BIBLIOMETRICS OF CALCIUM PHOSPHATE UTILISATION IN DENTISTRY

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Abstract
Calcium phosphates (CaPs) are frequently implemented in bone tissue engineering, especially in orthopaedics and dentistry, due to the resemblance of their inorganic constituent with bone or dental tissue. They have excellent biocompatibility, osseointegration and osteoconduction properties. The compounds are also widely available in nature and biological systems. Despite their excellent properties, various mechanical and physical factors affect their cell adhesion, proliferation, and bioactivity. Different applications have been highlighted such as synthesis techniques, coatings and composite scaffolds to utilise the bioactive characteristics of CaP in tissue engineering. A systemic data search was initiated using the "Article title, Abstract, and Keywords" search category of Scopus database to retrieve the original articles published in this field. With the aid of Scopus database and VOS Viewer software, the most contributing authors, countries, institution were retrieved. The most cited publication, publication year, and keyword co-occurrence network analysis facilitate the significant research focus and trends. This bibliometrics approach aims to quantify and analytically evaluate the research efficiency contributed in this specific area to the scientific community and reviews the substantial research trends of calcium phosphate application in dentistry.

Keywords: Bioceramics, Calcium Phosphate, Dental Materials, Hydroxyapatite, Tricalcium Phosphate

Introduction

Biomaterials have been applied in healthcare for over a thousand years. An artificial toe was the first functioning prosthetic body part discovered in Before Christ (1). From the health science perspective, 'materials that contain some novel characteristics that allow to come into immediate contact with the living tissue without provoking any undesirable immune rejection reactions' is known as biomaterials (2). They have been now widely researched in developing innovative medical gadgets, prosthetics, tissue repair or regeneration, drug delivery system and diagnostics approaches (3).

Calcium phosphates (CaPs) have attracted substantial interest in dentistry, orthopaedics and medicine during the previous decade due to their excellent performance. This utilisation is reasonable given that the mineral phase of hard tissues such as bone and teeth are similar. These compounds are widely available in nature and biological systems. Regarding the biological system, different types of CaP cycles are prominent and play a key role (4). However, the mineral phases of bone and dental tissue are composed of carbonate hydroxyapatite with varying degrees of crystallinity and small amounts of carbonate and magnesium (4, 5). Different types of CaP exist in pathological calcifications in humans (e.g. renal calculi, myocardial calcification, lung, joint cartilage and dental calculus) although only one type of calcium is often found in dental tissue (e.g. enamel, dentine and cementum) or bone tissue (4–6). Thus, CaP is known as a prospective biomaterial in tissue engineering. Tissue engineering such as bone or dental hard tissue regeneration is crosslinked with diverse physiological processes by different biomaterials and factors such as osteogenic differentiation, cell adhesion and proliferation, relationship between osteoblast and osteoclast and signalling pathways (7). CaPs have exhibited osteoinductive and osteoconductive properties that induce the osteogenic differentiation of mesenchymal stem cells (8). Therefore, the application of CaP has substantially increased for bone and dental tissue regeneration. The first successful utilisation of CaP cement for bone tissue engineering was reported in 1920 (9). Over five decades later, the first dental application of CaP was reported to repair surgically developed periodontal abnormalities as was the use of hydroxyapatite fillers for emergency tooth root replacement (10). In the early 1980s, Jarcho (11), deGroot (12) and Aoki et al. (13) reported the commercial use of calcium hydroxyapatite for dental and medical applications. Later, apatite derived from coral, coralline hydroxyapatite, and bovine bone was reported (14–16). CaP is also potentially used for drug delivery, fluorescence imaging and diagnosis. It is also extensively used in technological and industrial fields beyond biomedical such as sensors, low-cost adsorbents for removing organic and heavy metal pollutants, catalysts and catalyst carriers for chemical reaction (17). Despite its excellent diverse characteristics and application, CaP has major limitations in mechanical strength and physical properties which retain its uses in load-bearing areas (17). Over the last decade, researchers havd extensively investigated new scopes and modifications to overcome the drawbacks such as crystal morphologies, particle size, three-dimensional (3D) architectures, synthesis techniques, and coating process. In this review, we highlighted the trends of CaP advancements to application in tissue engineering since its discovery and acknowledged the contributors in this field.

Methods

On December 20, 2021, a systematic literature search was initiated in the 'Article title, Abstract and Keywords' sections of the Scopus database with no constraints on language, publication year or study design. The Preferred Reporting Items for Systemic Reviews and Meta-Analysis guidelines were followed. Specific keywords were searched, such as 'Calcium Phosphate in Dentistry' or 'Calcium Phosphate in Dental Tissue'. Initially, 5402 publications were obtained from the Scopus database using the specific keywords. Then, duplicate articles (n= 3526) were removed, whilst approximately (n=1061) articles that were not related to keywords were extracted through abstract screening. Lastly, review articles (n=71) were deducted. As a result, 309 original research papers were chosen for this bibliometric analysis, as shown in Fig. 1. Bibliometric parameters such as article title, author's contribution, affiliate institution, journal name, country of publication, year of publication, citation count, citation density and current citation index were obtained from the Scopus database.

