



Stem cell therapy for type 1 diabetes: a scientometric assessment of global research during the twenty-first century

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Abstract

Purpose We aimed to provide a scientometric assessment of global research in stem cell therapy (SCT) for type 1 diabetes (T1D) during 1999–2020.

Methods The published data on SCT in T1D were retrieved from Elsevier's Scopus database and analyzed using select bibliometric tools. We used VOSviewer software and the Biblioshiny app to construct and visualize bibliometric networks.

Results The global yield totaled 1806 publications in the 22-year study period, registering a 17.7% annual growth peaking at 196.9% in the last 11 years. The average citations per publication (CPP) decreased from 62.0 during 1999–2009 to 24.3 during 2010–2020. The funded publications were 727 (40.2%). Randomized controlled trials (RCTs) were only 2.4% (45). Amongst 70 participating countries, the USA led with a 38.6% share. Of the 388 global organizations, Harvard Medical School, USA, San Raffaele Scientific Institute, Italy, and the University of Florida, USA were the topmost contributors. Florina, Couri, and Trucco were the top productive authors, whereas Melton, Abdi, and Simoes were the most impactful. Only 129 (3.1%) publications were highly-cited; their total and average CPP were 31,228 and 214.0 (range 101–1841), respectively.

Conclusions The quantity of research in SCT for T1D has increased during the last two decades while the quality has dipped. The research landscape is dominated by high-income North-American and Western-European countries. There is a need for conducting large-scale RCTs and promoting research collaborations between high- and low-income countries for long-term sustainability and global impact.

Keywords Bibliometrics · Global publications · Scientometrics · Stem cell therapy · Treatment · Type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a chronic metabolic disorder characterized by autoimmune destruction of insulin-producing pancreatic β -cells resulting in life-long insulin dependency and is associated with significant morbidity and mortality

due to acute and chronic complications. The worldwide incidence of T1D has been increasing steadily; 5–10% of the estimated 425 million people with diabetes have T1D. The increase in average annual incidence has been steeper in countries with previously low incidence. For example, India has recently surpassed the USA in the number of incident cases of T1D [1]. Thus the global disease burden due to T1D remains high. Consequently, there also remains an urgent need for more effective therapies for T1D despite intense overall research in this field [2].

The past few decades have witnessed significant progress in therapeutic options for T1D, such as newer insulin analogs, smart insulins, oral and weekly insulins, artificial pancreas, durable human β -cell replacement, and selective immune manipulation to preserve β -cell function [3, 4]. Of all these therapies, biological approaches involving functional β -cells obtained from stem cells, even though very challenging, offer the biggest hope for patients with T1D [5]. Several experimental and clinical studies conducted

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in the last decade suggest that stem-cell therapy (SCT) is a promising therapeutic modality for treating T1D [6–8]. Two recent meta-analyses concluded that SCT has beneficial effects on T1D and is safe [9, 10]. However, there are several aspects of SCT that still need to be evaluated. For example, there is considerable uncertainty about which mechanism works for the therapeutic effect, the duration of therapeutic effect, and the selection of T1D patients most likely to benefit from SCT [10]. The recent meta-analyses recognize the need to address the gaps in SCT research through multiple high-quality, large-scale randomized controlled trials (RCTs) [9, 10]. However, large-scale research requires extensive collaboration between organizations and researchers located in several countries [11]. The first step for international collaboration is to identify researchers, organizations, and funding agencies that share research interests and is often achieved through scientometric or bibliometric studies [12]. Additionally, scientometric analysis is essential for assessing the quantity and quality of the published research in any field. There is thus a need for conducting a bibliometric evaluation of research output in the field of SCT in T1D.

