A review of bioceramics-based dental restorative materials

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Currently, much has been published related to conventional resin-based composites and adhesives; however, little information is available about bioceramics-based restorative materials. The aim was to structure this topic into its component parts and to highlight the translational research that has been conducted up to the present time. A literature search was done from indexed journals up to September 2017. The main search terms used were based on dental resin-based composites, dental adhesives along with bioactive glass and the calcium phosphate family. The results showed that in 123 articles, amorphous calcium phosphate (39.83%), hydroxyapatite (23.5%), bioactive glass (16.2%), dicalcium phosphate (5.69%), monocalcium phosphate monohydrate (3.25%), and tricalcium phosphate (2.43%) have been used in restorative materials. Moreover, seven studies were found related to a newly developed commercial bioactive composite. The utilization of bioactive materials for tooth restorations can promote remineralization and a durable seal of the tooth–material interface.

Keywords: Bioceramics, Dental adhesives, Dental composites, Calcium phosphates, Bioactive glass

INTRODUCTION

The ultimate research goal for restoration of tooth structure depends upon the use of durable, bondable and aesthetically acceptable material¹⁾. The efforts to develop ideal materials with better properties continue at a rapid pace. The main component of the tooth is a carbonated hydroxyapatite (HA) that contains other ions such as fluorine, chlorine, sodium *etc.*²⁾. Therefore, the key strategy to combat diseased teeth is to restore the damaged structure and to promote remineralization by means of a biomimetic approach³⁾.

Synthetic calcium phosphate (CP) materials consist of an inorganic phase and are mainly based on amorphous calcium phosphate (ACP), HA ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$), tetracalcium phosphate [TTCP, $(\text{Ca}_4(\text{PO}_4)_2\text{O})$], monocalcium phosphate monohydrate [MCPM, $(\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O})$], β -tricalcium phosphate [β -TCP, $(\beta\text{-Ca}_3(\text{PO}_4)_2)$], α -tricalcium phosphate [α -TCP, $(\alpha\text{-Ca}_3(\text{PO}_4)_2)$] and octacalcium phosphate [OCP, $(\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O})$]⁴⁾. Bioactive glass (BAG) is another type of bioceramic, which has gained popularity since its invention in 1969 by Prof. Hench. It consists mainly of silicon, calcium, sodium, phosphorous, and oxygen⁵⁾. These biomaterials have extensively been used in bone repair, tissue regeneration, coatings, drug delivery devices, and tumour treatment^{6,7)}.

The present trend in dentistry is to utilize new restorative materials to make dentistry more comfortable, durable, efficient and esthetically pleasing for the patient. Therefore, resin-based composites with bioactive remineralizing agents are in huge demand

nowadays. Bioactive fillers are incorporated in the resin matrix of composite restorations and *in vitro* studies have showed a sustained release of supersaturated ions of calcium and phosphate^{8,9)}. The CP composites have been shown to remineralize enamel and dentin lesions *in vitro*¹⁰⁾. These bioactive fillers can bond with the living tissue chemically by forming CP layer at the tooth–material interface that renders the restoration durable and prevents it from bacterial ingress¹¹⁾.

It is desirable that dental restorative materials should be bioactive which can improve the mechanical properties and bond strength, depending upon the dissolution behavior of ions from the surface and to have a microstructure morphology that can promote the toughening mechanisms of crack deflection and bridging¹²⁾. However, it is still not clear, which bioactive material should be incorporated in dental resins so as to fulfill this requirement of restorative materials, relevant to the oral environment. The authors did not find an exclusive review paper that covers the main aspects of bioactive dental resin-based composites (RBC) and adhesives. Therefore, the aim of this review was to organize this issue into its component parts and to provide evidence-based principles that are sound from a dental restorative perspective.

METHODS

The initial review began with a MEDLINE/PubMed, Scopus, Web of Science and Google Scholar search with laboratory and clinical trial findings. The structured search protocol adopted for the search is given in Table 1.

Color figures can be viewed in the online issue, which is available at J-STAGE.

