Heliyon 9 (2023) e21952

Contents lists available at ScienceDirect

Heliyon

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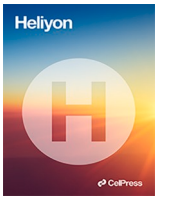

Current status and emerging trends of cardiac metabolism from the past 20 years: A bibliometric study

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A R T I C L E I N F O

Keywords:
Cardiac metabolism
Bibliometric
Glucose metabolism
Fatty acid oxidation
Heart failure

A B S T R A C T

Background: Abnormal cardiac metabolism is a key factor in the development of cardiovascular diseases. Consequently, there has been considerable emphasis on researching and developing drugs that regulate metabolism. This study employed bibliometric methods to comprehensively and objectively analyze the relevant literature, offering insights into the knowledge dynamics in this field.

Methods: The data source for this study was the Web of Science Core Collection (WoSCC), from which the collected data were imported into bibliometric software for analysis.

Results: The United States was the leading contributor, accounting for 38.33 % of publications. The University of Washington and Damian J. Tyler were the most active institution and author, respectively. The *American Journal of Physiology-Heart and Circulatory Physiology*, *Journal of Molecular and Cellular Cardiology*, *Cardiovascular Research*, *Circulation Research*, and *American Journal of Physiology-Endocrinology and Metabolism* were highly influential journals that published numerous high-quality articles on cardiac metabolism. Common keywords in this research area included heart failure, insulin resistance, skeletal muscle, mitochondria, as well as topic words such as cardiac metabolism, fatty acid oxidation, glucose metabolism, and myocardial metabolism. Co-citation analysis has shown that research on heart failure and in vitro modeling of cardiovascular disease has gained prominence in recent years and making it a research hotspot.

Conclusion: Research on cardiac metabolism is steadily growing, with a specific focus on heart failure and the interplay between mitochondrial dysfunction, insulin resistance, and cardiac metabolism. An emerging trend in this field involves the enhancement of maturation in human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) through the manipulation of cardiac metabolism.

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https://doi.org/10.1016/j.heliyon.2023.e21952
Received 21 April 2023; Received in revised form 30 October 2023; Accepted 1 November 2023
Available online 8 November 2023

1. Introduction

The heart requires a significant amount of energy for its daily functions, including excitation, contraction, relaxation, and the synthesis and breakdown of molecules. Proper functioning of the heart relies on the availability of adenosine triphosphate (ATP), which provides the necessary chemical energy [1]. ATP generation is fueled by various substrates, including fatty acids, glucose, ketone bodies, lactate, and amino acids [2]. Fatty acid oxidation supplies 40%–60 % of the heart's essential energy needs. Carbohydrate oxidation contributes 20%–40 % of the heart's energy, with glucose accounting for 20 % and lactate for 10 %. In contrast, ketone bodies and amino acids have a minor role in heart energy production, contributing only 10%–15 % and 1%–2%, respectively [3]. Fatty acid oxidation produces more energy than glucose metabolism, as each palmitic acid molecule produces 105 ATP molecules, while glucose only produces 31 ATP molecules. Nevertheless, the phosphate/oxygen (P/O) ratios (ATP and oxygen ration) of fatty acids and glucose are 2.33 and 2.58, respectively. This suggests that glucose is a more efficient fuel than fatty acids since it requires less oxygen to produce the same amount of ATP [4,5].

The metabolism of the heart is flexible and adapts to different factors such as substrate levels, energy needs, and hormone levels. Glucose and fatty acids compete for utilization, and an increase in fatty acid usage can limit glucose utilization and vice versa. In addition, the presence of ketone bodies affects the utilization of other substrates, particularly fatty acids [6,7]. Fuel substrates are absorbed by cells and catabolized in the cytoplasm. The resulting substrate then fluxes into the mitochondria for the citrate cycle and eventually proceeds to the electron transport chain (ETC) for oxidative phosphorylation to produce ATP. ATP is transported to meet the energy requirements of the creatine kinase (CK) system. Thus, cardiac energy production can be affected by the substrate concentration, expression of different enzymes involved in substrate metabolism, mitochondrial function, and CK system abnormalities [8]. Moreover, cardiac substrates have multiple functions, and abnormal substrate metabolism affects cell membrane components [9]. The accumulation of toxic intermediary metabolites can also impair cell function and activate relevant signaling pathways, leading to complex pathologies and ultimately causing cardiac dysfunction. Abnormalities in cardiac metabolism are observed in various diseases, including ischemic cardiomyopathy [10], arrhythmias [11], hypertension [12], obesity [13], diabetes mellitus [14], and heart failure [15]. However, whether these abnormalities are adaptive or non-adaptive is still a topic of debate.

The clinical application of drugs that regulate cardiac metabolism has shown promising effects in treating heart failure. For instance, sodium-glucose cotransporter-2 (SGLT2) inhibitors, which enhance ketone body oxidation [16,17] and trimetazidine, which inhibits fatty acid oxidation and promotes glucose oxidation [18], have demonstrated beneficial outcomes. These findings have increased a growing interest in the development and utilization of drugs that specifically target metabolic regulation.

Bibliometrics is an essential approach for assessing the significance and value of research [19]. It enables comparisons of research contributions from various countries, institutions, journals, and scholars, while also demonstrating the dynamic evolution of scientific inquiry through quantifiable assessments of associations and clusters of discoveries [20]. No bibliometric studies have been conducted on cardiac metabolism thus far. To address this research gap, we utilized CiteSpace, VOSviewer, and Scimago Graphica to analyze and visualize the existing literature on cardiac metabolism. The objective of this analysis was to enhance our comprehension of the field's knowledge base and identify hotspots and frontiers for further research.

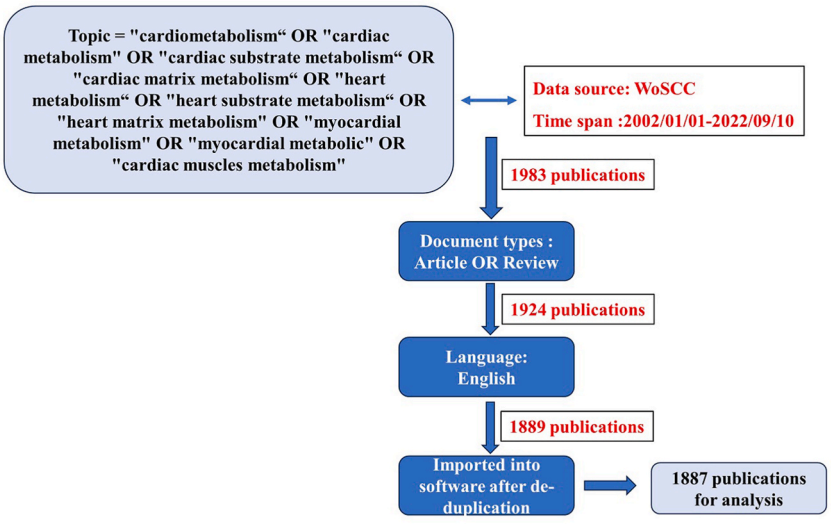

Fig. 1. The data collection flowchart.

2. Materials and methods

2.1. Data source and search strategy

We retrieved articles on the topic of cardiac metabolism from the Science Citation Index Expanded (SCI-E) of the Web of Science Core Collection (WoSCC). The search terms included "cardiometabolism," "cardiac metabolism," "cardiac substrate metabolism," "cardiac matrix metabolism," "heart metabolism," "heart substrate metabolism," "heart matrix metabolism," "myocardial metabolism," "myocardial metabolic," and "cardiac muscles metabolism." We limited the search to articles published in English between 2002 and 2022. Specifically, we focused on articles and review articles as the designated document types for this study. Our search yielded a total of 1889 papers. To ensure data accuracy and minimize biases caused by regular database updates, all searches were conducted on a single day, specifically September 10, 2022. The resulting findings, comprising comprehensive records and citation details, were exported as plain text files from WoSCC. These files, named download_xxx, were subsequently imported into the bibliometric software for thorough analysis. Fig. 1 illustrates the flowchart.

