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Review Article

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Bibliometric profiles of top 50 most cited articles on bioactive glass

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Abstract: Citation analysis of a certain publication acknowledges its impact on the scientific community. This study conducted a multivariate analysis of the top 50 most cited articles published on the field of Bioactive Glass. A systemic search was performed using the "All database" section of the Web of Science to retrieve the top 50 most cited original publications. The selected articles were then manually cross-matched with Elsevier Scopus and Google Scholar Database. Parameters such as article title, authorship, institution, country of publication, year, citation count, citation density, current citation index, and journal name were retrieved from Web of Science. Different ranges of citation numbers were retrieved for these publications in which 197-913 are from Web of Science, 209-962 are from Elsevier Scopus, and 269-1225 are from Google Scholar. A total of 153 authors contributed to this marked list, where Professor L.L. Hench contributed the highest number of articles (n=21). Imperial College London published the highest number of articles (n=21). In summary, this study provides a good scientometric picture of bioactive glass related publications, which illustrate the trend of biomaterials development over the years and suggests future scopes to the scientific community.

Keywords: Bioactive glass, Bioglass®, bibliometric analysis

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1 Introduction

Biomaterials from various sources have been used for centuries to regenerate human tissues and organs, which can be developed from bio-active, bio-inert, and biodegradable materials used in 1D to 3D functionalized products. These biomaterials not only possess good biological properties but also incite specific cell responses and induce tissue regeneration. In 1969, Professor L.L. Hench invented bioactive glass (BG) based on the idea of bonding a material to bone following an unexpected bus ride conversation with a United States Army colonel who had returned from the Vietnam War [1]. Prof. Hench planned to form a biodegradable type of glass, which exhibited rigid bonds with bone tissue as a substitute for metals or polymers available at the time due to their bioinert characteristics. Subsequently, he discovered a novel glass composition of 46.1 SiO_2-24.4 Na_2O-26.9 CaO-2.6 P_2O_5 (in mole percentages, mol.%), which was granted the Bioglass® trademark, that made a progressive bond with bone where it could not be removed from the implanted site without breaking the bone [2].

Bone disease is a significant medical condition in humans, directly affects a patient's health and quality of life, especially among the elderly. Nearly 1,230,000 bone fractures are treated in US every year using osteosynthesis materials that impose a heavy economic burden [3]. Approximately, 80% of these conditions require bone graft using autogenous and allogeneic bones [3]. However, autogenous bone collection causes damage to a healthy body, which may elicit an immunological response due to different genome sequences and the risk of inducing communicable diseases [4, 5]. Autografts have other drawbacks such as limited amount of bone supply from the donor, increased resorption level during healing, and anatomical and structural problems. These issues have been addressed since the invention of Bioglass® 45S5 in the early 1970. This product has been used to reconstruct jaw bones in more than a million patients and support orthopedic needs [6]. Subsequently, the variations and modifications of BG introduced the era of bioactive ceramics, glass-ceramics, and ceramics such as synthetic hydroxyapatite (HA) and other calcium phosphates, thereby creating a new dimension in this therapeutic field [7].

Based on a glossary of statistical terms from the Organization for Economic Co-operation and Development (OECD), bibliometrics refers to the statistical analysis of articles and citations, which uses data on numbers and authors as a measurable output [8]. Bibliometrics enables the analysis of thousands of papers written about a specific topic or field and finds the most effective publications, authors, journals, institutions, and countries to assist readers or researchers within a minimal period. Surprisingly, few bibliometric studies have been conducted in the biomaterial field, and none has specifically focused on BG materials. To provide a holistic update on this specific topic in recent decades, the current study focuses on identifying and analyzing the top 50 most cited original research publications that have received more than 100 citations on BG since its invention.

2 Methods

2.1 Study design and search strategy

This is a retrospective study that utilizes available publication data from several databases. A systematic literature search was performed on October 19, 2020 using the "All database" sections of the Web of Science (WoS), Elsevier Scopus (ES) and Google Scholar (GS) with no language restrictions, study design, or publication year range. The Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines were followed (Figure 1). The topic section was searched with the specific keywords using selected inclusion and exclusion criteria.

2.2 Inclusion and exclusion criteria

The inclusion criteria were (1) keyword terms for search 'Bioactive Glass' OR 'Bioglass' OR 'Bioactive Glass-