Received Feb 3, 2018; Accepted May 31, 2018

doi:10.4012/dmj.2018-039 JOI JST.JSTAGE/dmj/2018-039

Table 1 Keywords used for PubMed search and number of articles found with initial search with these keywords

Sr. #	Keywords	No. of Papers found on PubMed
1	Bioactive Dental Composite	179
2	Dental Resin Composites AND Hydroxyapatite	183
3	Dental Resin Adhesives AND Hydroxyapatite	62
4	Dental Adhesive AND Hydroxyapatite	476
5	Dental Resin Composite AND Calcium Phosphate	321
6	Dental Composite AND Calcium Phosphate	283
7	Dental Composite AND Amorphous Calcium Phosphate	91
8	Dental Resin Composite AND Amorphous Calcium Phosphate	82
9	Dental Adhesive AND Calcium Phosphate	516
10	Dental Resin Adhesive AND Calcium Phosphate	115
11	Dental Resin Adhesive AND Amorphous Calcium Phosphate	57
12	Dental Resin Adhesive AND Tricalcium Phosphate	10
13	Dental Adhesive AND Tricalcium Phosphate	94
14	Dental Composite AND Tricalcium Phosphate	110
15	Dental Resin Composite AND Tricalcium Phosphate	72
16	Dental Resin Composite AND Bioactive Glass	111
17	Dental Composite AND Bioactive Glass	101
18	Dental Adhesive AND Bioactive Glass	145
19	Dental Resin Adhesive AND Bioactive Glass	32
20	Bioceramics AND Dental Adhesives	9
21	Bioceramics AND Dental Resin Composites	6
22	Bioceramics AND Dental Composites	10
23	Bioactive Dental Composites AND Clinical Applications	8
24	Bioactive Fillers AND Dental Composite	21
25	Bioactive Fillers AND Dental Adhesive	21
26	Activa Bioactive	7
27	Activa Bioactive Restorative	3

Study selection

The search of the literature was performed without any restriction on a date and was done up to September 2017. Full texts of papers were obtained from the journals and the inclusion criteria for articles were;

- (1) bioceramics (*i.e.* BAG, HA, ACP, dicalcium phosphate (DCP), OCP, tricalcium phosphate (TCP), TTCP and MCPM) based dental restorative materials including adhesives and filling materials (denoted as composite in this article)
- (2) laboratory based analysis, *in-vitro* and *in-vivo*

testing with clinical trials on bioactive dental restorative composites/adhesives

- (3) bioactive restorative materials

The exclusion criteria for the review were;

- (1) literature not published in peer-reviewed journals
- (2) the grey literature, that is information not reported in the scientific journals
- (3) all papers in a foreign language (not in the English language), where full text was not available.
- (4) where these bioceramics were incorporated

in resin-modified glass ionomers and in glass ionomer cements.

Study quality assessment

The title and abstracts of all articles identified by the electronic search were read and assessed by two authors (ASK, MRS). The full-text article of all studies based on inclusion criteria was retrieved. As there are no defined guidelines for assessing the quality or risk of bias for *in vivo* and *in vitro* studies^{13,14}, therefore, the methodological quality of all selected full-text articles was assessed using the modified guidelines¹⁵. After application of the search strategy, two examiners (ASK and MK) reviewed and performed the selection by consensus with the objective of complementing the database searches. References in papers were checked and cross-matched with those from the original search. Where additional references were found to meet the inclusion criteria, then these were included in the review. After identifying the eligible studies in the above databases, these studies were imported into Endnote X7 software (Thompson Reuters, Philadelphia, PA, USA) to remove duplicates. Meta-analysis was considered if sufficient clinical studies existed.

RESULTS

Study selection

The original search strategy based on keywords mentioned in Table 1 resulted in 3,125 articles. However, the total number of papers, which met the inclusion criteria for the review, was 123, whereby 53.65% and 46.34% of the papers were based on adhesives and composites, respectively. The flow chart of obtained results of the literature search is given in Fig. 1. Non-automated manual searches were also conducted on the references within the selected articles. Among these studies, only two human trials^{16,17} and three *in vivo* studies¹⁸⁻²⁰ on rat models were conducted, the rest were

all analyzed *in vitro* conditions. Due to a lack of clinical studies, a meta-analysis was not considered.

Results based on individual bioceramics-based restorative material

The search data showed that articles published related to ACP, HA, BAG, DCP, MCPM, TCP, OCP and TTCP based dental resin-based restorative materials were 49 (39.83%), 29 (23.5%), 20 (16.2%), 7 (5.69%), 4 (3.25%), 3 (2.43%), 2 (1.62%), and 2 (1.65%), respectively. Moreover, the review showed 7 (5.69%) published articles related to ACTIVA BioACTIVE-RESTORATIVE (Pulpdent, Watertown, MA, USA).