2.2. Data analysis

This study employed VOSviewer, CiteSpace, and Scimago Graphica for bibliometric analysis and information visualization. Microsoft Excel 2019 for tabulation. To ensure the accuracy of the analysis results, data cleaning procedures were implemented. These procedures included combining synonyms, unifying word cases, and standardizing singular and plural forms, as well as full names and abbreviations. Subsequently, a co-authorship analysis of authors, countries, and institutions was conducted, along with a keyword co-occurrence analysis.

CiteSpace 5.7. R5 was utilized to generate visualization maps for the analysis of co-authorship and co-cited references. Developed by Professor Chaomei Chen, CiteSpace is a Java-based bibliometric visualization software for analyzing the structure, modality, and dissemination of scientific knowledge [20]. In the visualization maps produced by CiteSpace, research items were represented by nodes composed of colored annual rings, indicating the frequency of occurrence over time. The wider the annual rings in a specific year, the more frequently the item appeared in that year. The node size reflected the frequency of citations or appearances. Nodes with special properties were highlighted in red and purple in the network visualization. Red rings also served as visual cues for any citation bursts within the corresponding time slice. Additionally, when betweenness centrality (BC) exceeded 0.1, the purple ring was an additional ring whose thickness was proportional to the BC value [21]. BC was a numerical measure used to assess the importance of a node in a network. It showed the percentage of shortest paths for a given node. Nodes with high BC values were considered hubs, as they connected different clusters within the network [22]. The thickness and frequency of lines in the visualization indicated the strength of interconnections between nodes, while line color depicted the chronological sequence of items [23].

The analysis of authors and keywords was conducted using VOSviewer. VOSviewer facilitates the creation and visualization of bibliometric maps in a user-friendly manner [24]. The visualization presented study items as labeled circles. The size and label of each circle indicated the importance of the item, while the circle's color represented its category.

Country distribution maps were displayed using Scimago Graphica.

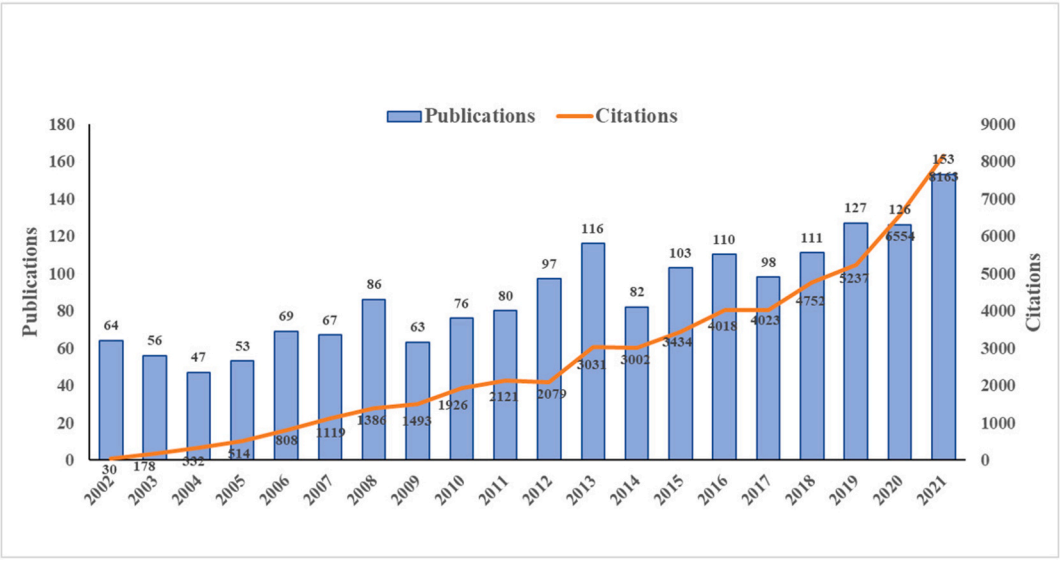

Fig. 2. The annual frequency of cardiac metabolism publications and citations. The number of publications and citations is represented by bar and line graphs, respectively, with the number for each year signaled above and below the respective graph.

3. Results

3.1. Trends in the evolution of publications and citations

The trends in the overall number of publications and citations on cardiac metabolism are shown in Fig. 2. Research on cardiac

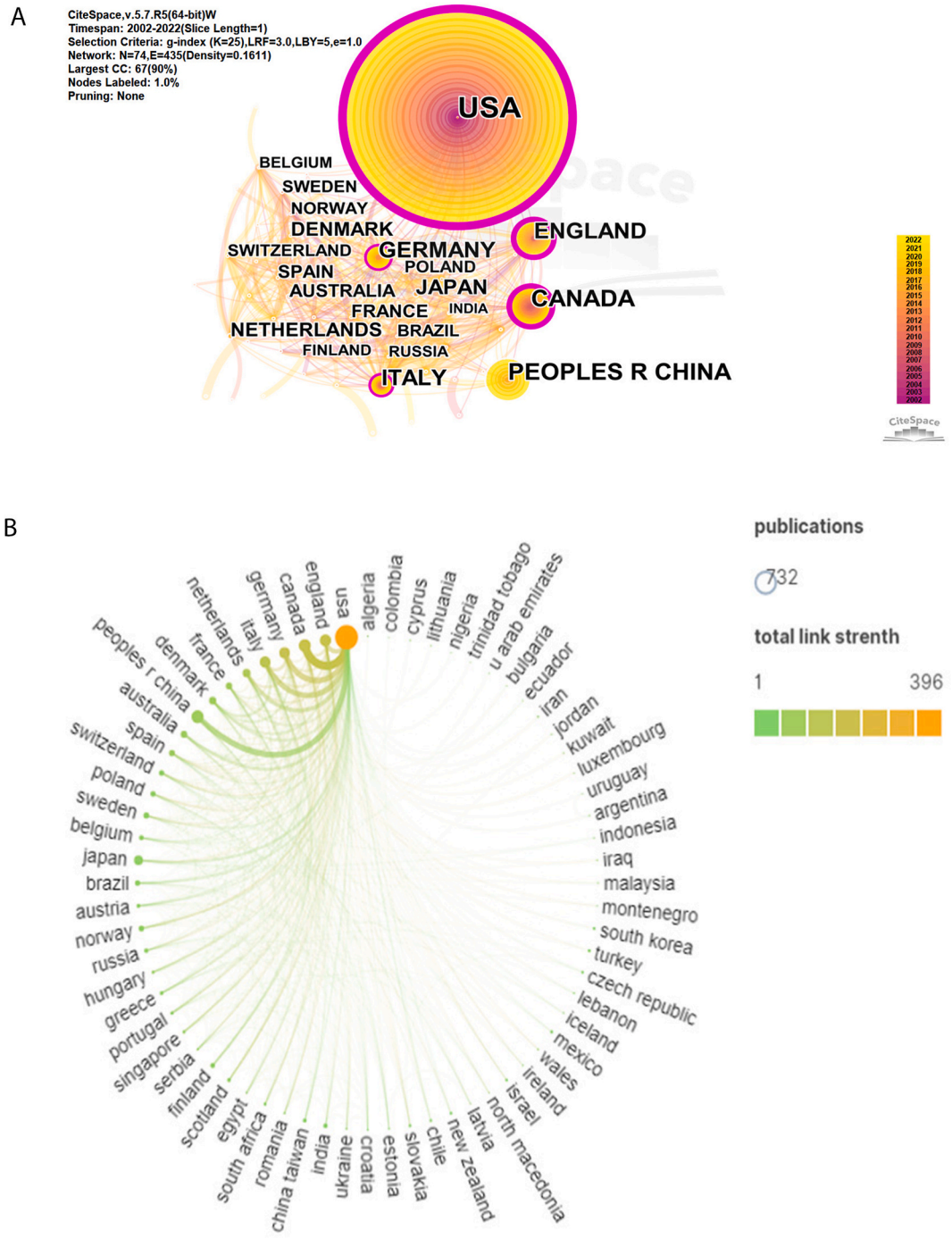

Fig. 3. The cooperation map of countries/regions with cardiac metabolism publications. **(A)** CiteSpace visualization map. In the upper-left corner of the network parameters, N is the node representing the research project, and E is the connection between the nodes, representing the cooperation between the projects; **(B)** Scimago Graphica visualization map. The nodes represent countries, and the lines represent the collaboration between countries. The node size and line thickness are proportional to the publication and collaboration strengths, respectively.