Several previous bibliometric studies have analyzed the research yield in SCT. However, the focus of these studies was either on research competencies, trends, or the use of SCT in diabetes and Parkinson’s disease [13–17]. Similarly, the bibliometric studies on T1D did not analyze the SCT separately [2, 18, 19]. A recent bibliometric assessment of SCT in type 2 diabetes (T2D) analyzed the research output of only China and the USA [20]. The present study was thus planned to provide a comprehensive evaluation of global research output in the field of SCT in T1D. We

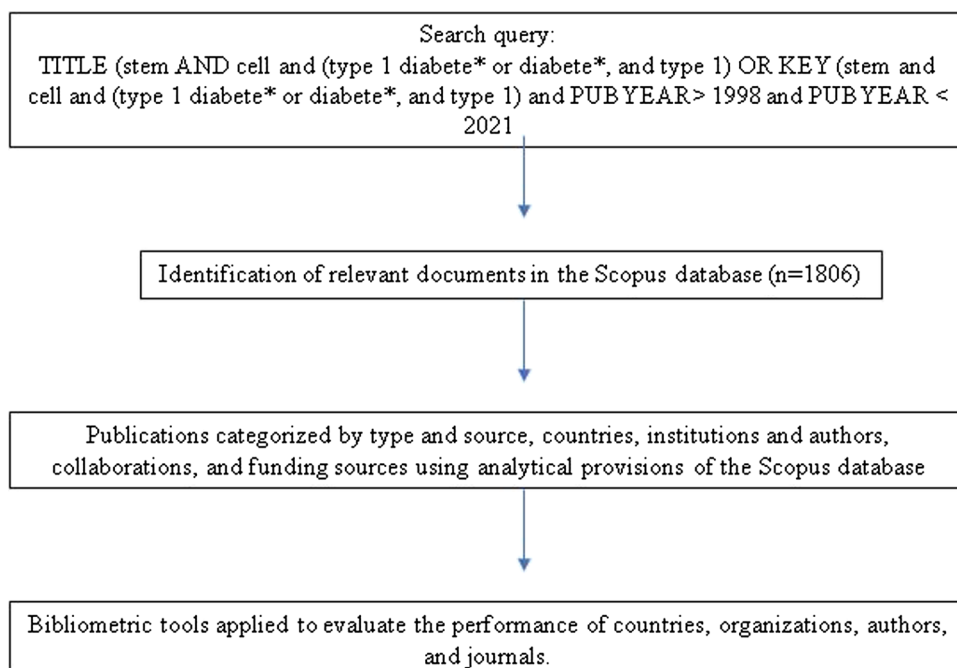
aimed to evaluate the publication types, annual and cumulative growth, and citation impact of published research in SCT for T1D and identify the most productive countries, organizations, authors, journals, and highly-cited publications (HCP) on this topic.

Methods

Data on SCT for T1D was retrieved from Elsevier’s Scopus database (<http://www.scopus.com>) using a defined search strategy with keywords “Stem Cell” and “Type 1 Diabetes” tagged to field tags “Keyword” and “Title” (Article Title), and confining output to the period ‘1999–2020’. The search strategy was similar to our recent bibliometric studies [21]. The details of data collection and analysis are shown in Fig. 1.

The research was quantified by the number of publications using the complete counting technique, i.e., every contributing author or organization included in multiple authorship papers was fully counted and received equal credit. We used several indicators of quality such as citations per paper (CPP), relative citation index (RCI), and h-index (HI). The CPP is the total number of citations divided by the total number of papers. The RCI refers to the influence of a publication and is calculated by the number of citations divided by the average number of citations that a publication usually receives in that same field [22]. H-index, or Hirsch index, is defined as the maximum value of h such that the given author/journal has published h papers that have each been cited at least h times. Publications that had received more

Fig. 1 Flow chart of data collection and analysis



than 100 citations were considered HCPs. The VOSviewer and Biblioshiny app for Bibliometrix were used to evaluate and visualize the interactions among countries, organizations, authors, and keywords. To understand changes in publications' growth and metrics over time, the study period was divided into two 11-year time periods. The citations were counted from the date of publication till February 5, 2021.

Ethical considerations

We used secondary data in this study that does not require approval from the ethics committee for research on humans. However, all the ethical principles recommended for such analysis were followed by respecting ideas and citations and referencing authors and their publications.