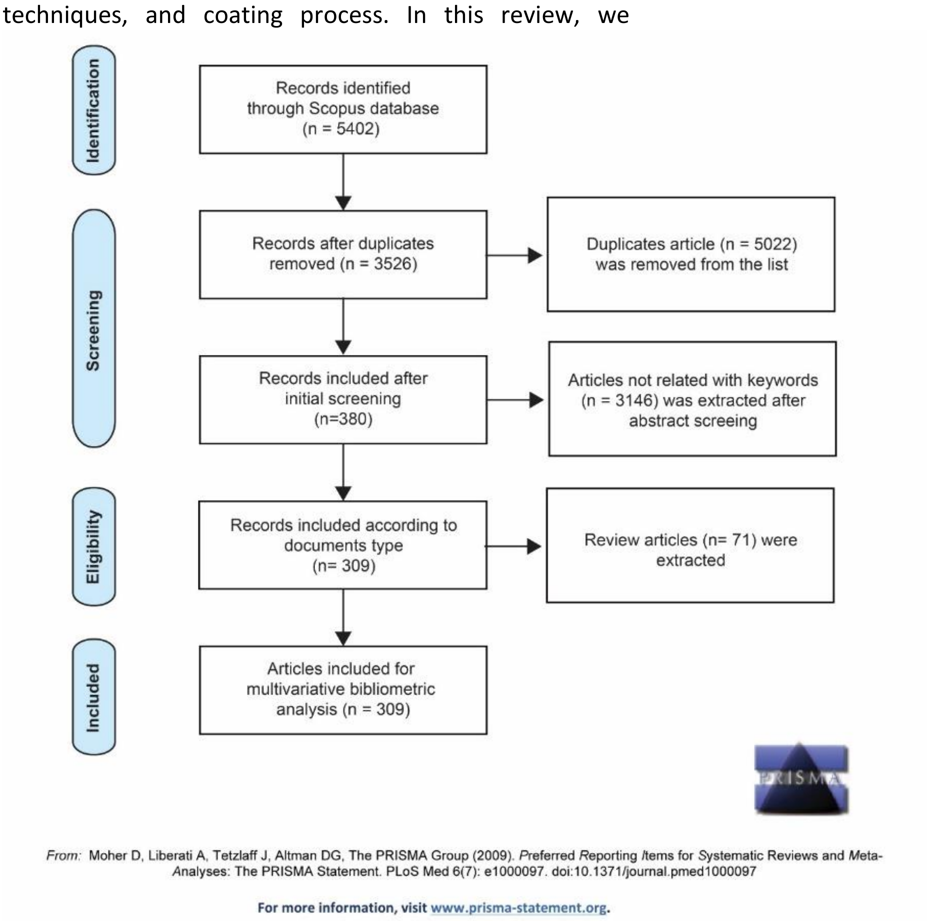

Figure 1: The PRISMA flow chart used in the identification of related articles

Outcome of bibliometric analysis

Most productive and influential authors

By the retrieval date of December 20, 2021, 1238 authors have contributed 309 original articles on CaP research in dentistry. Amongst the most influential authors, Table 1 exhibits the number of publications and citation count of authors with at least a publication threshold of five (n=5) following sorting analysis, where the highest number of publications from number 7 to 13 is five articles. 'Chow, Laurence C' tops the list with dominance in all statistical parameters such as publication quantity, total citations and citation density by publishing 11 articles with 852 total citation counts. Then, 'Daculsi, Guy' and 'Xu, Hockin H K' contribute 10 publications individually to this specific research field and rank second and third in the top contributing author's list. The remaining authors have publications ranging from eight to five.

Citation numbers with their output statistics can be used to investigate an author's impact on the scientific community. In contrast to output ranking, citation parameters have varying effects on ranks. For example, 'Antonucci, Joseph M' and 'Skrtic, Drago', who respectively rank seventh and eleventh based on output, surge to the top of this list when ranked by average citation per publication. 'Antonucci, Joseph M' and 'Skrtic, Drago' publish four articles that were cited more than 100 times by other researchers. Notably, authors who published in higher impacted journals frequently produce more highly cited publications.

Table 1: Top 13 most contributing authors

Rank	Author	Country	Publications (n)	Total Citation (n)	Average Citation (n)	CN ≥ 100
1	Chow, Laurence C	USA	11	852	77.5	2
2	Daculsi, Guy	France	10	700	70	3
3	Xu, Hockin H K	USA	10	682	68.2	2
4	Weir, Michael D	USA	8	572	71.5	2
5	Gandolfi, Maria G	Italy	6	436	72.7	2
6	Prati, Carlo	Italy	6	496	82.7	2
7	Antonucci, Joseph M	USA	5	473	94.6	4
8	Driessens, Ferdinand C M	Netherlands	5	345	69	0
9	Jansen, John A	Netherlands	5	459	91.8	1
10	Planell, Josep A	Spain	5	277	55.4	0
11	Skrtic, Drago	USA	5	473	94.6	4
12	Takagi, Shozo	USA	5	613	87.6	1
13	Weiss, Pierre	France	5	388	77.6	1

CN- citation number, n=number

Most productive countries and affiliated institutions

A total of 48 countries have contributed articles published on the research of CaP in dentistry (Fig. 2). Amongst them, Table 2 lists the bibliometric analysis of the top 10 leading countries with recognised productivity and influences in this specific scientific field. As indicated, the USA is the country with the most publications, with 68 original articles that were cited 5292 times. China (26 articles with 1026 citations) and Japan (23 articles with 901 citations) rank second and third, respectively. National Institute of Standards and Technology accounts for the highest number of publications (n=16), followed by Université de Nantes (n=11), University of Maryland Dental School (n=8), Academic Centre for Dentistry Amsterdam (n=7), Universidade de São Paulo (n=6) and 155 other institutions that have contributed to this research field (Fig. 3).