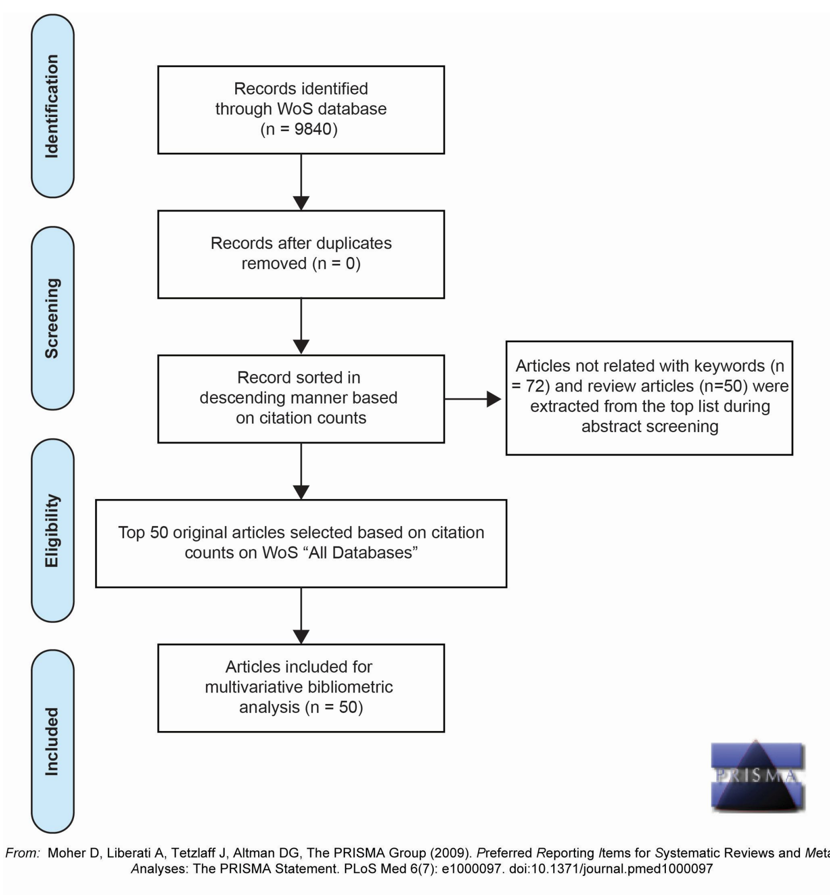

Figure 1: PRISMA 2009 Flow Diagram

Ceramics', (2) titles and abstracts of the published articles in peer-reviewed journals, and (3) original research papers.

The exclusion criteria were (1) articles published with less than 100 citations in the WoS, ES and GS repositories (2) articles published in low or no-impact factor journals, (3) review articles.

2.3 Data extraction and bibliometric parameters

A total of 9,840 publications were retrieved initially from the database of the WoS using the specific keywords (Figure 1). The publications were listed according to prevalence of citations in a descending manner. After abstract screening, approximately 122 articles were extracted from the top list that are not related to the keywords and review articles; thus, the top 50 most cited original research publications were selected based on citation frequency (Figure 1). Selected articles were cross matched with those on the ES and GS databases. All authors' contributions were recorded in the final list consisting of the following bibliometric parameters such as authorship, article title, affiliate institution, country of publication, year of publication, citation count (on WoS, ES, and GS), citation density, current citation index, and journal name from the WoS repository. Each article was then manually searched for keywords.

2.4 Data retrieval and statistical analysis

Data retrieved were subjected to RStudio, Biblioshiny, and Bibliometrix software (4.0.1, Boston, United States) to graphically represent the authors' contributions and collaborations with different affiliations [9]. Visualization of Similarities software (1.6.15, Leiden University, Netherlands) was used to illustrate the authors' keywords in mapping networks that have been used in the most cited articles. This free software platform has been used previously to present data in a simple graphical form [10, 11]. The IBM Statistical Package for Social Science, version 26.0 (IBM, Armonk, NY, USA) was used to analyze descriptive data. Data normality was evaluated by the Shapiro- Wilk test. Linear regression analysis was performed between independent and dependent variables to analyze associations between citation frequency with the age of publication and changes in trends of citation density with the age of publication. Furthermore, Kruskal- Wallis test was performed to investigate differences between multiple independent groups and ensure differences between variables, a *Bonferroni* Post-hoc test was conducted.

3 Results

3.1 Citation frequency, citation density, and current citation index

The top 50 most cited original articles published on BG along with their citation count in various databases, year of publication, citation density and current citation index are presented in Table 1.

In order to provide distinction between original research articles and reviews in the BG field, the top 10 most cited reviews on BG are presented in Table 2 because these reviews are also important in attracting readers and researchers to identify new knowledge or research gaps in the mentioned field.

The top 50 most cited published articles on BG have a citation frequency (CF) of 16,151 on WoS, 17,173 on ES and 22,267 on GS. The CF is defined as the number of times the article was cited in the literature, whereas the average number of citations per year is called citation density (CD). Articles available on the WoS have been cited with CF is in the range of 197-913 with an average of 1004 citations per year. For ES, CF is in the ranges of 209-962 with CD of 1068 while GS recorded a CF range of 269-1225 with CD of 1370.

The article entitled "Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass® 45S5 dissolution" is the most cited article by Ioannis D. Xynos with a CF of 913 (WoS), 962 (ES), and 1225 (GS), and a CD of 48 (WoS). The second article entitled "45S5 Bioglass® derived glass-ceramic scaffolds for bone tissue engineering" has a total of 822 (WoS), 879 (ES), 1129 (GS) citations, and a CD of 59 (WoS). "Ionic products of bioactive glass dissolution increase proliferation of human osteoblasts and induce insulin-like growth factor II mRNA expression and protein synthesis" is ranked third with 717 (WoS), 757 (ES) and 950 (GS) citations, and CD of 36 (WoS).

These citation counts and densities were analyzed with respect to the age of publication ranging from 0 to 50 years for the articles that have been available to scientific communities. Despite a slightly upward CF trend with the age of publication, these observations were not significant ($R^2 = 0.0041$, $p = 0.659$), as shown in Figure 2(A). However, a sharp downward trend of CD is recorded with the increase in age of publication as shown in Figure 2(B), and this result was statistically significant ($R^2 = 0.2243$, $p = 0.0002$).