Results

Citations and funding of research

There were 1806 publications in the 22-year study period, an average of 82.0 publications per year. The research registered a 17.7% annual growth, with a peak of 196.9% in the last 11 years (Table 1). The average CPP was 33.8 but showed a decrease from 62.0 during 1999–2009 to 24.3 during 2010–2020. 727 (40.2%) publications were funded by more than 100 national and international funding agencies. The number of funded papers increased by more than four-fold during the second half of the study period (Table 1). However, the average CPP of funded publications (38.4) was only marginally better than that of all publications (33.8). The leading funding agencies were the National Institute of Health, USA (357 papers), US Department of Health & Human Service (343 papers), National Institute of Diabetes & Digestive and Kidney Diseases (198 papers), and National Natural Science Foundation of China (77 papers).

The retrieved publications were classified as articles (58.4%), reviews (20.3%), notes (2.4%), editorials (2.2%), conference papers (2.0%), book chapters and short surveys (1.8% each), letters (0.6%), erratum (0.1%) and undefined (0.1%). Only 238 publications were clinical studies; the proportion of clinical to non-clinical studies showed an increase during the second 12-year period of the study (15/455, 3.3% versus 223/1351, 16.5%). Forty-five publications were RCTs. According to the type of stem cells used, the distribution of retrieved publications was as follows: Mesenchymal (452, 25.0%), Hematopoietic (302, 16.7%), Pluripotent (283, 15.6%), Embryonic (237, 13.1%), Multipotent (54, 2.9%) and Totipotent (5, 0.2%). Publications on multipotent stem cells recorded the highest average CPP of 42.2 followed

Table 1 Number of yearly publications on stem cell therapy in type 1 diabetes, their citations and funding during 1999–2020

Year	Number of publications	Citations	Citations per paper	Funded papers
1999	7	189	27.0	4
2000	11	867	78.8	0
2001	17	1302	76.59	4
2002	26	1262	48.5	4
2003	26	2681	103.1	6
2004	44	2943	66.8	10
2005	48	1895	39.4	17
2006	49	5119	104.4	13
2007	56	3854	68.8	14
2008	81	3942	48.6	36
2009	90	4173	46.3	29
2010	109	4507	41.3	34
2011	88	4331	49.2	25
2012	118	4752	40.2	41
2013	104	3825	36.7	38
2014	108	3073	28.4	36
2015	121	2997	24.7	44
2016	137	2978	21.7	59
2017	127	2488	19.5	70
2018	156	2100	13.4	89
2019	143	1324	9.2	79
2020	140	487	3.4	75
1999–09	455	28,227	62.0	137
2010–20	1351	32,862	24.3	590
1999–2020	1806	61,089	33.8	727

by mesenchymal (39.8), hematopoietic (38.9), embryonic (29.3), pluripotent (26.0) and totipotent (22.6) stem cells.

Research hot spots

Thirty-eight significant keywords were identified from the global literature on SCT in T1D that denote hot spots and trends in this domain. The frequency of their occurrence was the maximum (1098) for T1D, followed by insulin-dependent diabetes mellitus (1029), insulin (741), stem cells (676), pancreas islet beta cells (579), metabolism (560), stem cell transplantation (397) (Fig. 2).

Most productive countries

Of the 70 participating countries, the top 12 contributed 98.1% to the global publication output. The USA was the leading contributor with a 38.6% share. The USA, Canada, and Italy registered their RCI above the group average of 1.1 and were considered more impactful than others (Table 2). The average collaboration of the top 12 countries was 39.7%

1.7 were considered most impactful (Table 3). The research collaboration between the top 20 most productive organizations was high; their collaborative linkages varied from 1 to 26 (Fig. 4).