Table 2: Top 10 most contributing countries

Rank	Country	Publications (n)	Total Citation (n)	Average Citation (n)	h-index
1	USA	68	5292	77	47
2	China	26	1026	39	16
3	Japan	23	901	39	16
4	Brazil	22	542	24	11
5	India	21	409	19	11
6	France	20	1113	55	13
7	Germany	20	1252	62	15
8	Italy	20	917	45	15
9	Netherlands	17	1336	78	15
10	UK	14	659	47	10

n=number

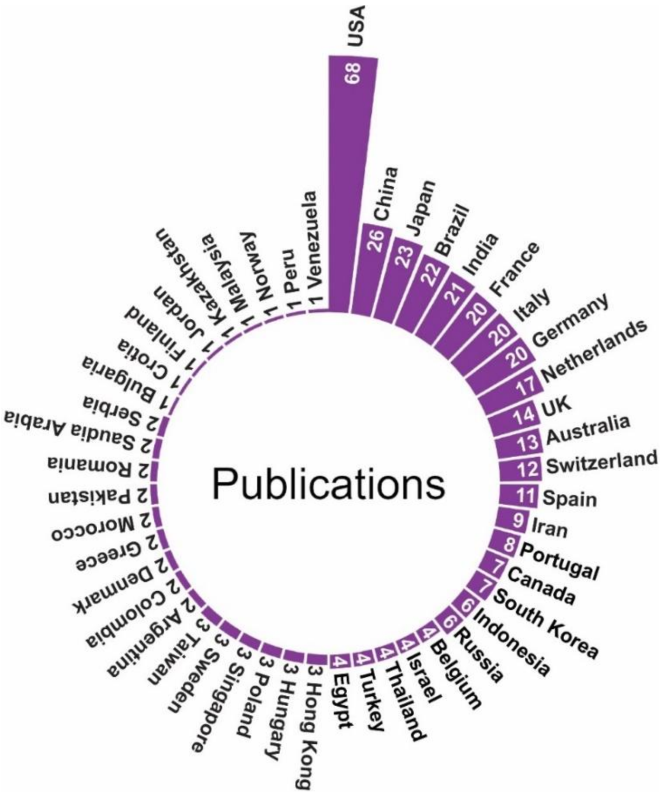

Figure 2: The publications contributed by all countries (n= number of publications)

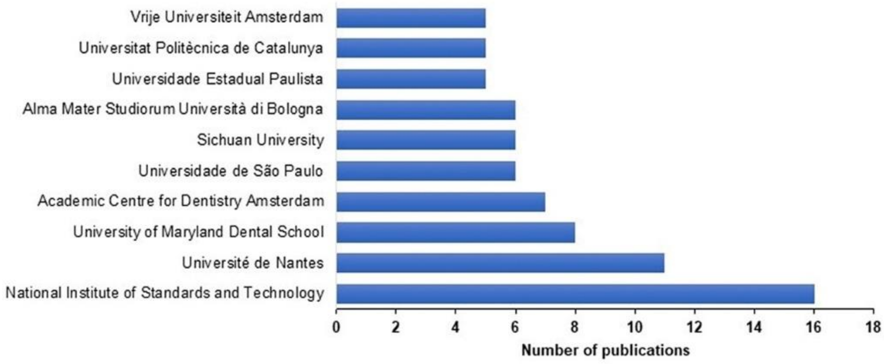

Figure 3: Top 10 list of affiliated institutions

Most cited publications

The most cited articles can be called ‘classics’ when cited more than 400 times or not less than 100 times in certain respected fields; others receive less recognition from relevant field experts, researchers or scientists (18). The citation rate can reflect the influence or relevance of a particular publication and its acknowledgement within the scientific community (19). Such an analysis includes current scientific and academic metadata, affiliations and research trends in a certain field. The phrase ‘citation’ is a frequently used and impactful term in research. The increased number of citations can be used to determine the quality of a publication (20).

The aim of identifying original research articles is to emphasise the actual contribution of scholars to a particular topic. The results are novel hypotheses, discoveries or innovations. Simultaneously, the influences of research reviews are phenomenal. Table 3 lists the ‘classic’ original articles that were cited more than 100 times since their publication. These articles were screened considering the aforementioned definition. The highest cited original article on CaP in dentistry is ‘The process of electrochemical deposited hydroxyapatite coatings on biomedical titanium at room temperature’ published in 2002 by Kuo and Yen (21) with 304 total citations. This study provides hydroxyapatite coating formed with a dense layer and rough surface morphology at room temperature. This coating may satisfy the requirements for dental implant materials and be favourable for bone tissue attachment. The second listed paper is ‘Tissue response to biphasic calcium phosphate ceramic with different ratios of hydroxyapatite/beta-tricalcium phosphate in periodontal osseous defects' (22), which aims to investigate the optimised ratio of calcium hydroxyapatite to beta-tricalcium phosphate in a biphasic porous CaP ceramic for the treatment of periodontal osseous deformities. Histological analysis indicated that a higher hydroxyapatite ratio in combination with beta-tricalcium phosphate results in increased attachment level and bone regeneration.

Table 3: Top ranking "classic" original article published on CaP in dentistry (21)–(54)