1. ACP

The search showed that a total of 49 studies^{8,10,12,16-19,21-62} had been conducted related to ACP-based resin restorative materials. Among these nano-amorphous calcium phosphate (NACP) had been used in 15 studies^{19,21-31,57,58,62}, and the rest were based on micro-ACP. Moreover, zirconia^{8,32-40} and silica^{8,39,41} had been hybridized with ACP to improve the mechanical and biological properties Nano-silver particles^{27,57} and HA powder⁴² were also mixed with ACP to analyze the antibacterial and mechanical properties, respectively. *In vivo* studies were found related to human^{16,17} and rat models^{18,19}. The laboratory and *in vitro* studies have been investigated in detail and are tabulated in Table 2.

2. HA

A total 30 studies^{20,63-91} was found to be based on the incorporation of HA in dental resin matrices, where microparticles^{20,63-72}, nano-particles/rods/fibers^{71,77-87,89,90} and whiskers/fibrous⁷³⁻⁸⁰ HA have been mainly used. A study showed the doping of silver in HA and investigated the *in vitro* bond strength⁸⁸. Only one other study exhibited an *in vivo* (rat model) biocompatibility analysis²⁰. The information about mechanical, physical and *in vitro* biological studies is given in Table 2.

3. BAG

Among bioceramics, BAG is a relatively new material which has been incorporated into dental resin composites and adhesives. A total 20 studies⁹²⁻¹¹¹ was found as per the inclusion criteria, whereby seven studies^{92,94-96,98,106,108} were based on fluoride-based bioactive glass (F-BAG). Few studies showed doping of zinc^{101,102,107}, silver¹¹⁰, and niobiophosphate¹⁰⁹ in BAG powders. Experimental dental adhesives were also prepared by adding mineral trioxide aggregate (MTA) in BAG powder^{103,104}. The mechanical, physical, structural and *in vitro* biological properties have been investigated in detail and it is summarized in Table 2. Limited studies were found where MCPM/DCP^{9,112-118} and TCP^{57,116,117,119} had also been incorporated in dental resin matrices, including the investigation of their mechanical properties, ion release and water absorption.

4. ACTIVA BioACTIVE-RESTORATIVE

ACTIVA BioACTIVE-RESTORATIVE (Pulpdent), has

Fig. 1 Flow chart of literature search showing number of articles based on bioceramics incorporated dental resins.

Table 2 Laboratory/*in vitro* studies conducted on bioceramics-based dental restorative materials

Bioceramics-based restorative materials	Laboratory/ <i>in vitro</i> studies	References
Amorphous calcium phosphate (ACP)	Mechanical properties:	
	Flexural properties	12, 21, 26, 27, 29-31, 36, 38, 40-50, 57, 58, 62)
	Bond strength	8, 12, 22, 24, 25, 51-56, 60, 61)
	Modulus of elasticity	43, 44)
	Fracture toughness	21, 23)
	Hardness	17,39)
	Diametral tensile/Compressive strength	42)
	Physical properties:	
	Ions (calcium and phosphorous) release	8, 22, 24, 29-31, 34-36, 39, 43, 44, 47, 49, 51, 62)
	Water sorption	35, 41, 47, 49)
	Polymerization shrinkage	39, 51)
	Remineralization potential	10, 24, 28, 34, 50, 52)
	Degree of conversion	37, 39, 42)
	Mineral changes	59)
	Acid neutralization	29-31)
Hydroxyapatite (HA)	<i>In vitro</i> biological:	
	Antibacterial study	21, 24, 27, 29-31, 45, 46, 57)
	Effect on dental plaque model	23-26, 58)
	Cytotoxicity	51)
	Mechanical properties:	
	Flexural strength	64, 69-72, 74, 75, 77-82, 85-87, 89)
	Modulus (flexural/Young's)	64, 69-72, 75, 77)
	Compressive strength	20, 64, 74, 75, 81, 84)
	Diametral tensile strength, hardness	20, 71, 72, 75, 78, 82, 84-87, 89, 90)
	Bond strength/tooth adhesion	20, 67, 68, 82, 83, 85, 88)
	Fracture toughness	77, 81)
	Flexural fatigue	81)
	Physical properties:	
	Degree of conversion	64-66, 73, 82)
Bioactive glass (BAG)	Water sorption	69, 70, 73, 76, 79, 90)
	Polymerization reaction kinetics	63, 65, 66)
	Ion release	67, 68)
	pH measurement	60)
	Depth of cure	85)
	Bioactivity	68)
	<i>In vitro</i> biological:	
	Cytotoxicity	89, 91)
	Dentin formation/pulp capping	67, 68)
	Mechanical properties:	
	Micro-tensile bond strength	103, 104, 107, 109, 110)
	Micro-hardness	94-96, 99, 100, 103, 104, 106)
	Shear bond strength/flexural strength/fracture toughness/fatigue crack growth	99, 105)
	Physical properties:	
	Degree of conversion	93, 109)
	Ion release	99, 106, 108, 111)
	Acid neutralization	99, 100, 106, 108)
	Water sorption	93, 100, 103, 104)
	<i>In vitro</i> bioactivity	110)
	Viscosity	93, 100)
	Optical	94-96)
	Dispersion analysis	93)
	Solubility	103, 104)
	Structural	107)
	<i>In vitro</i> biological:	
	Cytotoxicity	98)
	Dentin remineralization	92, 101-103, 106)
	Antibacterial testing	97, 110)
	Bacterial film formation	94-96)