Table 1: Ranking of the top 50 most cited original articles published on BG according to WoS database

No	Title of article	Year of publication	Total Citation Number			CD	CCI 2019
			WoS	ES	GS		
1	Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass® 45S5 dissolution [12].	2001	913	962	1225	44	53
2	45S5 Bioglass®-derived glass-ceramic scaffolds for bone tissue engineering [13].	2006	822	879	1129	54	73
3	Ionic products of bioactive glass dissolution increase proliferation of human osteoblasts and induce insulin-like growth factor II mRNA expression and protein synthesis [14].	2000	717	757	950	33	50
4	Surface-chemistry of bioactive glass-ceramics [15].	1990	617	615	820	19	17
5	Bioglass® 45S5 stimulates osteoblast turnover and enhances bone formation in vitro: Implications and applications for bone tissue engineering [16].	2000	529	560	716	24	26
6	Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities [17].	2004	481	500	562	28	41
7	Optimising bioactive glass scaffolds for bone tissue engineering [18].	2006	479	502	699	31	29
8	An investigation of bioactive glass powders by sol-gel processing [19].	1991	471	492	664	15	27
9	Highly bioactive P_2O_5-Na_2O-CaO-SiO_2 glass-ceramics [20].	2001	390	408	525	19	25
10	The effect of ionic products from bioactive glass dissolution on osteoblast proliferation and collagen production [21].	2004	383	383	510	22	14
11	Copper-containing mesoporous bioactive glass scaffolds with multifunctional properties of angiogenesis capacity, osteostimulation and antibacterial activity [22].	2013	366	387	463	45	73
12	The effects of strontium-substituted bioactive glasses on osteoblasts and osteoclasts in vitro [23].	2010	361	386	484	32	46
13	Bioactive sol-gel foams for tissue repair [24].	2002	330	350	455	17	14
14	Structural study of sol-gel silicate glasses by IR and Raman spectroscopies [25].	2009	328	342	432	27	46
15	Well-ordered mesoporous bioactive glasses (MBG): A promising bioactive drug delivery system [26].	2006	320	311	384	21	18
16	Nodule formation and mineralisation of human primary osteoblasts cultured on a porous bioactive glass scaffold [27].	2004	318	345	418	18	18
17	Effect of crystallization on apatite-layer formation of bioactive glass 45S5 [28].	1996	316	427	523	13	36
18	Calcium-Phosphate formation on sol-gel-derived bioactive glasses in-vitro [29].	1994	309	320	385	11	9

Table 1: ...continued

No	Title of article	Year of publication	Total Citation Number			CD	CCI 2019
			WoS	ES	GS		
19	Toxicology and biocompatibility of bioglasses [30].	1981	304	322	539	7	10
20	In vitro dissolution of melt-derived 45S5 and sol-gel derived 58S bioactive glasses [31].	2002	297	320	445	15	15
21	Coating of VEGF-releasing scaffolds with bioactive glass for angiogenesis and bone regeneration [32].	2006	292	297	378	19	21
22	Broad-spectrum bactericidal activity of Ag_2O-doped bioactive glass [33].	2002	290	304	380	15	22
23	Development and in vitro characterisation of novel bioresorbable and bioactive composite materials based on polylactide foams and Bioglass® for tissue engineering applications [34].	2002	289	306	398	15	11
24	Three-dimensional, bioactive, biodegradable, polymer-bioactive glass composite scaffolds with improved mechanical properties support collagen synthesis and mineralization of human osteoblast-like cells in vitro [35].	2003	283	296	422	15	16
25	The in-vitro bioactivity of mesoporous bioactive glasses [36].	2006	268	271	315	17	16
26	Kinetics and mechanisms of the conversion of silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solutions [37].	2006	267	289	369	17	26
27	Ordered mesoporous bioactive glasses for bone tissue regeneration [38].	2006	256	267	307	17	18
28	Porous poly(alpha-hydroxyacid)/Bioglass® composite scaffolds for bone tissue engineering. I: preparation and in vitro characterization [39].	2004	253	267	351	14	14
29	Hypoxia-mimicking mesoporous bioactive glass scaffolds with controllable cobalt ion release for bone tissue engineering [40].	2012	249	264	310	27	38
30	Interactions of bioactive glasses with osteoblasts in vitro: effects of 45S5 Bioglass®, and 58S and 77S bioactive glasses on metabolism, intracellular ion concentrations and cell viability [41].	2001	248	247	324	12	15
31	Bioactive glass stimulates the secretion of angiogenic growth factors and angiogenesis in vitro [42].	2005	247	263	348	15	19
32	Antibacterial effects of a bioactive glass paste on oral microorganisms [43].	1998	245	272	391	10	23
33	Processing and properties of sol-gel bioactive glasses [44].	2000	233	244	301	11	12
34	Characterization of melt-derived 45S5 and sol-gel-derived 58S bioactive glasses [45].	2001	232	261	367	12	29
35	Comparison of nanoscale and microscale bioactive glass on the properties of P(3HB)/Bioglass® composites [46].	2008	232	258	311	17	17
36	Novel biodegradable chitosan-gelatin/nano-bioactive glass ceramic composite scaffolds for alveolar bone tissue engineering [47].	2010	229	261	289	21	31