Rank	Title	Authors	Year	Total Citation (n)	Average Citation per year (n)
1	The process of electrochemical deposited hydroxyapatite coatings on biomedical titanium at room temperature	Kuo and Yen (21)	2002	304	16
2	Tissue response to biphasic calcium phosphate ceramic with different ratios of HA/beta TCP in periodontal osseous defects.	Nery et al. (22)	1992	265	9
3	Thermal processing of hydroxyapatite for coating production	Gross et al. (23)	1998	214	9
4	Maxillary sinus grafting with Bio-Oss® or Straumann® Bone Ceramic: Histomorphometric results from a randomized controlled multicenter clinical trial	Cordaro et al. (24)	2008	210	16
5	Degradation characteristics of α and β tri-calcium-phosphate (TCP) in minipigs	Wiltfang et al. (25)	2002	193	10
6	Degradation of hydroxylapatite, fluorapatite, and fluorhydroxyapatite coatings of dental implants in dogs	Gineste et al. (26)	1999	187	9
7	Induction plasma sprayed nano hydroxyapatite coatings on titanium for orthopaedic and dental implants	Roy et al. (27)	1999	187	9
8	Sinus floor augmentation with β-tricalcium phosphate (β-TCP): Does platelet-rich plasma promote its osseous integration and degradation?	Wiltfang et al. (28)	2003	175	10
9	In vivo setting behaviour of fast-setting calcium phosphate cement	Miyamoto et al. (29)	1995	165	6
10	Mechanical properties and biochemical activity of remineralizing resin-based Ca-PO_4 cements	Dickens et al. (30)	2003	157	9
11	Localisation of osteogenic and osteoclastic cells in porous β-tricalcium phosphate particles used for human maxillary sinus floor elevation	Zerbo et al. (31)	2005	152	10
12	Sinus augmentation using human mesenchymal stem cells loaded into a β-tricalcium phosphate/hydroxyapatite scaffold	Shayesteh et al. (32)	2008	145	11
13	Apatite formation on bioactive calcium-silicate cements for dentistry affects surface topography and human marrow stromal cells proliferation	Gandolfi et al. (33)	2010	142	13
14	A microanalytical procedure for the determination of calcium, phosphate and fluoride in enamel biopsy samples	Vogel et al. (34)	1983	137	4
15	Histomorphometric comparison of a biphasic bone ceramic to an organic bovine bone for sinus augmentation: 6- to 8-month postsurgical assessment of vital bone formation. A pilot study	Froum et al. (35)	2008	134	10
16	Biphasic calcium phosphate ceramics for bone regeneration and tissue engineering applications	Lobo et al. (36)	2010	129	12
17	Amorphous calcium phosphate-based bioactive polymeric composites for mineralized tissue	Skrtic et al. (37)	2003	129	7

	regeneration				
18	Synthesis and characterization of tricalcium phosphate with Zn and Mg based dopants	Xue et al. (38)	2008	127	10
19	Biocompatibility and degradation of poly(DL-lactic-co-glycolic acid)/calcium phosphate cement composites	Ruhe et al. (39)	2005	126	8
20	Advanced tissue engineering scaffold design for regeneration of the complex hierarchical periodontal structure	Costa et al. (40)	2014	125	18
21	Histological results after maxillary sinus augmentation with Straumann® BoneCeramic, Bio-Oss®, Puros®, and autologous bone. A randomized controlled clinical trial	Schmitt et al. (41)	2013	125	16
22	The anticariogenic effect of sugar-free gum containing CPP-ACP nanocomplexes on approximal caries determined using digital bitewing radiography	Morgan et al. (42)	2008	122	9
23	Effect of a CPP-ACP agent on the demineralization and remineralization of dentine in vitro	Rahiotis et al. (43)	2007	120	9
24	Effects of an anticariogenic casein phosphopeptide on calcium diffusion in streptococcal model dental plaques	Rose et al. (44)	2000	119	6
25	Biphasic calcium phosphate/hydrosoluble polymer composites: A new concept for bone and dental substitution biomaterials	Daculsi et al. (45)	1999	115	5
26	Improved properties of amorphous calcium phosphate fillers in remineralizing resin composites	Skrtic et al. (46)	1996	113	5
27	Crystallographic study of hydroxyapatite bioceramics derived from various sources	Murugan et al. (47)	2005	112	7
28	Growth of osteoblasts on porous calcium phosphate ceramic: an in vitro model for biocompatibility study	Cheung and Haak (48)	1989	112	4
29	Binding Characteristics of Streptococcus mutans for Calcium and Casein Phosphopeptide	Rose R.K. (49)	2000	111	5
30	Novel calcium phosphate nanocomposite with caries-inhibition in a human in situ model	Melo et al. (50)	2013	109	14
31	Case report - Histology of human alveolar bone regeneration with a porous tricalcium phosphate: A report of two cases	Zerbo et al. (51)	2001	108	5
32	Injectable and strong nano-apatite scaffolds for cell/growth factor delivery and bone regeneration	Xu et al. (52)	2008	104	8
33	Dental composites based on hybrid and surface-modified amorphous calcium phosphates	Skrtic et al. (53)	2004	104	6
34	Physicochemical evaluation of bioactive polymeric composites based on hybrid amorphous calcium phosphates	Skrtic et al. (54)	2000	104	5

n=number

A good research review summarises the specific subject, identifies gaps in the current knowledge and advocates for future research initiatives. Therefore, the top 10 most cited reviews are identified, as shown in Table 4. The top ranking review on CaP in dentistry entitled 'Biological and medical significance of calcium phosphates' was published in 2002 by Dorozhkin and Epple (55) and was cited 1555 times with an average of 82 citations per year. This article reviews the CaP as the primary inorganic component of animals' hard tissue (bones and teeth). For instance, atherosclerosis is a condition in which blood vessels get blocked due to a composite of cholesterol and

CaP. Moreover, tooth caries is developed by the mechanism of less soluble hard apatite replaced by the high soluble and soft calcium hydrogen phosphates, and osteoporosis is a bone demineralisation condition. As a result, from the material and chemical perspective, physiological (bone and teeth development) and pathological (dental calculus or urolithiasis) calcification processes are merely in vivo crystallisation of CaP. The similarity of chemical structure and properties of CaP with those of biological calcified tissue leads the researchers to widely use CaP in bone tissue repair or regeneration, dental tissue engineering or coating with CaP as substitute to titanium to facilitate the mechanical stability of implants. This bibliometric profile of CaP overviews the trends of its application in dentistry and acknowledges the researchers who have contributed to this field.