been used as a base or liner, as well as in bulk-fill, post, and core build-up procedures. It consists of a proprietary bioactive ionic resin, a rubberized resin, and is also photopolymerizable¹²⁰. A total of nine studies were found to be relevant to this material, however, seven studies^{121–127} were selected, as two studies^{128,129} were excluded as per the selection criteria. The flexural strength¹²², flexural fatigue¹²², wear¹²³, shear bond strength¹²⁴, cell viability¹²⁵, biomineralization¹²⁵, and bacterial leakage¹²¹ had been investigated in these studies.

DISCUSSION

The purpose of the current systematic review was to organize dental resin-based bioceramic restorative materials into its component parts. The review demonstrated that mainly structural, physical, mechanical, and biological effects of bioceramics based restorative materials have been investigated. Although bioactive dental resin-based materials have been studied since 1988, *in vitro* studies were mainly identified. There are inadequate clinical studies evaluating the relative benefits of these bioactive dental restorative materials.

Restorative materials based on bioceramics (ACP, HA, DCPD, TCP, and BAG) have been used in operative dentistry and periodontology and less commonly in prosthodontics and endodontics^{130,131}. These materials are biocompatible, harmless, non-irritating, non-inflammatory, and non-toxic, and have the benefits of minimal bioresorption^{132,133}. It is important to know, why most studies are based on ACP, HA and BAG and very few on MCPM, TCP, and TTCP. There are certain factors such as solubility, ion ratio, mode of synthesis, mechanical properties and morphology which determine the properties of these restorative materials.

It is suggested that if the ratio of calcium and phosphorous precursors is less than 1, then the solubility of the resulting material will be high, whereas with an increase in the ratio (*i.e.* close to 1.67), this parameter may decrease substantially¹³⁴. The Ca/P ratio of ACP, DCPD is 1.0 and for MCPM is 0.5. The apatite structure can be preserved with a Ca/P ratio as low as 1.5, therefore, HA with a lower than normal ratio (1.67) may be characterized as calcium deficient or non-stoichiometric. When the molar ratio is lower than 1.67, HA partially decomposes to β -TCP at a higher temperature¹³⁵.

Similarly, the solubility of BAG can be controlled by changing its composition, for example, by partially or fully replacing the silica with borate¹³⁶. Another possibility is to exploit the compositional flexibility of glass so that it can also serve as a source of many minor elements such as Zn, Cu, F, Mn, Sr and B. As the glass degrades *in vivo*, these elements are released at an acceptable rate and are known to favor biological tissue growth¹³⁷.

The solubility of these bioceramics (CP family and BAG) is mainly based on their mode of synthesis with varying reaction time, temperature, structure and pH. An increase in reaction time, temperature, crystalline structure and a decrease in pH can reduce

the solubility^{138,139}. The solubility determines the release of calcium, phosphate, and silica ions from dental resins, and consequently, the remineralization process.

The other factor that determines the resultant properties of restorative materials is the morphology of the bioceramic particles. The morphology depends upon the process of synthesis process and heat treatment. The heating temperature affects the particle shape and agglomeration, whereby at low temperatures the crystals are in a needle shape, whereas increasing the reaction temperature may change the crystal from a needle shape to a more circumscribed shape, or more close to a spherical shape^{140,141}.

Nano-particles, with a high surface area, has been shown to enhance the mechanical properties but agglomeration can decrease the physical and mechanical properties and these issues have been observed in various studies^{75,89}. As a uniform distribution is difficult to accomplish, manual spatulation was therefore mostly utilized in these experimental studies, so as to mix the fillers into resin matrices^{24,30,58,90}. However, it has been reported that the fillers should be stirred overnight⁷⁵ to avoid any aggregation and to achieve a uniform distribution. It was also suggested to use solvents *i.e.* acetone and ethanol for mixing⁹⁰, where ethanol is not reactive enough to interfere the reaction, rather residual ethanol can increase the polymerization reaction¹⁴².

