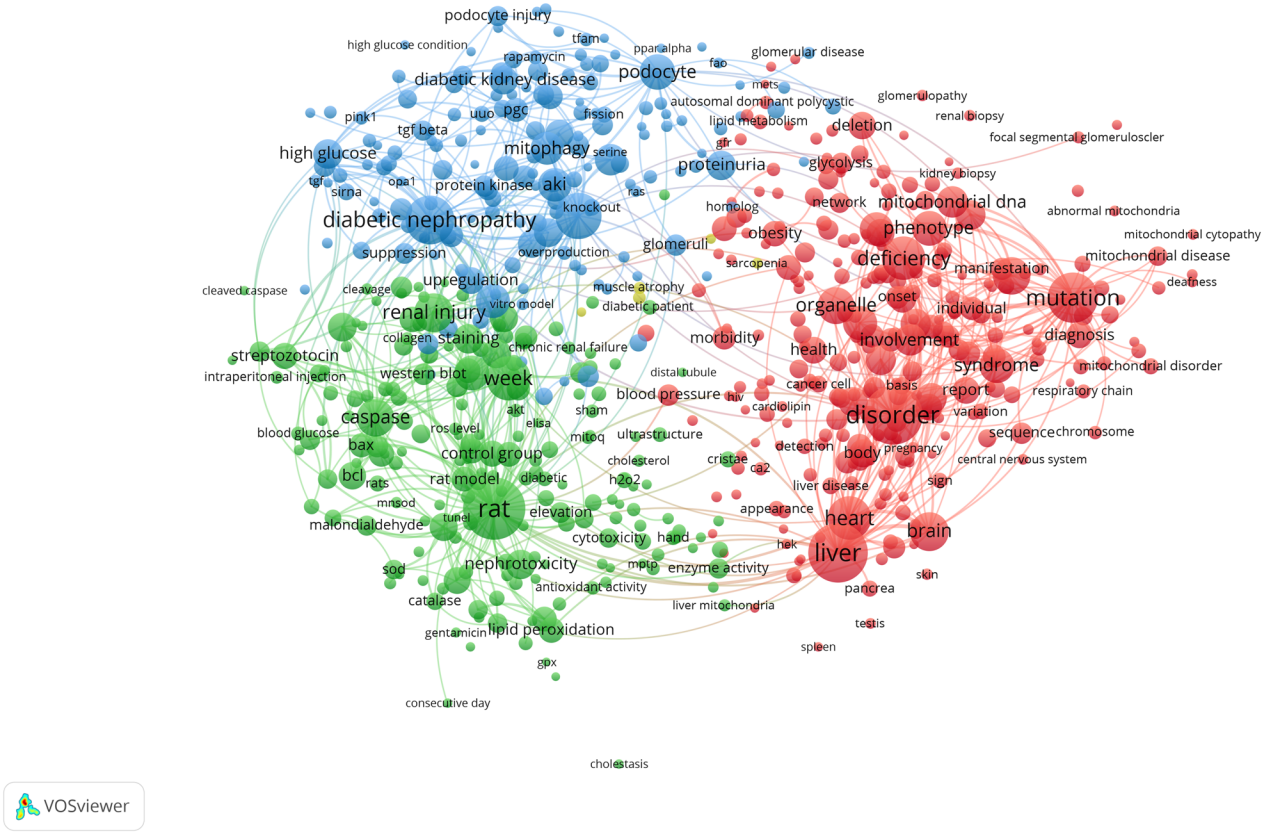

Figure 10. Cluster of keywords.