Table 1: ...continued

No	Title of article	Year of publication	Total Citation Number			CD	CCI 2019
			WoS	ES	GS		
37	Quantitative comparison of bone growth behavior in granules of Bioglass®, A-W glass-ceramic, and hydroxyapatite [48].	2000	229	247	341	10	11
38	Antibacterial activity of particulate Bioglass® against supra- and subgingival bacteria [49].	2001	229	254	384	11	17
39	Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability [50].	2011	223	231	275	22	26
40	Solution effects on the surface-reactions of a bioactive glass [51].	1993	221	248	317	8	8
41	Development and characterisation of silver-doped bioactive glasscoated sutures for tissue engineering and wound healing applications [52].	2004	221	246	319	13	17
42	Structural transformations of bioactive glass 45S5 with thermal treatments [53].	2007	215	236	294	15	17
43	Bioresorbable and bioactive polymer/Bioglass® composites with tailored pore structure for tissue engineering applications [54].	2003	213	231	321	12	9
44	PDLLA/Bioglass® composites for soft-tissue and hard-tissue engineering: an in vitro cell biology assessment [55].	2004	212	230	292	12	15
45	Bioactive glass particulate material as a filler for bone-lesions [56].	1991	211	229	357	7	9
46	Extracellular matrix formation and mineralization on a phosphate-free porous bioactive glass scaffold using primary human osteoblast (HOB) cells [57].	2007	209	222	287	15	7
47	Assessment of polyglycolic acid mesh and bioactive glass for soft-tissue engineering scaffolds [58].	2004	207	233	281	12	15
48	FTIR and XPS studies of bioactive silica-based glasses [59].	2003	200	209	269	11	32
49	Compositional dependence of the formation of calcium-phosphate films on Bioglass® [60].	1980	200	213	328	5	7
50	Remineralization of human dentin using ultrafine bioactive glass particles [61]	2007	197	209	313	14	14

R – Rank, WoS – Web of Science, ES – Elsevier Scopus, GS – Google Scholar, CD – Citation Density, CCI – Current Citation Index

Table 2: Ranking of the top 10 most cited review articles published on BG according to WoS database

No	Title of article	Year of publication	Total Citation Number		
			WoS	ES	GS
1	Bioceramics – From Concept to Clinic [62]	1991	3624	3805	5371
2	A Review of The Biological Response to Ionic Dissolution Products from Bioactive Glasses and Glass-Ceramics [63]	2011	1256	1314	1596
3	The Story of Bioglass® [1]	2006	1198	1248	1834
4	Review of Bioactive Glass: from Hench to Hybrids [7]	2013	1028	1094	1514
5	Bioactive Glass in Tissue Engineering [64]	2011	850	900	1207
6	Bioactive Glass-Ceramics: Properties and Applications [65]	1991	803	838	1188
7	Surface-Active Biomaterials [66]	1984	753	807	1185
8	Bioactive Materials [67]	1996	635	702	1010
9	Bioactive Glass and Glass-Ceramic Scaffolds for Bone Tissue Engineering [68]	2010	457	489	642
10	Effect of Bioactive Glasses on Angiogenesis: A Review of In Vitro and In Vivo Evidences [69]	2010	360	396	489

R – Rank, WoS – Web of Science, ES – Elsevier Scopus, GS – Google Scholar

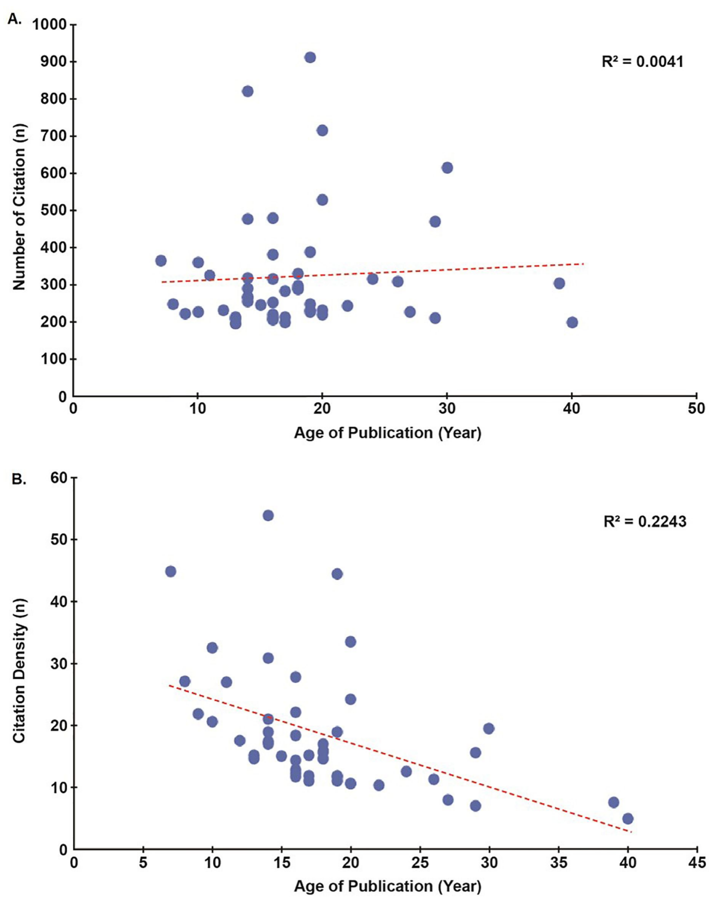

Figure 2: Association of CF (n = number) with age of publication (year) (A) and CD with age of publication (year) (B)