ACP based dental resins

Currently, almost 39.83% of studies are based on ACP based materials. However, a concern is observed about their inherent poor mechanical properties, therefore, it has been hybridized with other ceramics (zirconia, silica), and metals (barium, strontium, silver)¹⁴³. Its flexural strength is about half that of the unfilled resins which make it inefficient for use as a bulk restoration under masticatory load. ACP has been used as a filler in dental adhesives and composites due to its bioactivity, biocompatibility, osteoconduction and better cell adhesion with both hard tissues¹⁴⁴. It can increase alkaline phosphatase activities of mesoblasts, enhance cell proliferation and promote cell adhesion. Many enzymes, proteins and ions affect the biomineralization of ACP such as dentin matrix protein¹⁴⁵. The ACP based composites can potentially be used as restorations in small carious lesions, sealing pits and fissures in teeth where plaque can accumulate and may lead to secondary caries¹⁴⁶. The composites containing ACP fillers have shown a 71% recovery of the lost mineral content of decalcified teeth⁸. This material can be added in orthodontic adhesives and may help to avert demineralization of tooth enamel^{18,147}, minimize white spot lesion formation and prevent accumulation of bacterial plaque around fixed orthodontic brackets and bands⁵⁹. However, commercialization of the product would be difficult because approval from the Food and Drug Administration (FDA) requires the classification of these agents as a drug. The FDA has approved a therapeutic paste *i.e.* Recaldent™ (Recaldent Pty, Melbourne, Australia), in which the ACP has been used in

a paste that contains casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)¹⁴⁸. Another ACP-containing light-cured orthodontic adhesive product has been marketed as Aegis®-Ortho (The Bosworth, Skokie, IL, USA)⁵⁹. An *in vitro* study⁶⁰ has showed that Aegis® Ortho has an adequate bond strength for orthodontic purposes. An *in vivo* study¹⁶ involving the survival rate of orthodontic brackets over a 12-month period using Aegis®-Ortho as compared to a conventional adhesive, showed that the bond failure rates of the conventional adhesive and Aegis®-Ortho adhesive were 2.67 and 3.8%, respectively, and that there was no significant difference between these two systems. Thus, it can be concluded that ACP has the ability to effectively remineralize enamel caries lesions *in vitro*⁶¹.

Many studies have been carried out to improve the properties of fabricated NACP¹⁴⁹. Xu¹⁵⁰ patented and used NACP, wherein the particles size was about 10–500 nm, 5–90 wt% was used in the composite whereby comparable mechanical and antibacterial properties to commercial composites was decreased. Melo *et al.*²⁴ incorporated NACP (0, 10, 20, 30, and 40 wt%) and nano-silver 2-ethylhexanoate particles in Scotchbond™ Multipurpose (3M ESPE, St. Paul, MN, USA) and it was found that NACP and nano-silver based bonding agent exhibited a strong dentin bond strength and also showed a potent antibacterial activity. NACP itself had shown little antibacterial activity, however with the addition of 0.1% nano-silver, the antibacterial properties had improved, and the dentin bond strength remained stable with an increase in the concentration of NACP. Figure 2 shows the dentin-adhesive interface and it was observed that adhesives filled the dentinal tubules and the resin tags were formed. The hybrid layer was indicated to be between the adhesive and the underlying mineralized dentin. Numerous NACP nanoparticles in the adhesive layer were observed in the hybrid zone, as well as inside the dentinal tubules.

Zhang *et al.*⁶² used NACP and developed the first generation of rechargeable CaP composites, showing a substantial recharge together with the sustained long-term release of Ca²⁺ and P³⁺ ions for remineralization and caries-inhibition. In addition to low mechanical properties and its inability to resist cracking under masticatory stress, the inherent issue in ACP composites is an aggregation of ACP particles. This problem has been considered to be one of the main reasons for relatively poor interfacial ACP-resin interactions which also subsequently lead to low mechanical strength when compared with silanized glass-reinforced composites⁴³. Therefore, strategies have been developed to address this issue and to enhance the ACP filler-polymer matrix interfacial properties by better controlling the particle size distribution and surface properties, this being done by the fine-tuning of the resin¹⁵¹.