metabolism exhibited a wave-like evolution in annual publication trends spanning from 2002 to 2021. The previous 20 years were divided into three stages. During stage 1 (2002–2007), the average annual number of publications was 59, while Stage 2 (2008–2014) had an average annual number of publications of 86. In 2013, the first small peak in 20 years occurred, with 116 articles. However, in 2014, the number of published articles declined to 82. In Stage 3 (2015–2021), the average annual number of publications was 118, which was twice that of Stage 1, and this number further rose to 153 publications in 2021. Notably, the growth patterns of citations and publications exhibited inconsistency. Except for a slight decrease during individual years, the number of citations showed an annual increase.

3.2. Countries/regions and institutional statistics

The literature on cardiac metabolism originated primarily from 74 countries/regions (Fig. 3A) and 541 institutions (Fig. 4). The nodes of the United States (US) were the largest, indicating that the US had the largest number of publications in the field of cardiac metabolism than other countries/regions. Additionally, the thickest line connecting the US and Canada suggests a close collaboration between the two countries (Fig. 3B). Based on the presence of purple circles (BC $>$ 0.1) in their outermost chronologies (Fig. 3A), the US, Canada, England, Italy, and Germany could be identified as hubs, highlighting their significance in promoting international exchange and collaboration. Likewise, Washington University and Oxford University served as hubs connecting different institutions (Fig. 4).

According to Table 1, out of 1889 publications, the US ranked first with 724 (38.33 %) publications, Canada ranked second with 197 (10.43 %) publications, and China was the third most productive country with 193 (10.22 %) publications. These three countries collectively contributed to 58.98 % of the total publications. The H-index is a measure of the number h of papers published by a journal, author, or country that have been cited at least h times [25]. Both the H-index and number of citations per paper reflect the impact level of scientific research. Canada (51.42), the US (44.62), and Germany (38.83) were the three countries/regions with the highest number of citations per paper. The US had the highest H-index (92), followed by Canada (52) and England (41).

As presented in Table 2, the three institutions with the most published articles were Washington University (89 papers, 71.73 citations per paper, H-index of 36), the University of Oxford (68 publications, 34.84 average citations, H-index of 28), and the University of Alberta (39 publications, 83.41 average citations, H-index of 25).

3.3. Author analysis

As shown in Table 3, the most prolific author was Damian J. Tyler (35 articles), followed by M. E. Young ME (32 articles) and G. D. Lopaschuk (28 articles). The three authors with the highest number of average citations per article were E. Dale Abel (144.1), G. D. Lopaschuk (98.32), and H. Tegtmeyer (59.08). Furthermore, G. D. Lopaschuk, H. Tegtmeyer, S. Neubauer, and M. E. Young ranked among the top ten co-cited authors who were frequently cited together, with G. D. Lopaschuk having the highest co-citation intensity of 731. Fig. 5 shows the co-authorship network, which consists of multiple cooperative subnetworks centered around the mentioned

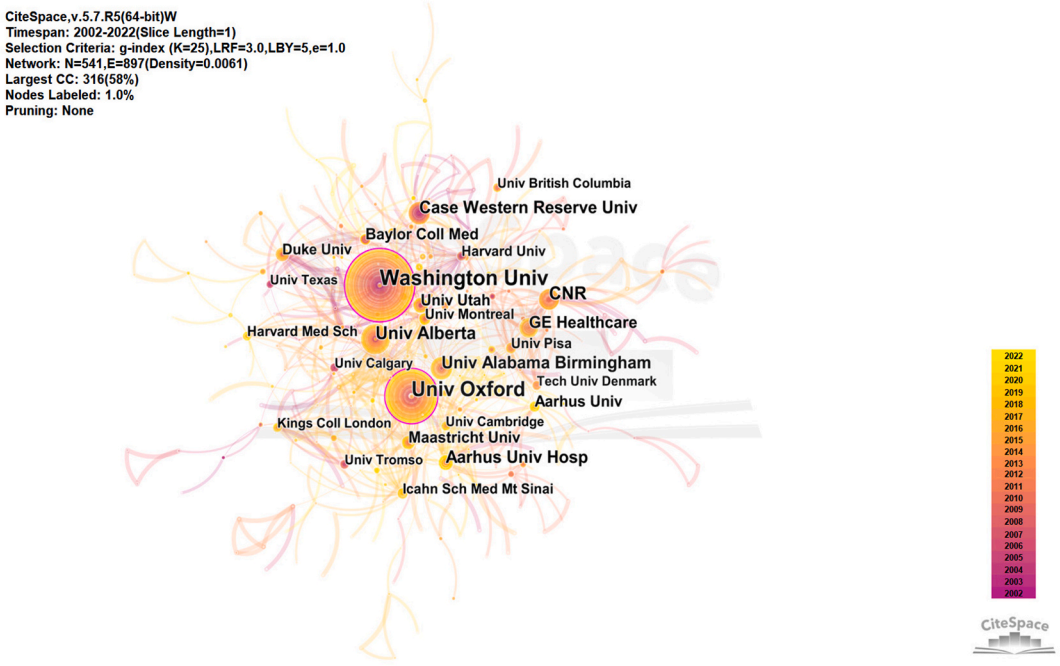

Fig. 4. CiteSpace visualization map of institutions with cardiac metabolism publications.

Table 1
Top ten most productive countries/regions in the field of cardiac metabolism.

Rank	Country/Region	Quantity	Percentage (N/1889)	Total Citations	Average Citations	H-index	Centrality
1	UNITED STATES	724	38.33	32,307	44.62	92	0.4
2	CANADA	197	10.43	10,130	51.42	52	0.25
3	PEOPLES R CHINA	193	10.22	2738	14.19	25	0.01
4	ENGLAND	175	9.26	6049	34.57	41	0.21
5	ITALY	155	8.21	5924	38.22	40	0.1
6	GERMANY	151	7.99	5864	38.83	37	0.11
7	JAPAN	107	5.66	1740	16.26	21	0.04
8	NETHERLANDS	83	4.39	2886	34.77	27	0.08
9	DENMARK	67	3.55	978	14.6	18	0.01
10	FRANCE	57	3.02	1960	34.39	24	0.07
10	AUSTRALIA	57	3.02	1754	30.77	22	0.03

Table 2
Top ten institutions performing studies on cardiac metabolism.