Most productive authors

A total of 526 authors were involved in research on SCT in T1D during 1999–2020. Of these, 447 authors published 1–5 papers each, 63 authors 6–10 papers each, and 16

authors 11–22 papers each. Ten of the top 20 authors were from the USA, whereas three each were from Brazil and Italy, two from Poland, and one was from India. The top 20 together contributed 15.4% (278 publications) of global output and 20.9% (12,799) of total citations. The scientometric profile of the most productive and most impactful authors is presented in Table 4. The research collaborations between top authors varied from 6–35; the highest linkages (14 each) on a one-to-one basis were noted between C.E.B. Couri and J.C. Voltarelli, G.P. Fadini, and A. Avogaro and A. Avogaro and M. Albiero (Fig. 5).

Table 3 Scientometric profile of the most productive and impactful organizations in stem cell therapy for type 1 diabetes during 1999–2020

S.no	Organization	TP	TC	CPP	HI	ICP	ICP (%)	RCI
Most productive organizations								
1	Harvard Medical School, USA	84	4964	59.1	28	45	53.6	1.8
2	IRCCS San Raffaele Scientific Institute, Italy	45	2401	53.4	32	7	8.3	1.6
3	University of Florida, USA	43	1995	46.4	15	4	4.8	1.4
4	INSERM, France	34	1073	31.6	20	3	3.6	0.9
5	University of Sao Paulo, Brazil	31	1346	43.4	14	3	3.6	1.3
6	Massachusetts General Hospital, USA	30	2316	77.2	15	4	4.8	2.3
7	Brigham & Women’s Hospital, USA	28	2568	91.7	14	5	6.0	2.7
8	Children’s Hospital, Boston, USA	28	2620	93.6	22	6	7.1	2.8
9	University of California, San Francisco, USA	27	2765	102.4	7	3	3.6	3.0
10	University of Alberta, Canada	26	1775	68.3	5	3	3.6	2.0
Most impactful organizations								
1	University of California, San Francisco, USA	27	2765	102.4	7	3	3.6	3.0
2	Stanford University School of Medicine, USA	19	1941	102.2	12	6	7.1	3.0
3	Children’s Hospital, Boston, USA	28	2620	93.6	22	6	7.1	2.8
4	Brigham & Women’s Hospital, USA	28	2568	91.7	14	5	6.0	2.7
5	Massachusetts General Hospital, USA	30	2316	77.2	15	4	4.8	2.3
6	Harvard University, USA	25	1884	75.4	5	6	7.1	2.2
7	University of Alberta, Canada	26	1775	68.3	5	3	3.6	2.0
8	University of Pittsburg, School of Medicine, USA	23	1548	67.3	8	5	6.0	2.0
9	Harvard Medical School, USA	84	4964	59.1	28	45	53.6	1.8
10	Harvard Stem Cell Institute, USA	22	1307	59.4	8	4	4.8	1.8

Abbreviations: TP, total publications; TC, total citations; CPP, citations per publication; HI, Hirsch Index; ICP, international collaborative publications; RCI, relative citation index

Fig. 4 Collaboration network of the prime organizations in research on stem cell therapy for type 1 diabetes. The box size and text dimension of each hub are relative to the organization’s research yield

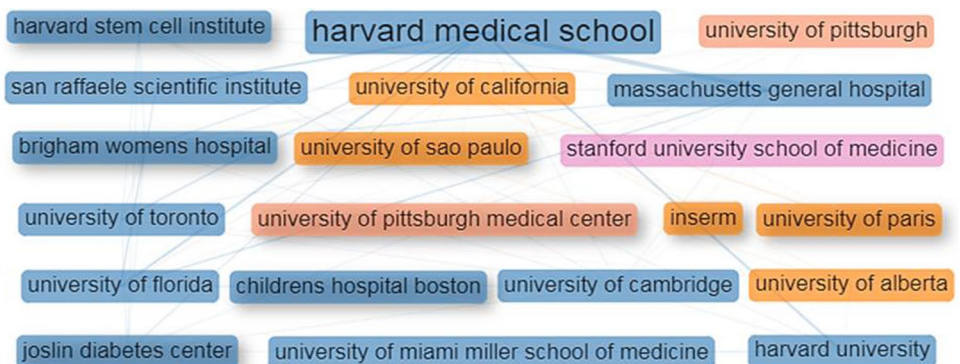


Table 4 Scientometric profiles of the most productive and impactful authors in research on stem cell therapy for type 1 diabetes during 1999–2020