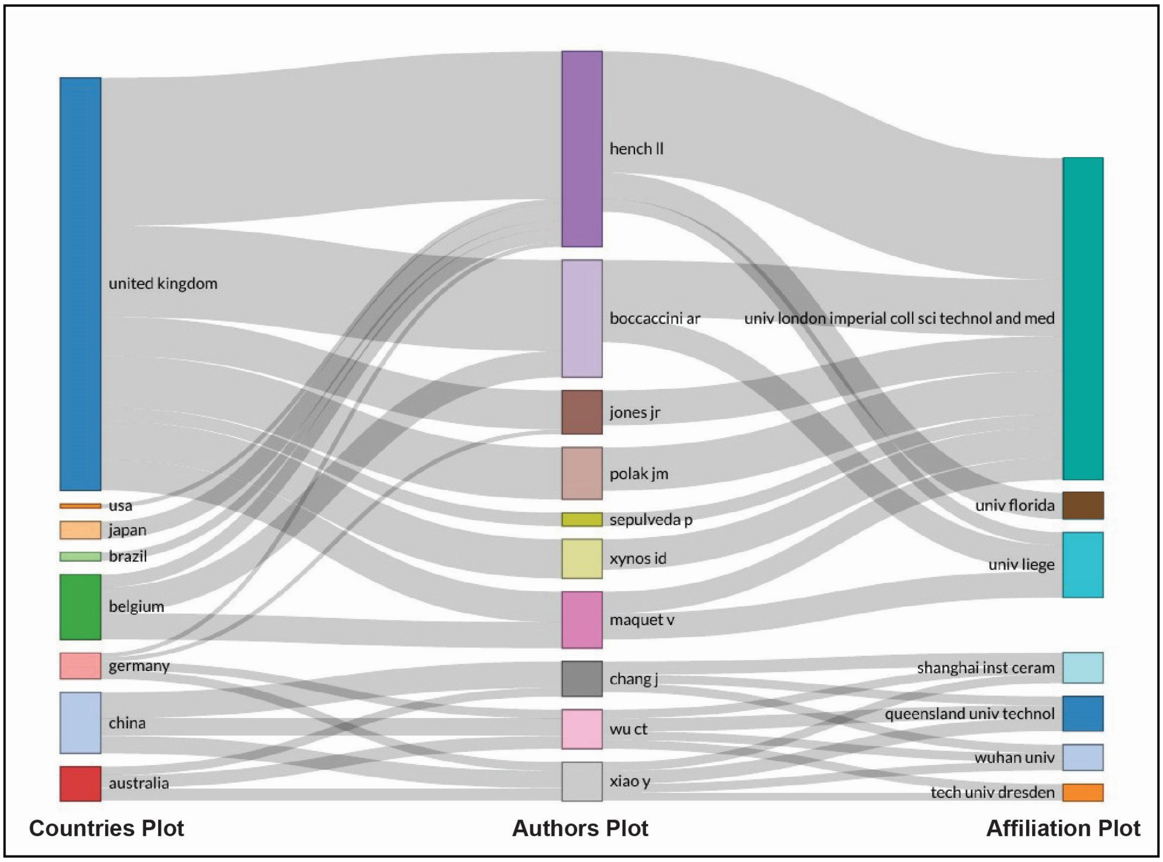

Figure 3: Three-Fields plot analysis of contributing authors, institutions and countries by Bibliometrix RStudio software

3.2 Contributing authors

The inventor of BG, Professor L.L. Hench, is the most frequent contributing author with 21 most cited articles, among which 4 articles credited him as corresponding author, followed by Professor A. R. Boccaccini who contributed 8 and Professor J. R. Jones who contributed 6 articles. A total of 158 authors were identified who contributed to the top 50 most cited articles; among them, 31 authors contributed 2 or more cited articles. Prof. Hench is the topmost collaborating author who works with various scientific groups in several countries (Figure 3) and is affiliated with the University of Florida (US) and Imperial College London (United Kingdom). Moreover, all the most cited articles contributed by Prof. Boccaccini were published when he was based at Imperial College London; 6 of these articles credited him as corresponding author.

3.3 Aflliated institutions and country of publication

A total of 15 countries contributed to the top 50 original articles published on BG. Among these, the UK contributed the highest number of publications (n=24), followed by US (n=11), China (n=6), Brazil (n=5), Belgium (n=5), and Australia (n=4) (Figure 3). Three publications each (n=3) were contributed from Japan and Spain. Two publications each (n=2) were contributed by Finland, Germany and Switzerland, and one publication each (n=1) by France, India, South Korea and Sweden.

Among 54 individual institutions, Imperial College London accounted for the largest number of publications (n=21), followed by the University of Florida (n=6), University of Liege (n=4), Chinese Academy of Sciences (n=3), Queensland University of Technology (n=3), Shanghai Institute of Ceramics (n=3), Fudan University (n=2), Tongji University (n=2), King's College London (n=2), University of Vigo (n=2), University of Pennsylvania (n=2), National Nuclear Energy Commission (Portugal) (n=2), Federal University of São Carlos (n=2), ETH Zurich (n=2) and 37 other institutions contributed in the top 50 list.

The UK and Imperial College London (based on RStudio software database, “Imperial College London” is also recognized as “University of London, Imperial College of Science, Technology, and Medicine”) is the topmost collaborating country and institution, respectively (Figure 3). Moreover, Prof. Hench (n=15), Prof. Boccaccini (n=6), Prof. Jones (n=6), and J. M. Polak (n=4) are affiliated with Imperial College London and contributed to all 21 articles published from this world-renowned institution.

3.4 Year of publication

The top 50 most cited published articles on BG were published between 1980 [61] and 2013 [7]. In 2004 and 2006, the highest numbers of articles (n=7 each year) were published (Figure 4). Furthermore, 36 articles were published in 2000-2009, followed by 7 articles in 1990-1999, 5 articles in 2010-2019, 2 articles in 1980-1989 (Figure 4). The 2000s represented the most productive decade in the history of BG research.