Rank	Institution	Country/Region	Quantity	Total citations	Average citations	H-index	Centrality
1	Washington Univ [a]	United States	89	6384	71.73	36	0.14
2	Univ Oxford [b]	England	68	2369	34.84	28	0.11
3	Univ Alberta [c]	Canada	39	3253	83.41	25	0.09
4	National Research Council (CNR)	Italy	35	1565	44.71	17	0.08
5	Case Western Reserve Univ [d]	United States	33	2386	72.3	19	0.05
6	Univ Alabama Birmingham [e]	United States	33	1080	32.73	20	0.06
7	Aarhus Univ Hosp [f]	Denmark	30	290	9.67	10	0.06
8	GE Healthcare	Global company	27	900	33.33	14	0.02
9	Aarhus Univ [g]	Denmark	21	192	9.14	9	0.02
10	Baylor Coll Med [h]	United States	21	1063	50.62	14	0.04
10	Maastricht Univ [i]	Netherlands	21	1063	50.62	14	0.08
10	Univ Utah [j]	United States	21	2513	119.67	19	0.03

[a] University of Washington.
[b] University of Oxford.
[c] University of Alberta.
[d] Case Western Reserve University.
[e] University of Alabama at Birmingham.
[f] Aarhus University Hospital.
[g] Aarhus University.
[h] Baylor College of Medicine.
[i] Maastricht University.
[j] The University of Utah.

Table 3
Top ten authors and co-cited authors who publish cardiac metabolism studies.

Rank	Author	Counts	Citations	Average citations	Country	Institution	Co-author	Co-citation
1	Tyler, Damian J	35	1212	34.63	England	Univ Oxford	Lopaschuk, GD	731
2	Young, ME	32	1579	49.34	United States	Univ Alabama Birmingham	Stanley, WC	528
3	Lopaschuk, GD	28	2753	98.32	Canada	Univ Alberta	Taegtmeyer, H	512
4	Taegtmeyer, H	26	1536	59.08	United States	UTHealth [a]	Neubauer, S	418
5	Neubauer, S	23	843	36.65	England	Univ Oxford	Young, ME	298
6	Clarke, Kieran	22	1045	47.5	England	Univ Oxford	Finck, BN	284
7	Aasum, Ellen	21	1236	58.86	Norway	UiT [b]	Schroeder, MA	226
8	Abel, E Dale	20	2882	144.1	United States	U-Iowa [c]	Kolwicz, SC	215
9	Dyck, Jason RB	20	1149	57.45	Canada	Univ Alberta	Opie, LK	206
10	Gropler, Robert J	19	709	37.32	United States	Washington Univ	Doenst, T	206

[a] The University of Texas Health Science Center at Houston.
[b] University of Tromsø - The Arctic University of Norway.
[c] University of Iowa.

authors. Scholars within the subnetwork demonstrated strong academic connections, while cooperative relationships with different strengths were observed outside the subnetwork. As shown in Fig. 5, Damian J. Tyler, S. Neubauer S, and Kieran Clarke had a close collaboration, whereas H. Tegtmeyer and E. Dale Abel had the closest collaboration. Additionally, M. E. Young collaborated closely with Jason R. B. Dyck.

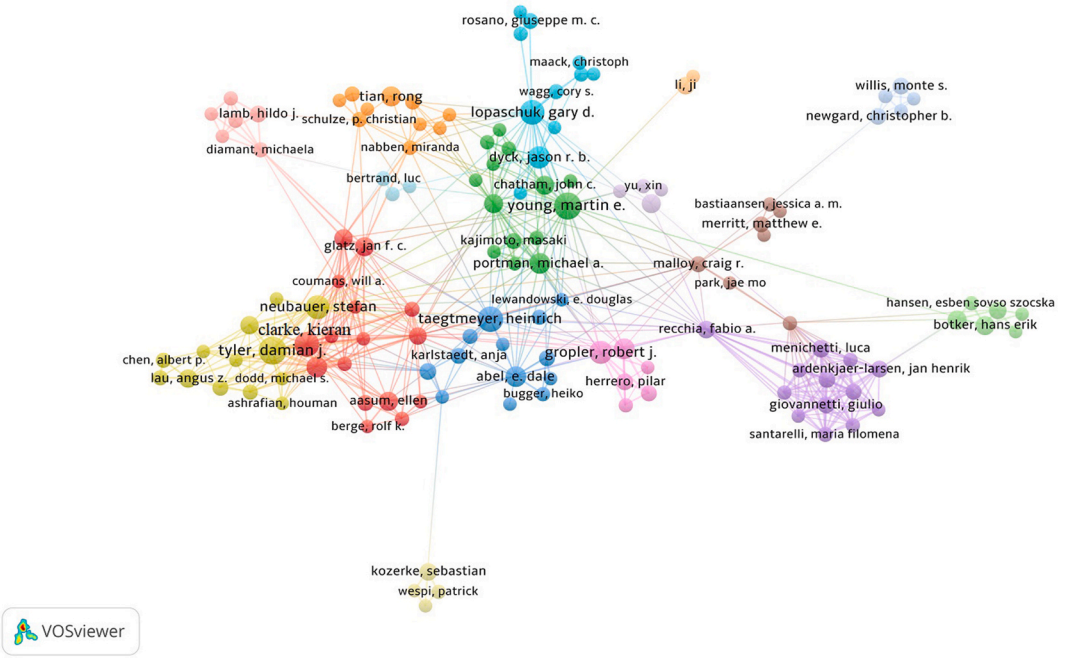

Fig. 5. VOSviewer visualization map of authors of cardiac metabolism publications. Nodes represent authors, and the node size is proportional to the number of articles published. The closer two nodes are, the better their cooperation. Nodes of the same color belong to the same cluster, indicating a high degree of homogeneity.

Table 4
Top ten journals in terms of publications and citations.

Rank	Journal	Publications	IF (2021)	JIF quartile	Journal	Total citation	Average citation	IF (2021)	JIF quartile
1	AM J PHYSIOL-HEART C [a]	94	5.125	Q2	CIRC RES[b]	4298	134.31	23.213	Q1
2	J MOL CELL CARDIOL[c]	60	5.763	Q2	AM J PHYSIOL-HEART C[a]	3340	35.53	5.125	Q2
3	CARDIOVASC RES[d]	43	13.081	Q1	J MOL CELL CARDIOL[c]	2427	40.45	5.763	Q2
4	CIRC RES[b]	32	23.213	Q1	J AM COLL CARDIOL[e]	2289	120.47	27.203	Q1
5	MAGN RESON MED [f]	31	3.737	Q2	CARDIOVASC RES[d]	2096	48.74	13.081	Q1
6	Plos one	30	3.752	Q2	J CLIN INVEST[g]	1866	169.64	3.93	Q1
7	J NUCL CARDIOL[h]	27	3.872	Q2	Circulation	1725	101.47	39.918	Q1
8	J AM HEART ASSOC[i]	26	6.106	Q2	Diabetes	1531	95.69	9.337	Q1
9	NMR BIOMED[j]	25	4.478	Q1	P NATL ACAD SCI USA[k]	1429	129.91	12.779	Q1
10	AM J PHYSIOL-ENDOC M [l]	24	5.96	Q1	AM J PHYSIOL-ENDOC M[l]	900	37.5	5.96	Q1
10	CURR PHARM DESIGN[m]	24	3.31	Q3					

[a] American Journal of Physiology-Heart and Circulatory Physiology.
[b] Circulation Research.
[c] Journal of Molecular and Cellular Cardiology
[d] Cardiovascular Research
[e] Journal of The American College of Cardiology.
[f] Magnetic Resonance in Medicine.
[g] Journal Of Clinical Investigation
[h] Journal of Nuclear Cardiology
[i] Journal of The American Heart Association
[j] Nmr in Biomedicine
[k] Proceedings of The National Academy of Sciences of The United States of America
[l] American Journal of Physiology-Endocrinology and Metabolism.
[m] Current Pharmaceutical Design