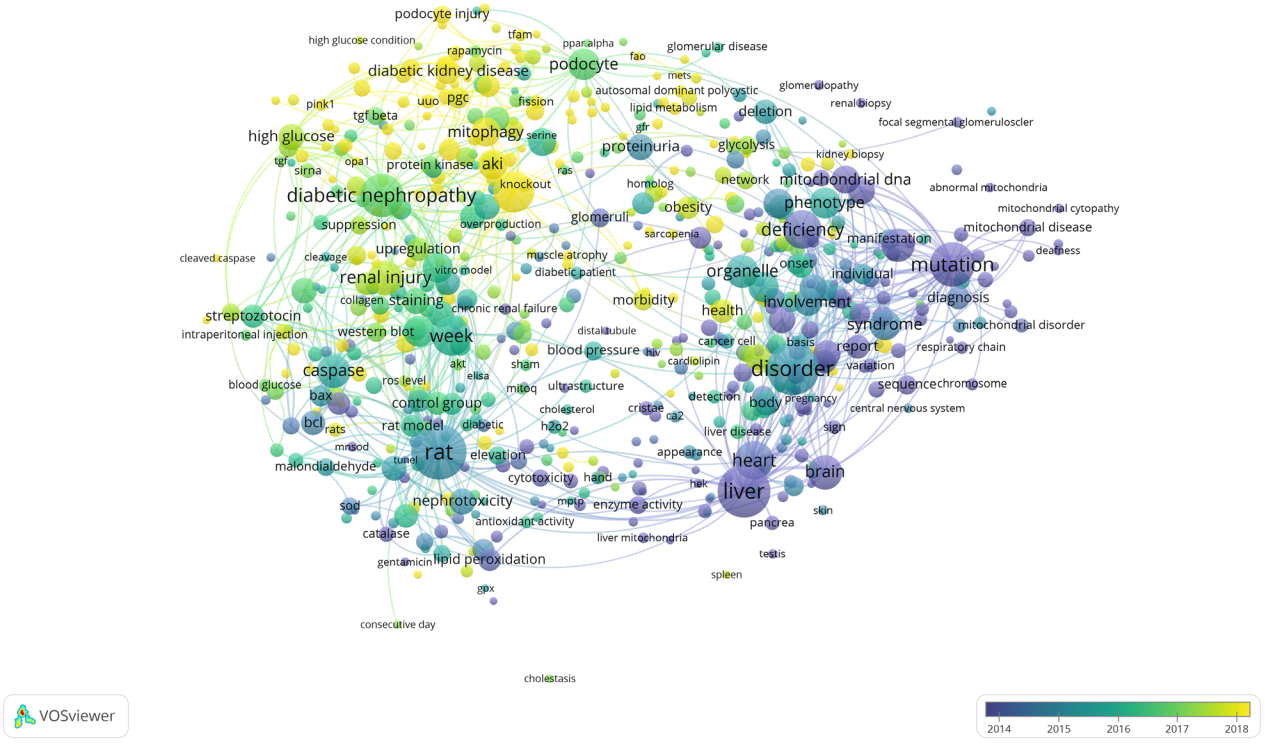

Figure 11. Emporal changes in keyword clustering.

mitochondrial dynamics [10,11], and the role of mitochondria in immunity [12,13]. This reminds us that mitochondria, as organelles, have been noticed by researchers, and the focus has gradually shifted from functional abnormalities to mechanisms and gradually refined in content.

The research hotspots of kidney disease and mitochondrial studies show different time distribution trends. The focus of kidney disease research has shifted from the pathological level to the molecular level, and the role of mitochondria has received varying degrees of attention from multiple perspectives. In the research process, interdisciplinary and holistic development characteristics are evident. In addition to focusing on how mitochondria participate in the progression of kidney disease, damaged mitochondria are also considered as therapeutic targets for kidney diseases. Studies on treatments are mostly in the preclinical phase, focusing on testing efficacy in experimental animals and investigating treatment mechanisms. Treatment methods involve earlier discoveries such as coenzyme Q10 (CoQ10) [14,15] and the popular extracellular vesicles (EVs) in recent years [16–18], as well as some traditional Chinese medicine treatments [19]. Using CoQ10 supplementation can significantly reduce the levels of various inflammatory factors (such as inflammatory mediators C-reactive protein, interleukin 6, and tumor necrosis factor-αNF-kappaβ) [20,21]. EVs may maintain the stability of mitochondrial genetic material by transferring mitochondrial-related proteins (TFAM), thereby inhibiting mtDNA leakage, repairing mitochondrial function, and ultimately achieving the goal of suppressing the occurrence and development of kidney diseases [18]. These results fully demonstrate that targeting mitochondria as a therapeutic target is a feasible direction for the treatment of kidney diseases.