S.no	Author	Affiliation	TP	TC	CPP	HI	ICP (%)	RCI
Most productive authors								
1	P. Florina	Harvard Medical School, USA	22	1239	56.3	14	21 (95.5)	1.7
2	C.E.B. Couri	University of Sao Paulo, Brazil	19	978	51.5	11	7 (36.8)	1.5
3	M. Trucco	University of Pittsburg Medical Center, Children's Hospital, USA	18	374	20.8	10	1 (5.6)	0.6
4	J.C. Voltarelli	University of Sao Paulo, Brazil	16	961	60.1	10	5 (31.3)	1.8
5	G.P. Fadini	Universita degli Studi di Padova, Italy	16	938	58.6	13	6 (37.5)	1.7
6	C. Ricordi	Diabetes Research Unit, Miami, USA	15	393	26.2	12	10 (66.7)	0.8
7	A.M.J. Shapiro	University of Alberta, Canada	15	360	24.0	8	3 (20.0)	0.7
8	A. Avogaro	Universita degli Studi di Padova, Italy	14	895	63.9	12	5 (35.7)	1.9
9	R.T. Lakey	University of California, Irvine, USA	13	371	28.5	9	9 (69.2)	0.8
10	M. Ben Nasr	Harvard Medical School, USA	12	162	13.5	6	12 (100.0)	0.4
Most impactful authors								
1	D.A. Melton	Harvard University, USA	11	1162	105.6	8	2 (18.2)	3.1
2	R. Abdi	Harvard Medical School, USA	10	918	91.8	8	6 (60.0)	2.7
3	B.P. Simoes	University of Sao Paulo, Brazil	12	890	74.2	8	7 (58.3)	2.2
4	M. Albiero	Universita degli Studi di Padova, Italy	10	699	69.9	10	5 (50.0)	2.1
5	A. Avogaro	Universita degli Studi di Padova, Italy	14	895	63.9	12	5 (35.7)	1.9
6	M.A. Atkinson	University of Florida, USA	20	1223	61.2	13	7 (35.0)	1.8
7	J.C. Voltarelli	University of Sao Paulo, Brazil	16	961	60.1	10	5 (31.3)	1.8
8	G.P. Fadini	Universita degli Studi di Padova, Italy	16	938	58.6	13	6 (37.5)	1.7
9	P. Florina	Harvard Medical School, USA	22	1239	56.3	14	21 (95.5)	1.7
10	C.E.B. Couri	University of Sao Paulo, Brazil	19	978	51.5	11	7 (36.8)	1.5

Abbreviations: TP, total publications; TC, total citations; CPP, citations per publication; HI, Hirsch Index; ICP, international collaborative publications; RCI, relative citation index



Fig. 5 The author collaboration network on stem cell therapy for type 1 diabetes. The top 20 authors are grouped into eight clusters; cluster 1 consists of 6 authors, clusters 2 and 3 of 3 authors each, clusters 4, 5 and 6 of 2 authors each, and clusters 7 and 8 of one author each

Top journals

96.4% (1742 articles) of the total publications appeared in 692 journals; 2.0% (37 papers) in book series, and 0.3% (5 publications) each as conference proceedings and undefined. The top 20 journals accounted for a 22.2% share of the global output; the most impactful journal was Proceedings of the National Academy of Sciences of USA, with a CPP of 149.4 (Table 5).