3.4. Journal analysis

Table 4 shows the top ten journals by publication and citation. The impact factor (IF) and quartiles of journals were based on the 2021 Journal Citation Report (JCR). The *American Journal of Physiology-Heart and Circulatory Physiology* (IF 5.125, Q2; 94 articles), *Journal of Molecular and Cellular Cardiology* (IF 5.763, Q2; 60 articles), and *Cardiovascular Research* (IF 13.081, Q1; 43 articles) had the most publications. The majority of the top ten journals in terms of publications had an impact factor ranging from 3 to 6, and most of them fell into the second quartile of their JCR category (Q2). Among the top ten journals in terms of total citations, 80 % were in the highest quartile score (Q1) of their JCR category, and 50 % had an impact factor of ten or higher. The journals that ranked among the top 10 in terms of both publications and citations were the *American Journal of Physiology-Heart and Circulatory Physiology* (IF 5.125, Q2), *Journal of Molecular and Cellular Cardiology* (IF 5.763, Q2), *Circulation Research* (IF 23.213, Q1), and *American Journal of Physiology-Endocrinology and Metabolism* (IF 5.96, Q1). The *Journal of Clinical Investigation* (IF 3.93, Q1) had the highest average number of citations, with 169 citations per article, followed by *Circulation Research* (IF 23.213, Q1; 134.31 citations per article) and *Proceedings of the National Academy of Sciences of the United States of America* (IF 12.779, Q1; 129.91 citations per article).

3.5. Co-cited reference analysis

Small and Marshakova introduced the concept of co-citation analysis in 1973 [26]. Co-citation refers to the simultaneous citation by one or more corresponding papers. The timeline view of reference co-citations shows the number of publications in each cluster, and the cluster that contains more publications indicates its importance. The CiteSpace clustering tag addition method was used to extract terms from the title, keywords, or abstract of the referenced literature to give names to the clusters of co-citations in the network. In this study, the WoSCC data on cardiac metabolism were classified into a total of 15 clusters (Fig. 6). The largest cluster was named #0 (failing heart), indicating that substantial research on “failing hearts " cited the literature in this cluster. The content of cluster #0 (failing heart) was similar to that of cluster #4 (heart failure). However, cluster #4 was studied before 2010, whereas cluster #0 was studied after 2010 and is ongoing. Currently, research is underway on cluster #0 (failing heart) and cluster #11 (disease modeling).

As shown in Table 5, the study by Aubert et al. (2016) published in *Circulation* [27] was the most co-cited reference, with 59 co-citations. This was followed by the studies published by Lopaschuk et al. (2010) in *Physiology Reviews* [28] and Bedi et al. (2016) in *Circulation* [29], with 58 and 48 co-citations, respectively. It is worth noting that seven of the top ten co-cited references belonged to cluster #0, highlighting its significance in the field of cardiac metabolism.

3.6. Keywords analysis

Table 6 lists the top ten keywords. The keywords with the highest frequencies were as follows: “cardiac metabolism” (445), “fatty acid oxidation” (443), “heart failure” (440), “glucose metabolism” (261), “myocardial metabolism” (251), “energy metabolism” (184), “insulin resistance” (178), “mitochondria” (178), “gene expression” (145), and “skeletal muscle” (138).

Fig. 7 shows ten clusters, six of which were large. The red cluster was the largest, with representative keywords that included “myocardial metabolism”, “ischemia”, “reperfusion”, “myocardial ischemia”, and “reperfusion injury”, followed by the green cluster,

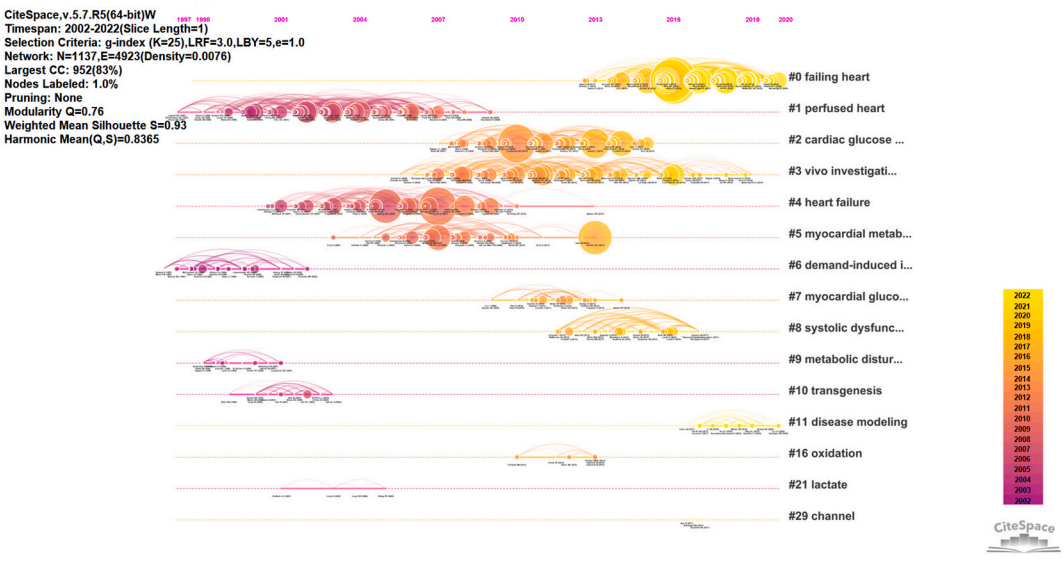

Fig. 6. A timeline view of co-citation references on cardiac metabolism. The nodes represent the publications, and the node size is proportional to the co-citation intensity. Publications with the same clusters are displayed on the same horizontal line, and the document's time is displayed at the top. Clusters are numbered in order of descending size, where the more members the cluster contains, the smaller the cluster number.

Table 5
Top ten co-cited cardiac metabolism references.

Rank	Reference	Type	Co-citation	In cluster
1	Aubert G, 2016, CIRCULATION, V133, P698, DOI 10.1161/CIRCULATIONAHA.115.017355 [27]	Article	59	#0
2	Lopaschuk GD, 2010, PHYSIOL REV, V90, P207, DOI 10.1152/physrev.00015.2009 [28]	Review	58	#2
3	Bedi KC, 2016, CIRCULATION, V133, P706, DOI 10.1161/CIRCULATIONAHA.115.017545 [29]	Article	48	#0
4	Neubauer S., 2007, NEW ENGL J MED, V356, P1140, DOI 10.1056/NEJMra063052 [30]	Review	46	#4
5	Stanley WC, 2005, PHYSIOL REV, V85, P1093, DOI 10.1152/physrev.00006.2004 [31]	Review	46	#4
6	Doenst T, 2013, CIRC RES, V113, P709, DOI 10.1161/CIRCRESAHA.113.300376 [32]	Review	41	#2
7	Kolwicz SC, 2013, CIRC RES, V113, P603, DOI 10.1161/CIRCRESAHA.113.302095 [33]	Review	33	#5
8	Jia GH, 2018, CIRC RES, V122, P624, DOI 10.1161/CIRCRESAHA.117.311586 [34]	Review	29	#0
9	Zinman B, 2015, NEW ENGL J MED, V373, P2117, DOI 10.1056/NEJMoa1504720 [35]	Article	29	#0
10	Bertero E, 2018, NAT REV CARDIOL, V15, P457, DOI 10.1038/s41569-018-0044-6 [36]	Review	27	#0
10	Finck BN, 2002, J CLIN INVEST, V109, *P*121, DOI 10.1172/JCI14080 [37]	Article	27	#1
10	Ponikowski P, 2016, EUR HEART J, V37, P2129, DOI 10.1093/eurheartj/ehw128 [38]	Practice Guideline	27	#0

Table 6
Top ten keywords for cardiac metabolism.