Table 4: Top cited review articles published on CaP in dentistry (4),(55)–(63)

Rank	Title	Authors	Year	Total Citation (n)	Average Citation per year (n)
1	Biological and medical significance of calcium phosphates	Dorozhkin and Epple (55)	2002	1555	82
2	Calcium phosphate-based osteoinductive materials	LeGeros R.Z.(56)	2008	882	68
3	Understanding peri-implant endosseous healing	Davies J.E (57).	2003	716	40
4	Calcium phosphates in oral biology and medicine.	LeGeros R.Z. (4)	1991	710	24
5	Biphasic calcium phosphate bioceramics: Preparation, properties and applications	LeGeros et al. (58)	2003	656	36
6	Calcium phosphate coatings for bio-implant applications: Materials, performance factors, and methodologies	Paital and Dahotre (59)	2009	505	42
7	Ceramics for medical applications: A picture for the next 20 years	Chevalier and Gremillard (60)	2009	485	40
8	Amorphous calcium phosphates: Synthesis, properties and uses in biomaterials	Combes and Rey (61)	2010	455	41
9	Bone regeneration: Molecular and cellular interactions with calcium phosphate ceramics	Barrère et al. (62)	2006	416	28
10	Calcium phosphate bioceramics: A review of their history, structure, properties, coating technologies and biomedical applications	Eliaz and Metoki (63)	2017	376	94

n=number

Advances in synthesis of CaP

Chemical composition and structure influence the performance of CaP material in applications. This section summarises the recent development in the synthesis of CaP particles with variable sizes ranging from the macroscale to nanoparticles, as well as various shapes including zero-dimensional (0D), 1D, and 2D phenotypic differences, and 3D porous or biomimetic scaffolds similar to hard tissue such as bone and tooth. Existing approaches for controlling the size and shape of CaP crystals are broadly classifed as follows:

- Dry methods: The dry processes, such as mechanochemical and solid-state reaction synthesis approaches are ideal for large-scale production that produces highly crystalline CaP crystals with low-cost raw materials (64). However, dry processes typically produce severely aggregated compounds with large crystal sizes and low peak integrity, as well as difficult to regulate size and shape of particles (65).
- sWet methods: Chemical precipitation, hydrothermal treatment, sol-gel technology, emulsion, diffusion, hydrolysis, biomimetic strategy, nonchemical and microwave methods can precisely control the size and shape of CaP crystals (66–70).

These processes can easily modify reaction settings to influence the morphology of CaP particles (67). They are the most promising methodologies for synthesising CaP particles with homogeneous morphologies. CaP crystals are also in solution with wet methods to obtain a better understanding of their development, biomineralisation, and phase modification (67–69). Synthesising pure granules in large quantities with a narrow range of sizes and no agglomerates is typically challenging. The majority of the wet method technologies are also complicated and time-consuming to implement (68).

- High temperature methods: High-temperature process, pyrolysis, combustion, molten salt synthesis and flux, flame-spray, and spray-drying produce highly crystalline CaP (71, 72). However, these approaches cost an enormous amount of energy, and the results generated from high-temperature procedures are typically mixed chemical phases with secondary aggregates which causes difficulty in controlling the morphology of CaP crystals (71, 72).
- Precursor transitions method: Using natural and manufactured solid precursors with varying sizes, morphologies and chemical compositions during the chemical phase transitions is a new strategy to control the size and shape of CaP crystals (73, 74). The 3D nano/microstructure surfaces of macroscopical bone transplants may also be easily fabricated to be compatible to the host body (73). In the meantime, functional inorganic elements can be concurrently integrated into CaP products to increase biological responses by employing precursors containing these elements (75). However, the precursor transformation approach often necessitates many processes and is restricted in the number of precursors that may be used. One of the key issues with this approach is the precise regulation of morphology, size, and orientation of the crystals (74).

Application of CaP in the biomedical field

CaP biocreamics are frequently applied in bone regeneration, especially in orthopaedics and dentistry, because of their excellent biocompatibility, osseointegration and osteoconduction. Minerals that contain calcium cations (Ca^{2+}) along with orthophosphate ($[PO_4]^{3-}$), metaphosphate (PO_3^-) or pyrophosphate ($P_2O_4^{7-}$) anions, and even hydrogen (H^+) or hydroxide (OH^-) ions in some cases (63). Various compounds of CaPs are developed with Ca/P atomic ratios between 1.5 and 1.67 and applied clinically, and their key characteristics are summarised and listed in Table 5.

Table 5: Characteristics and uses of different CaP phases for biomedical applications (5), (63), (76)

CaP	Ca/P ratio	pH stability range	Characteristics	Uses
Monocalcium phosphate mohydrate (MCPM) $Ca(H_2PO_4)_2.H_2O$	0.5	0.0-2.0	The most acidic and water-soluble CaP phase	Dental sealer, Bone cement
Monocalcium phosphate anhydrous (MCPA) $Ca(H_2PO_4)_2$	0.5	[a]	More soluble and similar characteristics to MCPM	Bone cement, Polyphosphates
Dicalcium phosphate dihydrate (DCPD), mineral brushite, $CaHPO_4{\cdot}_2H_2O$	1.0	2.0-6.0	Greater solubility; precursor to DCPA	Cements, Coatings
Dicalcium phosphate anhydrous (DCPA), mineral monetite, $CaHPO_4$	1.0	[a]	Solubility is slightly higher to DCPD; precursor to HA	Cements, Coatings
Octacalcium phosphate (OCP) $Ca_8(HPO_4)_2(PO_4)_4{\cdot}_5H_2O$	1.33	5.5-7.0	HA formation in in-vivo during initial crystalline phase; highly stable at physiological pH and temperature; at alkaline circumstances, it converts to HA	Coatings, Bone graft
α-Tricalcium phosphate (α-TCP) α-$Ca_3(PO_4)_2$	1.5	[b]	More soluble than HA; precursor of OCP or CDHA; common component of CaP cement; faster bone growth rate	Cements
β-Tricalcium phosphate (β-TCP) β-$Ca_3(PO_4)_2$	1.5	[b]	More soluble than HA; super stability to α-TCP; common component of CaP cement	Bone graft, Cements, Composites
Amorphous calcium phosphates (ACP) $Ca_xH_y(PO_4)_z{\cdot}nH_2O$ n 3–4.5; 15–20% H_2O	1.2-2.2	5-12	Glass-like physical characteristics; release Ca^{+2} and PO_4^{3-} in acidic environment	Cements, Coatings