3.5 Journal titles for publications

The top 50 most cited articles on BG were published by 19 different peer-reviewed journals from well-known publishers as shown in Table 3 below. The *Biomaterials* journal published by Elsevier accounted for the highest number of publications (n=18), followed by the *Journal of Biomedical Materials Research* (n=11), *Journal of Non-Crystalline Solids* (n=4), *Acta Biomaterialia* (n=2) and 15 other renowned journals that each published one article. A significant ($p < 0.05$) association was found between the number of publications and citation count, where the *Journal of Biomedical Materials Research* and *Acta Biomaterialia* counted more citations per year for every article compared with other journals.

Table 3: List of journals that published the top 50 most cited articles published on BG

No	Journal Name	No. of Publications	Impact Factor (2019)
1	Biomaterials	18	10.317
2	Journal of Biomedical Materials Research	11	3.525
3	Journal of Non-Crystalline Solids	4	2.929
4	Acta Biomaterialia	2	7.242
5	Acta Materialia	1	2.929
6	Acta Odontologica Scandinavica	1	1.537
7	Angewandte Chemie-International Edition	1	12.959
8	Antimicrobial Agents and Chemotherapy	1	4.680
9	Biochemical and Biophysical Research Communications	1	2.985
10	Calcified Tissue International	1	3.437
11	Chemical Engineering Journal	1	10.652
12	Chemistry of Materials	1	9.940
13	Composites Science and Technology	1	7.094
14	Journal of Applied Biomaterials	1	2.000
15	Journal of Biomedical Materials Research Part A	1	3.525
16	Journal of Controlled Release	1	7.727
17	Journal of Materials Science-Materials in Medicine	1	2.489
18	Journal of Oral Rehabilitation	1	2.580
19	Tissue Engineering	1	3.616

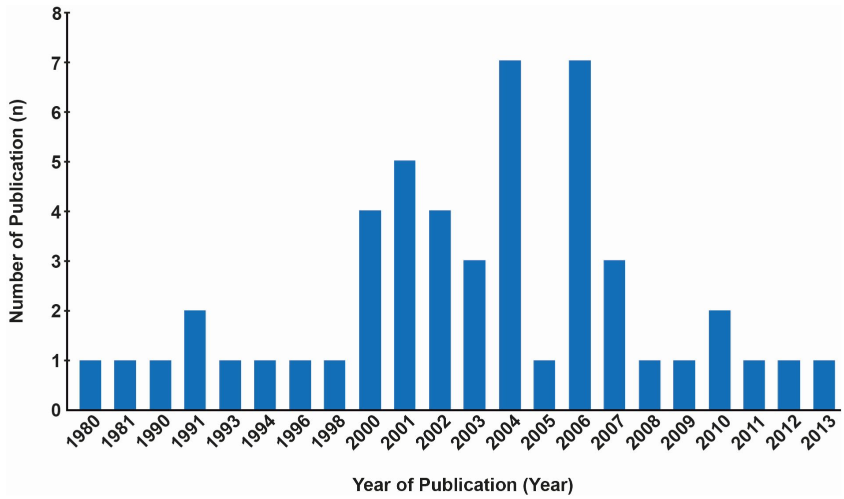

Figure 4: Number of articles published per year among the top 50 most cited original articles on BG

3.6 Keywords

Among the top 50 most cited published articles, 306 unique keywords are highlighted. The most frequently occurring keywords are "bioactive glass" followed by *"in-vitro"*, "bone", "hydroxyapatite", "differentiation", "osteoblast", "bioactivity", and "tissue engineering". Figure 5 illustrates a graphical trend visualization network map of keywords and their link strength with other clusters.