In the most cited article, 'Oxidative Stress and Diabetic Complications' [22], the main argument emphasizes the progress in understanding the role of reactive oxygen species(ROS) generated by metabolism in the development of diabetic complications. Oxidative stress plays a vital role in the development of microvascular and cardiovascular complications in diabetes. The experiments discussed in this review indicate that metabolic abnormalities in diabetes lead to mitochondrial superoxide dismutase overexpression. This increased superoxide production is the central and primary mediator of diabetic tissue damage, leading to the activation of five pathways involved in the pathogenesis of complications, as well as the direct inactivation of two anti-atherosclerotic enzymes eNOS and prostacyclin synthase. This explains why diabetes leads to increased ROS generation, and also provides strong theoretical support for the study of kidney disease associated with diabetes and mitochondrial relevance.

In the second most cited article, 'A Mitochondrial Paradigm of Metabolic and Degenerative Diseases, Aging, and Cancer: A Dawn for Evolutionary Medicine' [23], the focus is on how mitochondrial DNA mutations affect our health. This review mentions that mtDNA may provide a direct link between our genes and the environment, helping our ancestors adapt to their surroundings and influencing our health today.

Kidney diseases are diverse and can be classified as acute or chronic, primary or secondary, and further differentiated based on pathological changes. Regardless of the type of kidney disease, it may eventually lead to renal failure and even death. Given the kidney's dependence on energy and the concurring increase of ROS activity, mtDNA leakage, changes in mitochondrial dynamics, etc., it is worth exploring the role of mitochondria in kidney disease progression. Numerous studies focus on targeting mitochondria in the treatment of kidney diseases; although most are animal-based, treating mitochondria is believed to have great potential as a therapeutic approach for kidney disease.

5. Conclusions

In our research, we have found that over the past decade, there has been an increasing focus on mitochondrial studies in regard to kidney disease. The role of mitochondria in kidney diseases is diverse. In many renal conditions, varying degrees of mitochondrial dysfunction have been observed.

On one hand, mitochondrial damage directly contributes to the onset of renal diseases: there is evidence suggesting that mitochondrial impairments directly lead to dysfunction in renal tubular reabsorption. On the other hand, mitochondria indirectly participate in the inflammatory responses of kidney diseases through some of their byproducts. In systemic immune disorders, mitochondrial dysfunction can also disrupt the immune system, such as the leakage of ROS, causing damage to surrounding cellular lipids and proteins. Additionally, mitochondrial DNA leakage into bodily fluids becomes an antigen, further exacerbating renal inflammation. Focusing on the relationship between mitochondrial dysfunction and kidney diseases from a fundamental perspective of energy metabolism helps us gain a deeper understanding of renal disorders and offers new avenues for the treatment of kidney conditions. Similarly, due to the widespread involvement of mitochondria, their connection to kidney pathology may be more pronounced in systemic diseases. Viewing mitochondria as a target for treatment and a research hotspot could provide us with a window into understanding kidney damage in some systemic diseases.

This article provides a comprehensive review of the progress and trends in research on kidney disease and mitochondria from the perspective of bibliometrics. This review helps to advance medical research in kidney disease and mitochondria by facilitating interdisciplinary collaboration, identifying the framework for mitochondrial kidney disease correlation studies, and promoting new perspectives for future research.

Funding

This work was supported by the National Natural Science Foundation of China under 338 Grant (No. 82070758).

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