Calcium-deficient hydroxyapatite (CDHA or Ca-def HA), $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ (0 < x < 1)	1.5-1.67	6.5-9.5	Poorly crystalline and of submicron dimensions; convert to β-TCP or HA+β-TCP when heating above 700 °C; all component commercially available in CaP cement	Cements
Hydroxyapatite (HA, or HAp) $Ca_{10}(PO_4)_6(OH)_2$	1.67	9.5-12.0	Bioactive and osteoconductive; major mineral component of bones and teeth	Bone graft, Coatings, Composites
Oxyapatite (OA, OAp or OXA) $Ca_{10}(PO_4)_6O$	1.67	b	Good structural flexibility and chemical stability in alkaline environment	Coatings
Tetracalcium phosphate (TTCP, or TetCP) mineral hilgenstockite, $Ca_4(PO_4)_2O$	2	b	Slowly hydrolyses to HA and calcium hydroxide; metastable in wet environment	Cements

pH stability range in aqueous solutions at 25°C
a Stable at temperatures above 100°C
b These compounds cannot be precipitated from aqueous solutions

Application of CaP in dentistry

CaPs are a group of bioactive synthetic materials that include the minerals hydroxyapatite and tricalcium phosphate, which are most frequently employed due to their crystallographic structures, osteoconductive characteristics and chemical compositions that are identical to those of bone and dental tissue. They are classified based on their resorbability or degradation rate in the body. ‘Nonresorbable’ and ‘resorbable’ are two terms that have been used to characterise the properties of hydroxyapatite and tricalcium phosphate, respectively (5, 77).

Despite the excellent bioactive and osteoconductive qualities of hydroxyapatite, it has low mechanical strength and fracture tensile properties, which makes it unfavourable for use in load-bearing areas (78). Typically, the crystallinity properties of hydroxyapatite (α axis: 9.430%, β axis: 6.891%, crystallinity index: 100%) are more similar to those of enamel (α axis: 9.441%, β axis: 6.880%, crystallinity index: 70%–75%) than those of bone (α axis: 9.41%, β axis: 6.89%, crystallinity index: 33%–37%) (79). Thus, improving the mechanical properties of hydroxyapatites would increase their scope of applications in dentistry (80). In several human and animal experiments, hydroxyapatite has been applied for pulp capping, apical barrier development, repair of periapical defects and repair of bifurcation perforation (81–84). Dentin formation induced by tricalcium phosphate–hydroxyapatite is faster and thicker than that by calcium hydroxide, as found in an in vitro study (81). Hydroxyapatite has also been used as filler in dental resin (85), periodontal defects (86), and coating for both orthopaedic and dental implants (87). In the 1960s, bioactive coatings made of hydroxyapatite and tricalcium phosphate were proposed as an alternative to cemented fixation for load-bearing implants. According to several studies, hydroxyapatite dissolution in the host body is too low to produce optimal effects. However, tricalcium phosphate dissolves too quickly for bone formation or osteogenesis (22, 88–90). Biphasic calcium phosphate ceramics composed of tricalcium phosphate and hydroxyapatite have been investigated extensively to improve bone transplant dissolving rate (22, 91). Tricalcium phosphate is known to be more soluble and bioresorbable than hydroxyapatite (92). The utilisation of hydroxyapatite coatings has been claimed to significantly improve clinical success, with a failure rate of less than 2% over a 10-year follow-up research by Furlong and Osborn (93). Given that osseointegration is key to the therapeutic efficacy of orthopaedic and dental implants, the bone-contacting devices should have coatings that are similar in composition, structure and function to human bone tissue. Okamoto et al. (94) state that hydroxyapatite had a greater cell adhesion than uncoated titanium. For 12 weeks, Wong et al. (95) studied the osseointegration phase of industrially fabricated implants in mature miniature pigs, and the results showed that implants coated with hyrdoxyapatite exhibit remarkable osseointegration.

Polymorphs of tricalcium phosphate are found in diverse forms (α, β, γ, and super-α) (96). Only α and β phases are commonly applied as biomaterials. These phases have attracted considerable attention amongst researchers (97). Tricalcium phosphate was first employed in dentistry by Levine et al. (98) to treat periodontal defects of dogs. Koenigs et al. (99) applied resorbable tricalcium phosphate ceramic to close the apical wound. Human permanent pulp less teeth with wide open apices were successfully closed by Roberts and Brilliant (100) using tricalcium phosphate ceramic. It has also been applied for apexification (101), cleft palate reconstruction (102), and apical barrier fixation (103). Shayesteh et al. (32) used a scaffold made of a combination of beta-tricalcium phosphate and hydroxyapatite and loaded with mesenchymal stem cells for maxillary sinus augmentation. The study suggested that the combination of mesenchymal cells and bone substitute may enhance bone formation.

Various CaP-related products are also available commercially. Toothpaste with hydroxyapatite nanoparticles known as Megasonex® is the first nano-ceramic based toothpaste, and is usually utilised in electric and ultrasonic toothbrushes (104). Nano-hydroxyapatite remineralise enamel in a safe environment, which potentially restores the primary stage of tooth decay, white spot lesions and harmful encrusting bacteria (104). Augmentos® 3D bone scaffold is used for filling or repairing bone defects that are adequately stabilised (105). The fabricating process does not require any heat treatment. It is the first 3D printed CaP scaffold. Calcibon® self-setting cement granules consisted of α-tricalcium phosphate, dicalcium phosphate, calcium carbonate, and hydroxyapatite (106).