Rank	Keyword	Counts
1	cardiac metabolism	445
2	fatty acid oxidation	443
3	heart failure	440
4	glucose metabolism	261
5	myocardial metabolism	251
6	energy metabolism	184
7	insulin resistance	178
8	mitochondria	178
9	gene expression	145
10	skeletal muscle	138

with representative keywords that included “coronary artery disease”, “positron emission tomography” (PET), “PET”, “blood flow”, and “left ventricular dysfunction”. The blue cluster had representative keywords that included “glucose metabolism”, “fatty acid oxidation”, “energy metabolism”, “mitochondria”, and “skeletal muscle”, and the yellow cluster had representative keywords that included “cardiac metabolism”, “failing heart”, “pyruvate”, “oxidation”, and “magnetic resonance”. The purple cluster had representative keywords that included “gene expression”, “cardiomyocyte”, “transcription”, “chronobiology”, and “diurnal variations”, and the cyan cluster had representative keywords that included “oxidative stress”, “apoptosis”, “autophagy”, “AMPK” (Adenosine 5‘-monophosphate -activated protein kinase), “endoplasmic reticulum stress”, “mitochondrial dynamics”, “sirt1” (Silent mating type information regulation 2 homolog- 1), and “sirt3” (Silent mating type information regulation 2 homolog-3).

4. Discussion

4.1. General information

Over the past 20 years, research on cardiac metabolism has exhibited a growing trend. The past 20 years can be divided into three phases in terms of publications. The average number of publications increased from 59 in the first phase (2002–2007) to 118 in the third phase (2015–2021), with a peak of 153 in 2021. Although the number of publications each year fluctuates, the overall growth has been steady. The trend in publications does not align with the trend in citations, as the latter has been consistently increasing each year., This could be attributed to the cross-content of cardiac metabolism with other topics, such as metabolic remodeling and metabolic flexibility, leading to an increase in citations. The research focus has ranged from alterations in cardiac metabolism and related molecular pathways in cardiovascular and metabolic diseases to clinical and basic research on drugs to improve cardiac metabolism. Notably, the utilization of SGLT-2 inhibitors to improve heart failure by regulating cardiac metabolism has received considerable attention in recent years. This may also explain why more publications have been published in recent years. Therefore, cardiac metabolism should receive more attention in the future. The US, Canada, and England have exerted the greatest influence on cardiac metabolism research, as evidenced by their combined impact in terms of publications, citations, and the H-index. The US is in the lead position, far ahead of other countries/regions, largely because of its influential institutions and scholars. Among the top ten institutions with the highest publication count, five are located in the US. Washington University, ranked first in terms of publication count, H-index, and centrality, stands out as the most influential institution in the field of cardiac metabolism. In addition, four of the top ten most productive authors are from the US, highlighting a significant disparity in research productivity between other countries/regions and the US, demonstrating an uneven spread of research power in the field of cardiac metabolism. Extensive bibliometric findings suggest that the US holds the highest level of influence in this field, potentially attributed to its distinctive federal government management system, substantial research funding, and comprehensive scientific research infrastructure.

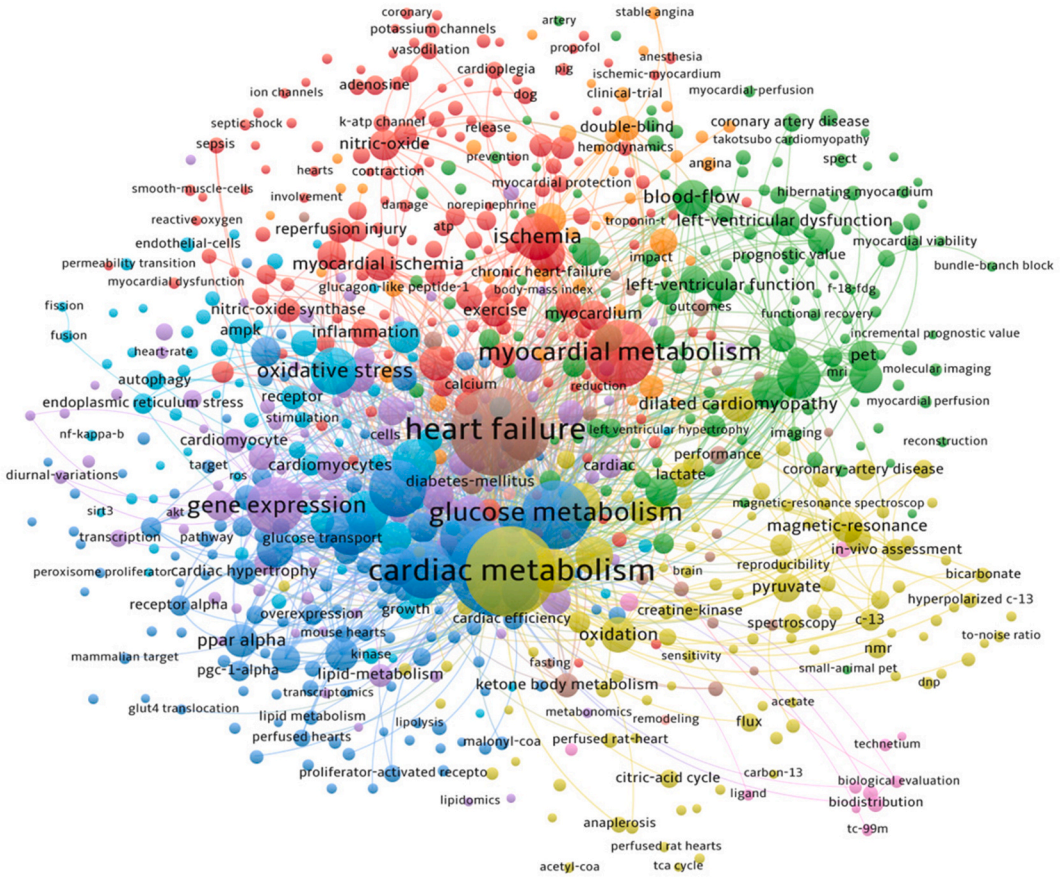

Fig. 7. VOSviewer visualization map of keywords. The keywords are represented by circles with labels. The sizes of the circles and labels are proportional to the keyword frequency, and circles of the same color belong to the same cluster.

The author analysis results indicate that collaboration is closer within the same country, region, and institution. For instance, Damian J. Tyler, S. Neubauer, and Kieran Clarke closely collaborate with Cambridge University in the United Kingdom. There is also multinational teamwork, such as that between Jason Dyck from the University of Alberta in Canada and M. E. Young from the University of Birmingham in the US, reflecting the close cooperation between the US and Canada in the field of cardiac metabolism, which is essential for expanding the scope of research and removing disciplinary barriers. Damian J. Tyler, the most productive author, focuses on the application of noninvasive imaging techniques to assess cardiac metabolism in different diseases. G. D. Lopaschuk, the most co-cited author, focuses on diabetic heart metabolism and the ischemia-reperfused heart. In addition, authors who have both the top ten publications and co-citations include H. Tegtmeyer H, who mainly focuses on cardiac metabolic alterations in obesity and heart failure and their molecular mechanisms; M. E. Young, who mainly focuses on circadian rhythms in cardiac metabolism; and S. Neubauer, who is on the same team as Damian J. Tyler, both of whom work on the application of noninvasive imaging techniques in cardiac metabolism. Apostolos I. Beloukas has also acknowledged the contributions of G. D. Lopaschuk's and H. Taegtmeyer's teams in the field of cardiac metabolism [39].