HA-based dental resins

HA is the most stable form of CP compounds *in vivo*¹⁵². Okazaki and Ohmae²⁰ were the first to use crystallized HA in dental composites and claimed that when the

Fig. 2 SEM micrographs of dentin-adhesive interfaces. (A) Scotchbond Multipurpose, (B) Primer and adhesive+nano-silver+20% NACP, (C) Primer and adhesive+nano-silver+40% NACP, (D) P+NAG, A+NAG+20% NACP at a higher magnification, and (E, F) at even higher magnifications. Arrows indicate NACP in the dentinal tubules (Courtesy to Melo *et al.*)²⁴.

Ap/R ratio~1 then it is almost equal to that of teeth and the composites adhered well to enamel without a bonding agent. Various studies^{70,90} were conducted to compare silanized and non-silanized HA in resin matrix and an enhancing effect was found on the mechanical and physical properties of the composite with silanized HA⁹⁰. However, it has been previously reported that by adding nano-HA as a filler, the material then becomes unsuitable for clinical performance and is hydrolytically unstable as compared to composites with microscopic particles^{86,87}. The hydrophilicity of HA is due to the presence of the –OH group in its hexagonal structure that can easily attract surface moisture¹⁵³, however it can be addressed with surface grafting during *in situ* synthesis¹⁵⁴.

This review study reflects a trend towards the use of nano-filler particles/fibers in dental resins, which could be due to their inherent characteristics of a high surface area, offering good mechanical interlocking with the polymer matrix. However, it has been reported that flexural strength, fracture toughness and compressive strength values decreased with an increase in the concentration of nano-HA and nano-HA whiskers in resin matrices^{74,77}. It has been suggested in these studies that a specific decrease in the percentage of filler content might be related to the agglomeration of fillers⁷³. HA has relatively better mechanical properties than ACP, however still not at a satisfactory level. The fracture toughness of dense and porous HA has been reported to be 0.8–1.2 MPa.m⁻¹ and 0.45–0.75 MPa.m⁻¹, respectively¹⁵⁵. The reported bending and compressive strength of dense and porous HA were found to be 38–250 MPa, 120–150 MPa, and 2–11 MPa, 2–100 MPa, respectively¹⁵⁶⁻¹⁶⁰. Due to its low mechanical properties,

Fig. 3 SEM images after 36 h of cell culturing on composite resins, (A) 100% resin matrix, (B) Resin matrix+HA30%, (C) Resin matrix+HA50%, (D) Resin matrix+HA15%/silica15%, and (E) Resin matrix+ HA25%/silica25% (Courtesy to Chadda *et al.*)⁹¹⁾.

this material has limitations in load-bearing clinical applications. The main reason for its low mechanical properties is its porosity, which makes it easier for micro and macro cracks¹⁶¹⁾. Therefore, in some studies, instead of using particulates; fibers and whiskers have been used which have yielded relatively better mechanical results. The same trend has been observed when HA nano-fibers were added with micro-size silica particles. The dental composite with 3 wt% nano-HA fibers and 57 wt% silica micro-particles had a 29.2% higher biaxial flexural strength in comparison with the control specimen without nano-HA. It was thus suggested that the double-edged effects *i.e.* the reinforcing and weakening effects may be due to well dispersion and agglomeration, respectively, and can be produced with the impregnation of nano-HA fibers into dental resin⁸⁰⁾.

Recently, in a similar study⁸⁹⁾, nano-whiskers were incorporated (0–100 vol%) into dental resin and the mechanical properties thereof were compared to commercial composites. It was found that HA whiskers with a 20 vol% showed comparable results to commercial composites. Khalid *et al.*¹⁶²⁾ added silanized nano-HA in dental resins in two different ratios and compared it to micro-hybrid and flowable composites. It was revealed that experimental composites had a better degree of conversion and minimal leaching of unreacted monomers when compared to commercial composites. The *in vitro* cytotoxicity of HA-based dental composites was evaluated and it was found that all experimental composites with

HA and HA/silica were non-toxic, signifying that these composites exhibited favorable biological behavior which may also support cell proliferation⁹¹⁾. Figure 3 shows the attachment of human bone marrow (hBM) mesenchymal stem cells (MSC) to all composite resins based on HA and HA/silica. The features of cell attachment were observed to be different on the surfaces of these composites based on their material properties. The most commonly observed morphologies were unipolar, bipolar, rounded, and flattened (amoeboid) shapes. However, they all supported hMSC attachment, whereby prominent cell spreading was seen in composites with HA/silica.