Trends of calcium phosphate research in dentistry

A keyword network analysis was conducted using VOS viewer (version 1.6) to analyse the 'author keywords' reported by the original authors to obtain an overview of CaP research trends in dentistry. Keyword co-occurrence data can be used to obtain insights into the main key points covered in a publication. Fig. 4 illustrates a graphical network of 367 keyword co-occurrences with a threshold of five and above. The top 10 keywords that are most frequently used by the authors are CaP, hydroxyapatite, biomaterial, bone, bone regeneration, chemistry, bone prosthesis, dentistry, biocompatibility, enamel and dental caries. Colours indicate the clusters, and five clusters are formed by the analysis. The association strength method was used for analysis where the resolution was set to 0.9 and the minimum cluster size set to 20.

Comprehensively examining the depicted network highlights the keywords that share a similar denominator in each cluster. The colour red represents the largest cluster. Keywords such 'CaP', 'materials testing', 'chemistry', 'x-ray diffraction', 'ions', 'calcium', 'particle size', 'apatite', 'pH', 'infrared spectroscopy', 'biomimetics' and 'tooth' are recognised in this cluster, which exhibits the importance of CaP characterisation in dentistry. The second largest cluster is represented by the colour green. The cluster head term 'hydroxyapatite' reflects the application of hydroxyapatite in bone and dental tissue engineering. Terms such as 'tissue engineering', 'tissue scaffolds', 'titanium', 'tricalcium phosphate' and 'implant' are subjected in this cluster, which encompasses a wide range of hydroxyapatites in bone implant coatings. Keywords like 'cell proliferation', 'biocompatibility', 'osteoblast', 'gene expression' and 'histology' are well specified, which implies that bone tissue engineering is a significant application of hydroxyapatite. The colour blue represents the third largest cluster, which contains terms like 'enamel', 'dental caries', 'tooth demineralisation', 'dental procedure', 'amorphous calcium phosphate', 'CPP-ACP' and 'drug effect'. The major interest of this cluster appears to be CaP employed in dental tissue engineering. The colour yellow exhibits the fourth cluster, which widely describes the biomaterials like beta-tricalcium phosphate applied for bone prosthesis fabrication, bone regeneration or dental implantation. Keywords like 'biomaterial', 'bone regeneration', 'bone prosthesis', 'dental implantation' and 'beta-tricalcium phosphate' appear in this cluster.

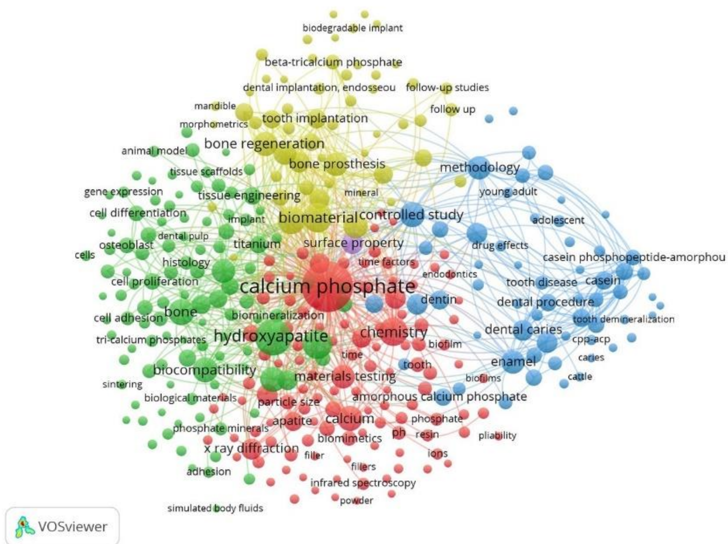

Figure 4: Co-occurrence network analysis of author keywords. Colours indicated the clusters, while circle size is based on the number of occurrences

Fig. 5 shows the trends of CaP application after examining the chronological overview of correlation network analysis between keyword occurrence and recent years of publications. The terms ‘materials testing’, ‘solubility’, ‘pH’, ‘microscopy electron scanning’ and ‘animal experiment’ appear in the purple colour in the network. Therefore, CaP development in the earlier 2000s was mostly testing in a laboratory. The first investigation of synthesis of biodegradable porous tricalcium phosphate scaffold was reported in 1971 (107). Only after 2 years, the first research paper on the fabrication and implantation of biodegradable and porous CaP (particularly, tricalcium phosphate) was published (108). The chemical resistance and outstanding biocompatibility of hydroxyapatite made it an appealing and ideal material for the dental community in the early 1980s when it was used to enhance bone. Consequently, orthopaedic surgeons began utilising hydroxyapatite as an implant covering and to supplement bone defects (108). In 1998, CaP bioceramics were used in tissue engineering for the first time, and CaP scaffold was introduced clinically in the same year (109). Bone tissue regeneration or bone development or bone defect repair was the major experimental topic using CaP in the first decade of the 20th century. Collaterally, dental tissue engineering or restorative material developmental research also obtained the primary attention in this period. In 2008, a new biphasic CaP bone ceramic was used for maxillary sinus grafting by Cordaro et al. (24). Beta-tricalcium phosphate was used successfully and clinically applied for maxillary sinus floor augmentation in 2003 (28). After a few years, CaP composite like scaffold made of beta-tricalcium phosphate/hydroxyapatite was applied in combination with human mesenchymal cells for better cell proliferation (32). Rahiotis and Vougiousklkis (43) successfully investigated the effect of the combination of casein phosphopeptide and amorphous calcium phosphate for remineralisation of potential dentin. The yellow link strength of keywords represents the recent focus on CaP research trends such as ‘Biofilm’, ‘Biomimetics’ and ‘Nanoparticles’. In 2016, Schlafer et al. (110) presented a new methodology to control dental caries. The CaP–osteopontin particles were engineered to interact with bacterial found in biofilms and prevent the formation of biofilms without inhabiting the microflora by releasing phosphate ions to buffer bacterial acid production. Thus, CaP–osteopontin particles may be used in managing caries.