Journal are the main route for disseminating research findings. The low impact factor (IF) of high-production journals, compared to highly cited journals, indicates a lack of high-quality publications in the field of cardiac metabolism. However, this does not imply that articles published in low-impact journals are inherently of lower quality than those published in high-impact journals. For example, the *Journal of Clinical Investigation* (IF 3.93, Q1) has the highest number of average citation, attributed to the publication by Finck et al. titled "The cardiac phenotype induced by PPARα overexpression mimics that caused by diabetes mellitus," which discovered that mice with myocardial restricted overexpression of PPARα exhibited the same characteristics as those with diabetic cardiomyopathy, demonstrating an increased fatty acid utilization and decreased glucose utilization with ventricular dysfunction [37]. The top ten journals in terms of both publications and citations include the *American Journal of Physiology-Heart and Circulatory Physiology* (Q2, IF 5.125), *Journal of Molecular and Cellular Cardiology* (Q2, IF 5.763), *Cardiovascular Research* (Q1, IF 13.081), *Circulation Research* (Q1, IF 23.213), and *American Journal of Physiology-Endocrinology and Metabolism* (Q1, IF 5.96), indicating that these journals not only publish a large number of articles but also guarantee the quality of the articles in the field of cardiac metabolism. Thus, scholars can choose the journal that best aligns with their research findings.

Reference co-citation analysis aids in identifying influential literature on a research topic, while the cited literature builds the

field's knowledge base, facilitating more comprehensive analyses. The article published by Aubert et al. [27] was highly co-cited and revealed alterations in fuel substrates in the failing heart, including reduced fatty acid oxidation and increased ketone body oxidation, highlighting the significance of ketone bodies as energy suppliers [27]. Not only did cluster #0 (failing heart) have the highest number of publications but the study was still ongoing, suggesting that heart failure is a major focus of research in the field of cardiac metabolism. Cluster #11 (disease modeling) has been under study since 2017, indicating that disease modeling, which focuses on human pluripotent stem cell technology and hiPSC-CM as powerful tools to model cardiac disease in vitro, is an emerging frontier in cardiac metabolism research. The key to mature hiPSC-CM is the consistency of their metabolism with cardiac metabolic characterization in vitro [40,41].

Keywords are regarded as external expressions of the key insights of a paper, and high-frequency keywords are often used to identify research hotspots in scientific research. According to the results of the keyword clustering analysis, the field of cardiac metabolism has been categorized into six main directions: myocardial metabolism in the ischemia-reperfused heart (red cluster), imaging diagnosis of ventricular dysfunction (green cluster), cardiac substrate energy metabolism (blue cluster), altered cardiac metabolism in heart failure (yellow cluster), influence of the circadian clock on cardiac metabolism and gene expression (purple cluster), and pathological mechanisms of cardiac metabolism (cyan cluster). Among the top ten keywords, "glucose metabolism" and "fatty acid oxidation" are part of substrate metabolism, which together with "energy metabolism" form cardiac metabolism. In addition to topic-related keywords, "heart failure" was the most frequently occurring keyword, indicating that heart failure is a focal point of cardiac metabolism research. Keyword co-occurrence analysis revealed that "insulin resistance," "skeletal muscle," and "mitochondria" often co-occur with "heart failure," suggesting that insulin resistance and mitochondria-mediated cardiac metabolism play important roles in the development of heart failure.

4.2. Hotspots and frontiers

Heart failure has been the primary focus of cardiac metabolism research, as supported by the findings from the co-citation reference analysis. In particular, the crosstalk between mitochondrial dysfunction, insulin resistance, and cardiac metabolism in the etiology of heart failure and hiPSC-CMs are emerging trends in future research.

4.2.1. Heart failure

Heart failure, the terminal stage of cardiac disease, often coexists with several comorbidities including hypertension, ischemic cardiomyopathy, and diabetes mellitus. The effects of these conditions on substrate metabolism vary depending on the underlying cause and stage of heart failure.

In individuals with diabetic heart failure, insulin resistance results in elevated levels of circulating lipids and the upregulation of fatty acid transporter protein 1 (FATP1) in adipose tissue [42]. Consequently, this leads to an augmentation in myocardial fatty acid uptake and the activation of peroxisome proliferator-activated receptor alpha (PPARα)/PPARγ coactivator 1α (PGC-1α) by free fatty acids (FFAs). Activation of PPARα/PGC-1α upregulates the expression of malonyl-coenzyme A decarboxylase (MCD) and carnitine palmitoyl transferase 1 (CPT1) [43], leading to reduced intracellular malonyl-coenzyme A levels and enhanced fatty acid oxidation. Another study suggests that the expression of uncoupling proteins (UCP) 2 and 3, which are progressively upregulated in heart failure, may be associated with an elevation in fatty acid oxidation [44]. UCPs have the ability to disperse proton gradients and dissipate the mitochondrial membrane potential [45], This, in turn, can affect the uptake of mitochondrial Ca^{2+} [46]. PPARα/PGC-1α regulates pyruvate dehydrogenase kinase 4 (PDK4) and inhibits pyruvate dehydrogenase (PDH) activity, resulting in reduced glucose oxidation [45–48]. Fatty acid oxidation increases mitochondrial oxygen consumption, thereby reducing ATP synthesis efficiency. Additionally, this process leads to an imbalance in mitochondrial dynamics due to increased production of reactive oxygen species. Consequently, this imbalance ultimately leads to posttranslational modifications of dynamin-like protein (DNM1L; also known as DRP1) and mitochondrial optic nerve atrophy 1 (OPA1), resulting in mitochondrial DNA damage [49]. Moreover, the buildup of detrimental byproducts from lipid metabolism, such as triacylglycerol, diacylglycerol, and ceramide, can have adverse effects on mitochondrial function, potentially resulting in cell death through apoptosis or autophagy. This mechanism could be associated with the activation of the insulin receptor substrate (IRS)- phosphoinositide 3 kinase (PI3K)- protein kinase B (AKT)- forkhead box O1 (FOXO1)/mammalian target of rapamycin (mTOR) signaling pathway [50–52]. Moreover, decreased glucose oxidation in the myocardium lead to an upsurge in alternative glucose pathways, such as the hexosamine or polyol pathways, resulting in the generation of advanced glycosylation end products (AGEs). AGEs stimulate cardiac fibroblasts, leading to the dysregulation of collagenase, matrix metalloproteinase (MMP), and tissue inhibitor of metalloproteinases (TIMP). Consequently, this dysregulation inhibits MMP expression and upregulates TIMP, ultimately affecting the degradation of the extracellular matrix (ECM). This process results in heightened cardiac stiffness, leading to cardiac injury, structural changes, and functional disorders [53]. In conclusion, abnormal metabolism of the cardiac matrix is the primary mechanism behind heart failure in individuals with diabetes. This leads to detrimental effects on cardiac energy production, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and cardiac fibrosis. Ultimately, these factors contribute to damage to the myocardium and dysfunction of the heart. The alterations in cardiac substrate metabolism during ischemia or pressure overload-induced heart failure have been the subject of debated and are frequently linked to differences in models, disease progression, and severity. Studies indicate that a failing heart relies less on fatty acid oxidation and instead relies more on glycolysis [54]. Nevertheless, the oxidation of glucose at a later stage is disconnected from glycolysis, and elevated levels of glucose-6-phosphate (G6P) activate the mTOR signaling pathway. This activation can induce endoplasmic reticulum stress, initiating a response that affects protein folding and impairs systolic function [55,56]. Moreover, reduced glucose oxidation can cause an increase in G6P entry into other pathways, resulting in the generation of AGEs. Sympathetic nerve activation in heart failure leads to elevated levels of FFAs and

increased uptake of FFAs by cardiomyocytes. However, the asynchronous uptake and oxidation of fatty acids in cardiomyocytes results in lipid accumulation, which can cause lipotoxicity [36] and promote insulin resistance. This can further impact glucose oxidation, ultimately resulting in decreased oxidation of both fatty acid and glucose. Consequently, the heart experiences greater difficulty in generating energy. Ketone body oxidation increases in heart failure, regardless of its association with diabetes [57]. However, whether this increase is compensatory or noncompensatory remains controversial. Ketone bodies, particularly beta-hydroxybutyrate (βOHB), are highly efficient fuels and are commonly referred to as superfuels. Nevertheless, studies have demonstrated that ketone bodies competitively inhibit the oxidation of both fatty acids and glucose. The infusion of ketone supplements into isolated hearts leads to an increase in ATP levels but does not enhance cardiac efficiency [58].