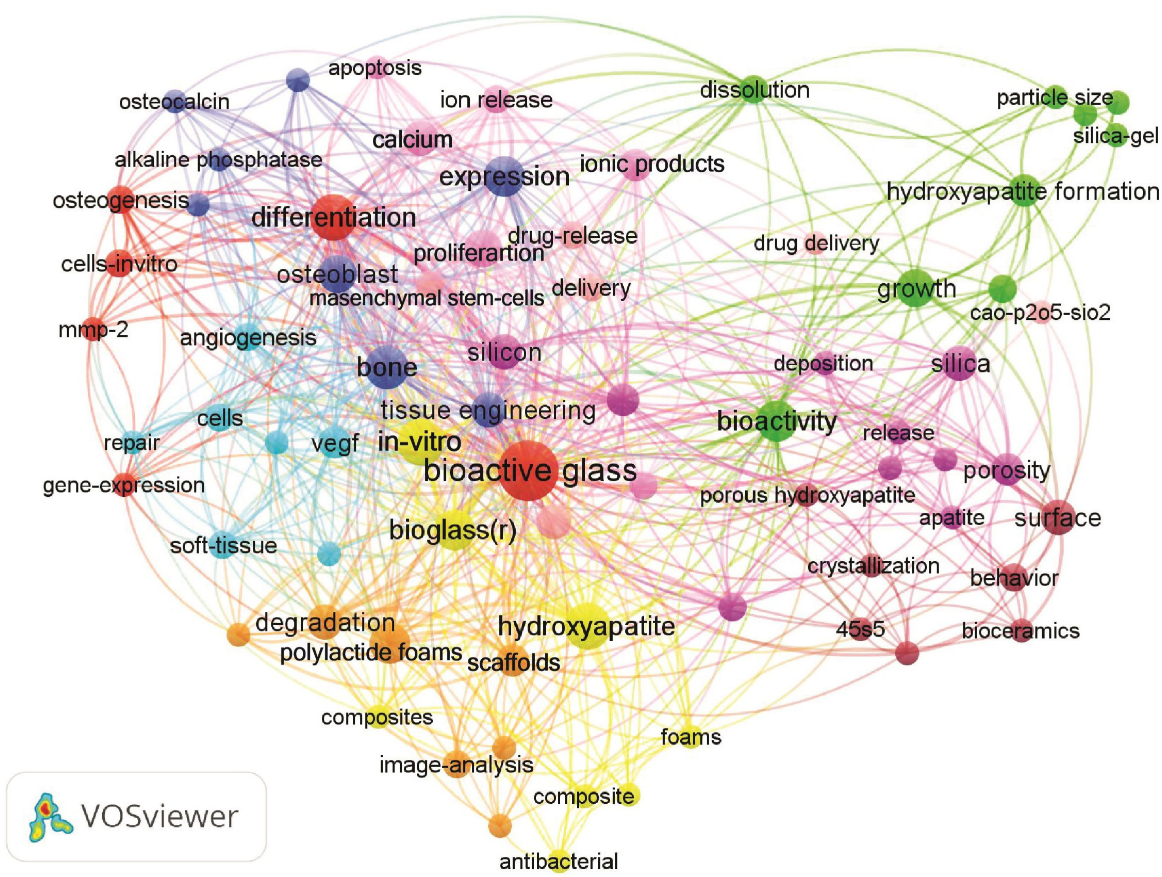

Figure 5: Network analysis of keywords extracted from the top 50 most cited articles published on BG using VOS viewer

4 Discussion

The scientific community across the world spends a considerable amount of time in laboratories to discover novel methods, materials, or protocols to ameliorate human living standards. BG is a novel material that was not invented coincidentally compared with many other significant inventions that have been discovered through laboratory experiments. BG was invented by Prof. Hench in 1969 to restore the basic living standards of war-affected soldiers in accordance with the concept of, “a material that could bond with the bone and sustain the invasive environment of the human body” [1]. He developed the hypothesis in between 1967-69 and funded for a year to test the hypothesis from the US Army Medical Research and Development Fund. The first test was conducted for six weeks in which BG was implanted on rat femoral with the composition of 45% SiO_2-24.5% Na_2O-24.5% CaO-6% P_2O_5. They reported these ceramics implant bonded in place and these implants did not come out from the bone. In 1971, Prof. Hench published their findings first time in “Bonding Mechanisms at the Interface of Ceramic Prosthetic Materials” which was cited for 3539 times in GS database. This highly cited original article was absent from the top 50 most cited original articles list reported in this study because WoS database records articles beginning from 1975.

A bibliometric analysis of the most cited articles that have become “classics” when cited more than 400 times or not less than 100 times in certain respected fields with fewer researchers acknowledges the excellence and scientific contributions of the relevant field experts, researchers, or scientists [70]. Moreover, such an analysis exhibits updated scientific and academic information, affiliation, and current research trends in a specific field. The term “citation” is a common and impactful term in research. The quality of a publication is evaluated based on the increased CF [71]. In the scientific community, an article is considered as “classic” when it has been cited more than 100 times [72].

To the best of our knowledge, this study is the first bibliometric analysis to classify and analyze the top 50 most cited “classic” articles published on BG research. The selection of these articles was based on the aforementioned definition. The purpose of choosing original research articles is to appreciate the actual contribution of researchers in a particular field. The outcomes are new hypotheses, findings, or inventions. Simultaneously, the impact of research reviews is immeasurable. A good review article can provide an overview of that specific research area, identify research gaps, and endorses the future directions. Therefore, we acknowledge the contribution of top 10 most cited reviews as shown in Table 2. Furthermore, all original articles are ranked 1st to 50th based on the number of citations. The article ranked 1st [12] was cited 913 times and the article ranked 50th [61] was cited 197 times according to the WoS database.

An irregular trend of citation counts was observed among the various databases searched. For instance, the top 50 publications found in this study were cited more than 15,000 times based on the WoS database. This result indicates the importance of database selection to avoid bias in the study. The WoS database by Clarivate Analytics is recognized as the benchmark. Since 1975, WoS had widespread distribution within the database that is capable of recording citation names, types, and counts as well as bibliographic features are unique, innovative, and beneficial for researchers [72]. In contrast, the ES database records citation indicators from 1996 [73], thereby creating limitations for bibliometric analysis and the factors of selecting top listed articles based on citation count. Moreover, the GS database records higher citation counts because it includes citation counts from published articles, books, theses or dissertations, conference papers, and preprints [72].

However, a slightly upward trend of CF with the age of publication and a sharp downward trend of CD with the increase in the age of publications recorded in the current study is in accordance with the work of Arshad *et al.* [11]. Nevertheless, significant differences were observed between CD and age of publication, which contrasts with the findings of previously published bibliometric analyses on dental caries [11]. The trend analysis revealed that the influence of age of publication on CD decreased the citation count. However, the citation index for 2019 argued that the reason for these findings may be that an article published in the scientific community attracts few citations in the beginning and additional citations over time. This condition implies that a classic article has a strong impact on the future direction of research and invention.

A hypothesis is proposed that according to the literature of bibliometric analysis, at least two decades are needed for the published article to gain actual publication impact [11, 73, 74]. The current study observed a similar incidence. A debate would arise when we consider that the accessibility in various peer-reviewed journals, archives, or libraries improved significantly in the last two decades due to the digital technology revolution. This argument is supported by the current study, which shows the greatest number of “classics” (n=41) published in the last two decades. This condition indicates that to become the most cited “classics” in the digital era, articles may have to mature in only a few years.