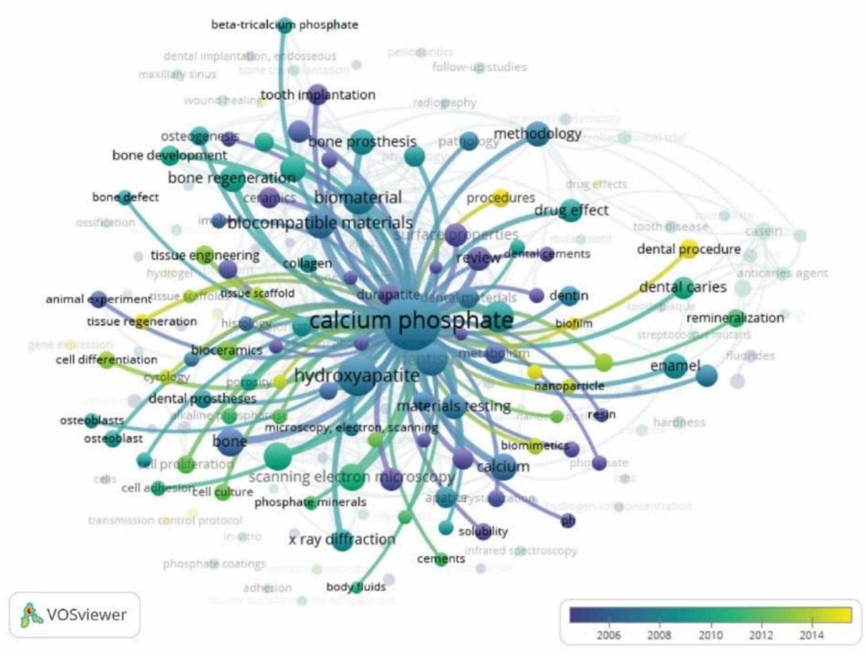

Figure 5: Bibliographic analysis and time evaluation of keywords occurrence in CaP research in dentistry. Node size is based on publications numbers, colour is used to identify the average publication per year

However, particular proteins in mineralising tissues influence the formation and development of CaP crystals in vivo. Some of the molecules have been shown by other researchers to produce bone-like apatite nucleation in a biomimetic manner (111, 112). An efficient method for creating charged surfaces with polar head groups can be achieved using the self-assembled monolayer approach. The formation of bone-like apatite may enhance the biological properties of possible restorative materials. Consequently, biomimetic methodologies have been developed to engineer new materials that are expected to enhance the biomechanical and biological performance of biomaterials (113, 114).

A new class of materials, functionally graded materials, has recently gained considerable attention. It is a type of advanced composite material with a smooth variation in material properties across its entire surface area. A gradual change in the relative mass fractions and crystal structure of the material elements is obtained by constructing the composite material. Thus, functionally graded materials can be customised to enhance their inhomogeneity strengths (115).

Conclusion

The bibliometric approach analyses thousands of papers published on a specific subject or topic and facilitates the research trends to the viewers. This way allows quick identification of the most influential publications, authors, journals, institutions, and countries to assist readers or researchers in a short amount of time. This bibliographic study discusses CaP materials used in dentistry and the progress of the research area since it was discovered. Bioactive and osteoconductive features of CaP materials result in fast osteogenesis and strong biological adhesion to bony tissues. However CaP has limited mechanical strength, which inhibits its use in load-bearing areas. By improving the mechanical properties of CaP, the scope of possible applications for these materials will be widened. Chemical composition and structure (particle sizes, crystal shapes/morphologies and 3D architectures) influence the performance of CaP materials in applications. Many methods have been explored to synthesise CaP compounds. Dry and high-temperature methods compared with wet chemical approaches exhibit high crystallinity, low phase purity and difficulty in regulating crystal morphology. They are time consuming, less costly and can be synthesised on a large scale for commercial application. On the other hand, wet methods have been proposed as influential perspectives for obtaining a clear understanding of the in vivo biomineralisation process, as well as the nucleation, phase change, growth and self-assembly routes of CaP particles. CaP crystals with precisely adjustable sizes are difficult to produce until recently. An alternative strategy to precisely synthesise and regulate CaP crystal sizes is to use the recently created microfluidic system, which combines microfluidics with microemulsion technology.

Hydroxyapatite and beta-tricalcium phosphate are important CaP bioceramics that share similar physical and chemical similarities to bone minerals. They have been implemented in various biomedical applications and are expected to be employed in bone and dental tissue regeneration. Hydroxyapatites are widely considered to be significantly biocompatible, which makes them an ideal material for hard tissue applications (e.g. dental implants or bone regeneration). However, hydroxyapatite-based materials react differently with different types of tissues and cell lines, and CaP cement can be directly injected into the bone defect and permitted to be set in situ. Given that CaPs have been synthesised at room or body temperature, they can also be utilised as a drug delivery medium for anticancer drug, anti-inflammatory drugs, antibiotics and growth factors. In dentistry, they are being studied clinically for use in furcation sealing, root canal filling, root apex sealing and root surface desensitisation materials. CaPs have great potential as a dentine regenerating pulp capping or lining material due to their self-setting properties, adequate compressive strength and biocompatibility. Considering the osteoconductivity, osteotransductivity and acceptable mechanical characteristics of CaP cement systems, they have also been employed to deliver bioactive compounds and bone fillers.

Novel approaches for synthesising CaP ceramics also need to be developed in designing new materials. Biomimicry and/or functionally graded concepts are the newest trends for enhancing the mechanical and biological characteristics of CaP. CaPs are expected to perform better physiologically and mechanically owing to such new fabricating trends.

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Competing interests

The authors declare that they have no competing interests.

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