The relationship between metabolism and heart function indicates that targeting energy substrate metabolism may be a promising approach for developing novel heart failure therapies [59]. Increasing glucose oxidation in the heart improves cardiac health. These compounds include well-known clinical drugs, such as trimetazidine and ranolazine, and preclinical drugs, such as etomoxir, perhexiline, dichloroacetic acid (DCA), sulfo-*N*-succinimidyl-oleate (SSO), and CBM301106. Trimetazidine, an anti-angiogenic drug, improves cardiac metabolism and has therapeutic effects on hemodynamics. It competitively inhibits long-chain 3-ketoacyl-coenzyme A thiolase (3-KAT), leading to reduced fatty acid oxidation and increased glucose oxidation through the reversal of Randle cycle [18]. Studies have demonstrated that trimetazidine effectively inhibits fatty acid oxidation and promotes glucose oxidation in rats with right ventricular hypertrophy, resulting in improved right ventricular function [60]. Clinical trials have demonstrated that trimetazidine improves left ventricular function in patients with systolic heart failure [61]. Ranolazine exhibits structural and functional similarities to trimetazidine in terms of inhibiting fatty acid oxidation and promoting glucose oxidation. While Ranolazine has been shown to increases ejection time in patients with stable angina [62], further research is needed to determine its efficacy in treating heart failure. Both Etomoxir and perhexiline, which are inhibitors of CPT1, inhibit fatty acid oxidation while enhancing glucose oxidation [63,64]. In patients with chronic heart failure, both Etomoxir and perhexiline have been shown to improve cardiac function and increase the left ventricular ejection [65,66]. However, the potential for severe side effects, including liver toxicity, hinders the widespread clinical utilization and implementation of these medications. DCA is a PDK inhibitor that increases PDH levels and promotes glucose oxidation. DCA has demonstrated the ability to improve left ventricle and reduce myocardial oxygen consumption in congestive heart failure patients [67]. However, severe neurotoxicity limits its clinical application. Conversely, SSO inhibits cluster of differentiation 36 (CD36) [68], reducing fatty acid oxidation and enhancing glycolysis in the hearts of hypoxic diabetic rats. This ultimately improves cardiac dysfunction [69]. The inhibition of MCD by CBM301106 results in increased levels of malonyl-coenzyme A. Consequently, this increase hampers the activity of CPT1, resulting in decreased fatty acid oxidation and a compensatory increase in glucose oxidation [70]. Nevertheless, clinical evaluations of both compounds are lacking. Furthermore, recent studies have increasingly shown the cardioprotective effects of enhanced ketone body oxidation in the failing heart [29,71]. SGLT2 inhibitors have the potential to provide benefits in heart failure, and one possible mechanism for this benefit could be the enhanced utilization of ketone bodies [72]. Possible therapies for treating cardiovascular diseases by targeting cardiac metabolism encompass glucose transporter-1 (Glut1) agonists, AMPK agonists, deacetylating agents (such as nicotinamide riboside), mitochondrial UCP3 agonists, fatty acid-binding protein 4 (FABP4) inhibitors, and agonists of the nuclear receptors estrogen-related receptor alpha (ERRα) and ERRγ [73–77].

4.2.2. HiPSC-CMs

Despite the potential of HiPSC-CMs in modeling cardiovascular diseases, their physiological characteristics are not comparable to those of adult cardiomyocytes. They share similarities to fetal cardiomyocytes, including a lack of excitation-contraction coupling, immature calcium handling, and metabolism, which restricts their usage [78]. Research has identified that targeting cardiac metabolism, specifically shifting the cardiomyocyte's reliance on the glycolytic energy supply towards fatty acid oxidation, may enhance the functionality of hiPSC-CMs [79]. Gentillon et al. [80] discovered that inhibitors of hypoxia-inducible factor 1alpha (HIF-1α) increase fatty acid oxidation. Furthermore, they observed the combination of these inhibitors with PPARα agonists, triiodothyronine hormone T3, insulin-like growth factor-1, and dexamethasone enhances the oxidation of hiPSC-CMs and promotes mitochondrial maturation. Hu et al. [81] conducted a study which showed that downregulating the HIF1α/lactate dehydrogenase A (LDHA) axis in hiPSC-CMs resulted in decreased glycolysis, increased fatty acid oxidation, and improved myonodular length and contractility. Yang et al. [82] conducted a separate study which found that supplementing the culture medium with fatty acids led to enhanced fatty acid oxidation, improved force production in cardiomyocytes, and improved calcium kinetics in hiPSC-CMs.

4.3. Limitations

First, our literature was sourced only from the WoSCC database, and only articles and reviews were included, which may have led to the omission of some publications. However, compared to other publisher websites, WoS offers a more accurate document type assignment [83] and provides a comprehensive collection of articles. Second, different bibliometric analysis tools or parameter settings can yield different results. However, bibliometrics can be a valuable tool for newcomers to quickly understand the current trends, hotspots, and frontiers in cardiac metabolism research. It provides a concise and efficient way to gain familiarity with the field.

4.4. Conclusion

Our study utilized CiteSpace, VOSviewer, and Scimago Graphica software to analyze 1889 articles in the field of cardiac metabolism research. Our findings indicate that the field of cardiac metabolism research is currently experiencing steady growth, with a significant increase in publications in recent years. The US has a notable influence on this field, as evidenced by the highest number of

publications and citations. Among institutions, Washington University has made the most significant contribution to this area of study. Damian J. Tyler is the most prolific author, whereas G. D. Lopaschuk is the most frequently co-cited. To further advance this field, it is crucial to strengthen the cooperation and communication among countries, institutions, and authors' teams. The *American Journal of Physiology-Heart and Circulatory Physiology*, *Journal of Molecular and Cellular Cardiology*, *Cardiovascular Research*, *Circulation Research*, and *American Journal of Physiology-Endocrinology and Metabolism* were the most influential journals on cardiac metabolism. Our study reveals that cardiac metabolism research primarily focuses on heart failure, with particular emphasis on the interplay between mitochondrial dysfunction, insulin resistance, and cardiac metabolism in the development of heart failure. Improving cardiac metabolism hold the key to future treatments. Furthermore, the research frontier in this field aims to target cardiac metabolism to facilitate the maturation of hiPSC-CMs.

Funding

This study was supported by Technology Innovation of the China Academy of Chinese Medical Sciences (CI2021A01407, CI2021A01408, and CI2021A01406), the National Natural Science Foundation of China (no. 81774143), and the China Academy of Chinese Medicine Scientific Foundation (ZZ13-YQ-010).

Informed consent statement

There were no human or animal subjects in this study, and the need for informed consent was not applicable.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Hongqin Wang: Writing – review & editing, Writing – original draft, Conceptualization. **Xiaolin Liu:** Writing – original draft. **Qingbing Zhou:** Writing – review & editing, Supervision. **Li Liu:** Visualization, Data curation. **Zijun Jia:** Methodology, Formal analysis. **Yifei Qi:** Methodology, Data curation. **Fengqin Xu:** Supervision, Writing - review & editing. **Ying Zhang:** Writing – review & editing, Supervision, 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.

Acknowledgments

We appreciate the CiteSpace and VOSviewer developers for providing the software free of charge.

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