Highly-cited publications

Only 129 (3.1%) publications were HCPs; their total and average CPP were 31,228 and 214.0 (range 101–1841), respectively (Fig. 6). The USA contributed the most HCPs (76 publications), followed by Italy (14 papers), the UK (13 papers), Japan (9 papers), Germany (7 papers), China (6 papers), etc. Harvard Medical School, USA, San Raffaele Scientific Institute, Italy, Children's Hospital, Boston, USA, Howard Hughes Medical Institute, USA contributed 11, 7, and 6 HCPs, respectively. Of the 83 journals that published 129 HCPs, Diabetes published the maximum numbers (9 papers) followed by Proceedings of the National Academy of Sciences of USA (7 papers), Circulation and Diabetologia (4 papers each), etc.

Discussion

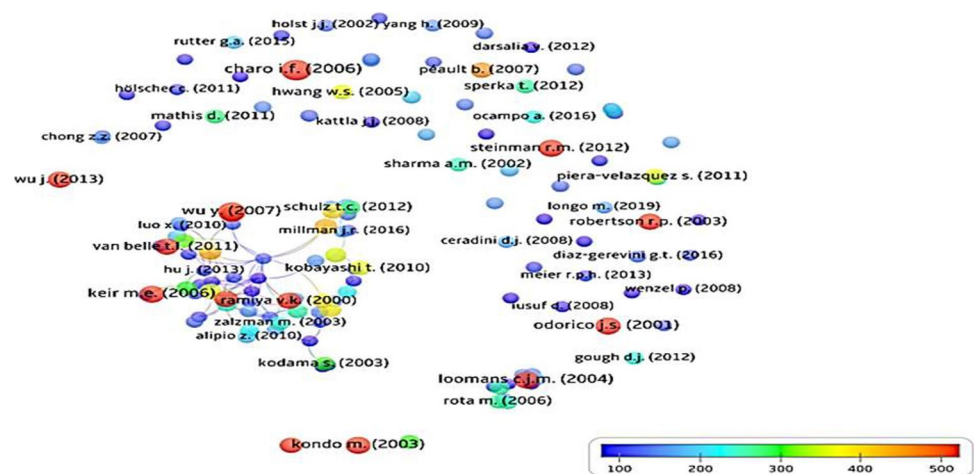
Our analysis shows that research in SCT for T1D showed an impressive growth during the twenty-first century, increasing by almost threefold in the second 11-year period of the study. In addition, the funding support increased by nearly fourfold. But even as the quantity increased, the quality of research dipped. This finding is consistent with a general decline in

Table 5 The most productive journals in stem cell therapy for type 1 diabetes during 1999–2020

S.no	Journal	TP	TC	CPP
1	Diabetes	56	1032	18.4
2	Diabetologia	32	1455	45.5*
3	PLOS One	31	1241	40.0*
4	Stem Cell Research & Therapy	26	411	15.8
5	Current Diabetes Report	25	282	11.3
6	Cell Transplantation	18	253	14.1
7	International Journal of Molecular Sciences	18	310	17.2
8	Stem Cells	18	2690	149.4
9	Stem Cell Transplantation Medicine	18	475	26.4
10	Advances in Experimental Medicine & Biology	17	184	10.8
11	Pediatric Diabetes	16	118	7.4
12	Proceedings of National Academy of Sciences of USA	16	2502	156.4*
13	Diabetes Research & Clinical Practice	14	191	13.6
14	Diabetes Care	13	830	63.9*
15	Diabetes Metabolism Research & Review	13	358	27.5*
16	American Journal of Transplantation	12	258	21.5
17	Cell Stem Cell	12	238	19.8
18	Frontiers in Immunology	11	139	12.6
19	Regenerative Medicine	11	600	54.6*
20	Science	11	854	77.6*

*impactful journals

Abbreviations: TP, total publications; TC, total citations; CPP, citations per publication

Fig. 6 Network visualization of the citation counts of the 129 highly-cited publications in stem cell therapy for type 1 diabetes

the quality of scientific research over the last decades, which has been attributed to several reasons such as an increase in the number of researchers, and linking the quantity of publications to academic promotions, job retention, job mobility, and professional development, which has led to competitive pressure to publish at all costs, sometimes compromising the quality of research publications [23, 24]. It is also perplexing to note that the quality of research in SCT for T1D declined despite increased funding support during the last decade; the quality of funded publications was only slightly better than non-funded publications. Funding is generally associated

with improved research quality, as indicated by the citation impact of publications [24, 25]. Conversely, lack of funding support adversely affects the quality of research [26]. However, the increase in the growth of clinical studies during the last decade may indirectly indicate quality improvement in SCT research, as more researchers appear to now focus on the clinical application of research.