The three-plot analysis of this study (Figure 3) illustrates that the greatest number of “classics” contributed by the UK, China, the US, Australia and Japan indicates that publication productivity is directly correlated with the economic power of these countries. These developed countries are known for funding the research and development sector. Imperial College London exhibits its significance in the field of BG by contributing 21 “classics” out of 50 published articles and collaborating with various institutions and countries (Figure 3), which explains the presence of enormous financial support and active expert researchers. The number of contributions from the US in BG “classics” was affected by the time span of WoS database. Some of highly cited articles from Prof. Hench published in between 1971-74 is not listed in this study because the WoS database’s records started from 1975. Moreover, in the mid 1990’s, Prof. Hench moved to the UK, and afterwards, he published many papers on BG, which could affect the number of contributions from the US.

Keywords are the most fundamental part of a systematic search method to discover any publication in a specific field. Interestingly, keywords were introduced in an article as early as 1995. The keyword network analysis indicates the words “bioactive glass”, “*in-vitro*”, “bone”, “bioactivity”, “angiogenesis” “surface” and “degradation” as cluster centers. The trend of keywords used in the most cited “classics” indicates that BG is still widely used in bone tissue regeneration. Nevertheless, the current trend of BG application opens various horizons in biomaterials, for instance- in soft tissue regeneration, advanced 3D manufacturing, and combined application with other materials such as polymer and carbon nanotubes [7, 75]. The current study proposes various scopes of BG application that needs further focus in the near future.

In the 1960s, the choice of biomaterials was limited and mostly proven pathogenic or toxic as its application was not intended for or based on immune response [76]. Later in this decade, the first generation of BG was developed to ensure minimal toxic reaction in the host, and approximately 2-3 million prosthetics were implanted annually in the US. The aim of the second generation of BG was to produce bioactive components that have a controlled reaction in the physiological environment [66]. The complex composition of BG (Na_2O-CaO-P_2O_5-SiO_2) bonded with the living tissue through 11 reaction steps [62]. This generation of BG is widely used in hard tissue repair or regeneration, such as orthopedic and dental fields, in the form of powders, coatings on the metallic surface, or porous implants [76]. Resorbable properties of BG represent another achievement of this material, where foreign components were completely replaced by regenerating tissues and no visible difference was observed between the implant and host sites [77]. Finally, the future of BG begins with the development of a third-generation designed to incite cellular response at the molecular level, where BG dissolutions ions can enhance osteoblast cell responses through activation of certain pathways such as RANKL and NKF-β [23].

Indeed, as highlighted in the aforementioned keyword network analysis, the effect of cobalt-containing bioactive glasses in angiogenesis through activation of hypoxia inducible factor (HIF) pathway proposed a new method of mesenchymal stem cell survival and regeneration [78] and also bone repair [79]. The effects of biologically active ions released from BGs on cellular responses when in contact with stem cells (not only osteoblast) have been reported to include human umbilical cord perivascular cells (HUCPVCs) [80], osteoblast-like cells (MG-63) and human dermal microvascular endothelial cells (hDMECs) [81], and human adipose stem cells (hASCs), which highlight the widespread applications of BG for human benefit. The emerging field of BG applications in wound healing and soft tissue regeneration paves the new way for the use of BG in combination with biodegradable polymers and natural products such as patches, dressings, and films through advanced fabrication methods that promote soft tissue regeneration and combat bacterial infection [82–84].

In tissue engineering, the combined application of BG, stem cells and scaffolds can grow the cells *in-vitro* and mimic natural tissues. These engineered tissues are later implanted in the damaged or diseased sites of the patients. Subsequently, the scaffolds will be absorbed and replaced by host tissues with blood supply and nerves. For example, the combined application of dental pulp stem cells, BG, and scaffolds could repair or regenerate the dental-pulp tissue. This scope of BG application in regenerative dentistry needs to get more focus and embarked further.

Research has to be highlighted on 3D advanced manufacturing and processing rather than powder form as progenitor cells mimic the 3D structure during differentiation that, thereby providing greater accuracy of regenerated tissue. The BG gold standard four compositions has received much attention and current research focuses on simple compositions (two or three components) rather than complex compositions. From melt-derived to sol-gel BG form, the components advance to nano size. Closer focus is needed on nano sized components and improvement of using BG as a nanocarrier for drug delivery.

4.1 Limitations

Conducting bibliometric analysis based on citation count is a subjective limitation in judging the quality of a publication. First, author reputation in a specific field or preference of high-impact journals may influence the citation count. Second, the affiliation of co-authors cannot be documented as the address and affiliation of the corresponding author was used for analysis; therefore, the contribution from other countries and organizations remains detached from the scientific community. Finally, the WoS database recognizes only the publications from index journals. Some articles with a high citation count from non-index journals may be extracted from this study, although we manually cross checked the articles in ES and GS databases.

5 Conclusion

This study represents the first bibliometric analysis of top 50 most cited articles published on BG, which recognize the benchmark publications in this field. This study shows that citation count increases with the increase in the age of publication, but most cited "classics" requires a few years to get its attribute. Articles published in the *Journal of Biomedical Materials Research* and *Acta Biomaterialia* were cited more per year compared with others. This bibliometric analysis can be a useful guide for researchers to obtain knowledge on the trends of BG research over the years and identify potential research direction in the future.

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