TCP/MCPM based dental resins

It has been suggested that pure HA has a too low dissolution rate, therefore, improvisations such as the usage of biphasic apatites (HA/TCP) can provide optimum resorbability and dissolution rates. Furthermore, pure TCP is highly soluble and has high dissolution rate which forms HA. The dissolution order of the CP family is: TTCP> α -TCP>DCPD>DCPA>OCP> β -TCP>HA¹⁴⁴⁾. β -TCP has been used primarily in synthesizing biphasic or monophasic bioceramics and α -TCP is part of many bone cements. β -TCP has been used more extensively in clinical applications of dentistry, maxillofacial surgery, tissue engineering and orthopedics than α -TCP¹⁶³⁻¹⁶⁵⁾. In dental composite, TCP as a filler has been reported to increase water absorption due to the loss of minerals when it comes into contact with water, which further causes weakening of the mechanical strength of filling. The mechanical properties (flexural strength and modulus) have been shown to decrease with the addition of CP; however, the lowest obtained value was 101 MPa, which showed comparative strength to commercial composites. It has been reported that these composites have the potential to solve issues of microleakage and recurrent caries as well as to promote the remineralization of demineralized dentin. Tri strontium phosphate, polylysine, and MCPM have been incorporated into dental resins and the results showed that this promoted hygroscopic expansion, apatite formation, and early polylysine release¹¹⁸⁾. A newly developed apatite layer was formed after immersing these composites in simulated body fluid (SBF) for 4 weeks and it was further observed that after 4 weeks the layer thickness was approximately 20 μ m as shown in Fig. 4.

BAG based dental resins

In 1969, Larry Hench and his co-workers laid the foundation of bioactive ceramics by developing Hench's 45S5 Bioglass®, which was found to be successfully bonded in a chemical manner to the hard tissues. There are different types of biocompatible BAG, for example, conventional Hench's Bioglass®, as well as phosphate-based bioglass and borate-based bioglass which have been later introduced^{166,167)}. Sauro *et al.*¹⁰⁷⁾ investigated the therapeutic effects of Bioglass 45S5 and zinc-polycarboxylated BAG-based dental composites on the bonded-dentin interface. The dimethacrylate-based

Fig. 4 SEM images of resin-based composites with MCPM/Tri-strontium with (F1) and without (F2) polylysine showing apatite layer after immersing in SBF for periodic time interval (Courtesy to Panpisut *et al.*)¹¹⁸.

resin matrices were used, and the concentration of these particles was 33 wt%. The experimental composite showed an increase in nano-mechanical properties, while simultaneously reducing the micro-permeability along the dentin-bonded interface, this occurring by means of the therapeutic remineralization of imperfect mineral-depleted areas as shown in Fig. 5. Furthermore, the surface of the specimen exhibited several ‘funnelled’ dentinal tubules with no exposed collagen fibrils and it was mainly protected by residual resin and mineral crystals which were embedded within a resin/collagen network. Both BAG and F-BAG resins induced the precipitation of mineral contents inside the dentinal tubules and onto the surface. Also, the F-BAG resins showed a higher modulus of elasticity (13%) and an increase in stiffness of demineralized dentin when compared to BAG-based samples and control samples. This might be due to the release of fluoride and phosphate ions, which can accelerate the remineralization process. Recently, F-BAG and BAG have been added in dimethacrylate based resins and it has been found that F-BAG based composite shows more bioactivity than conventional BAG, as well as accelerated dentin remineralization, F-BAG furthermore showed a higher ability to reduce the solubilization of C-terminal cross-linked telopeptides (ICTP) and C-terminal telopeptides⁹². Khvostenko *et al.*⁹⁶ synthesized BAG (15 wt%) and incorporated it into resin matrices along with strontium

Fig. 5 (A) AFM image showing the resin–dentin interface created with resin based on BAG/Zn after 3 month storage in SBF showing a clear indentation mark on the hybrid layer (HL), (B) This confocal scanning microscope image showing a clear HL with long resin tags penetrating the dentinal tubules (t) and a substantial presence of BAG-Zn filler (FL) within the adhesive layer, (C) Reflection/fluorescence lacune mode showing a resin–dentin interface characterized by a porous HL completely infiltrated by the LY dye (pointer) after 24 h of SBF solution storage, and (D) The confocal scanning microscope single projection image captured from resin–dentin interfaces after prolonged SBF storage (3 m) showing a strong reflection signal both in HL and dentinal; a limited microporosity at the bottom of the HL is also evident (pointer) (Courtesy to Sauro *et al.*)¹⁰⁷.

glass and their *in vitro* study showed a significant antimicrobial effect by reducing the extent of bacterial biofilm penetration into pre-existing marginal gaps.