An important finding of our analysis was the dominance of the research landscape of SCT for T1D by high-income North-American and Western-European countries. Previous bibliometric studies have reported similar dominance

by these countries in other research fields also [2, 27]. The quality and quantity of research in these countries appear to be driven by the availability of adequate infrastructure and funding support essential to conduct highly organized research activity in any field and their governments' commitment to research [28]. The eminence of China in SCT research reflects the enhanced spending on biomedical research in general, which has resulted in an exponential growth in publications over the past few decades [28, 29]. However, the quality of research indicated by CPP and RCI has remained low, an observation also reported for other fields of medical research from China [29]. The inclusion of India in the top-performing countries is largely due to the research initiatives of a few dedicated organizations and researchers in SCT for T1D [30, 31] and T2D [32, 33]. There was no representation of low-income countries in the most productive or most impactful countries in SCT research for T1D. This is probably due to a meager investment in medical research and several other challenges of conducting biomedical research in low-resource countries [34]. We also noted a worrying trend of lack of collaboration between the high-income and low-income countries in SCT research for T1D. Most of the partnerships occurred amongst researchers and organizations located in high-income countries. However, the improvement in the long-term impact and sustainability of global research requires strengthening of collaborations between high- and low-income countries [35]. Thus, high-income countries need to foster research endeavors and capacity-strengthening initiatives in low and middle-income countries in the area of SCT for T1D.

The gold standard for measuring the effectiveness of any intervention or treatment is RCTs [36]. However, our data show a striking lack of RCTs on SCT in T1D; only 2.4% were RCTs. Recently published meta-analyses that used multiple databases have also highlighted the small number of RCTs in the field of SCT in T1D and suggested large-scale RCTs to confirm the efficacy and safety of SCT in T1D [9, 10].

Our analysis also revealed a lack of SCT studies on children and adolescents with T1D as the analyzed publications did not contain these keywords. The ethical issues and the complexity of the translational pathway probably did not allow younger age groups to be included in RCTs [10]. Only two previous RCTs on mesenchymal SCT probably included young adults with T1D as indicated by the participants' mean age of 17.6 ± 8.7 and 19.67 ± 2.5 years mentioned in the reports [8, 37]. Thus, future studies should aim to include children and adolescents as T1D is mainly diagnosed during childhood and adolescence, and SCT may benefit this age group the most in the long term [30].

Our analysis had some limitations. Although we tried to address the issue of synonyms or homonyms in authors' names by using other specific fields such as affiliations, some

publications may still have remained uncaptured. Additionally, with the use of a single database compared to multiple databases, it is possible to miss some data [38]. We chose Scopus as it is considered the most authoritative and widely-used medical bibliographic database [39]. Its content coverage, search analysis tools, citation accuracy, and funding information are considered better than PubMed or Web of Science [38, 39]. A vast majority of bibliometric studies also use a single database [38, 40]. Notwithstanding the limitation of using a single database, we could accomplish our study's stated objectives within its protocol and provide the first global architecture of research on SCT for T1D. The study also provides a framework for researchers, policymakers, organizations, and countries to develop more meaningful collaborations on future research in this field.

Author contributions Conceptualization: Brij Mohan Gupta; Methodology: Brij Mohan Gupta; Formal analysis and investigation: Brij Mohan Gupta and Ghose Modin Mamdapur; Writing—original draft preparation: Brij Mohan Gupta and Devi Dayal; Writing—review and editing: Pamali Nanda and Latika Rohilla; Writing manuscript and supervision: Devi Dayal.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Competing interests None.

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