In the last five years, the trend has shifted towards BAG based dental restorative materials as compared to HA and ACP. One reason could be due to the inherent property of remineralization as well as the inhibition of bacterial decay. The antimicrobial effect of BAG is attributed to the release of ions such as those from calcium and phosphate that have a toxic effect on oral bacteria, which also tend to neutralize the local acidic environment⁹⁶.

ACTIVA BioACTIVE-RESTORATIVE

A relatively new resin modified restorative material product ACTIVA BioACTIVE (Pulpdent) was marketed in 2013 and has shown continuous passive diffusion of calcium, phosphate and fluoride ions through the restorative material. According to manufacturers, ACTIVA RESTORATIVE is the first commercial bioactive dental material with ionic resins¹²⁶. ACTIVA

is a dual cure material with self-adhesive properties and comes in the form of bulk-fill flowable (<http://www.pulpdent.com/activa-bioactive-bulk-fill>).

It consists of diurethane modified by the insertion of hydrogenated polybutadiene and other methacrylate monomers, polyacrylic acid, silica, and sodium fluoride¹²³. Another study has confirmed the presence of BAG (55.4 wt%) in this material¹²⁹, however, the actual composition is not known due to commercial reasons. ACTIVA BioACTIVE-RESTORATIVE is a bioactive composite that can chemically bond to teeth, restricts bacterial ingress, releases fluoride, and therefore delivers all the advantages of glass ionomers in a strong, resilient, resin matrix¹²⁴. This composition allows for the release of calcium, phosphate, and fluoride; it enhances wear-resistance and fracture-resistance; protects against microleakage; and has antibacterial properties¹²⁰. ACTIVA BioACTIVE-RESTORATIVE has also shown less bacterial leakage (80% less) compared to RMGIC and zinc phosphate cement¹²¹.

Bansal *et al.*¹²³ investigated the wear pattern of Activa Bioactive and it was observed that abrasive wear occurred due to shear forces applied by the antagonist subsequently causing a fracture in the microscopic surface of materials. The elastic modulus of this bioactive composite was higher than that of RMGIC and conventional GIC *i.e.* 4.45 GP, 2.89 GPa, and 2.57 GPa, respectively. Due to the high modulus of Activa Bioactive, it withstood the repeated cyclic stress and its superior flexural fatigue attributed to the resilience of its modified resin matrix. An *in vitro* study¹²⁵ with human dental pulp stem cells (hDPSC) showed that the elutes of Activa Bioactive were more cytotoxic compared to calcium hydroxide-incorporated (Dycal Dentsply, York, PA, USA) and MTA-like incorporated (Theracal, Bisco, Schaumburg, IL, USA) pulp capping materials. Furthermore, it was claimed that Activa Bioactive exhibited the potential to stimulate biomineralization at the same level as other pulp capping materials and that it released the same amount of Ca and OH ions.

The comparison of the shear bond strength of Activa Bioactive with Biodentine (Septodont, Orange, CA, USA), Ever X posterior (GC, Tokyo, Japan) and SDR surefil (Dentsply) showed that Activa had a higher bond strength as compared to Biodentine but lesser than SDR and Ever X. However, it was claimed that the physical properties of Activa were comparable to that of RBC. The other advantage is easy handling as the material is left undisturbed for about 20 s after injection, the physical handling thereof thus allowing the polyacid component to etch the tooth¹²⁴. Another study¹²² compared the flexural strength and flexural fatigue of ACTIVA BioACTIVE-RESTORATIVE to flowable composite (Tetric Evo Flow), resin modified glass ionomer cement (Geristore) and conventional GIC (Fuji IX), whereby it was found that the flowable composite demonstrated a higher flexural strength (115.2 MPa) and flexural fatigue (68.4 MP) as compared to ACTIVA BioACTIVE-RESTORATIVE (105.4 and 63.7 MPa, respectively). However, the flexural strength of flowable composite

and ACTIVA BioACTIVE-RESTORATIVE were above the minimum requirement of ISO 4049 for occlusal restorations *i.e.* 80 MPa. Thus, these materials are suitable in stress-bearing areas. However, the flexural strength values of RMGIC and conventional GIC did not meet the minimum requirement of ISO specification. This new class of bioactive materials with remineralizing properties offers promise to reverse tooth decay, regain lost minerals, and inhibit recurrent caries¹²⁰.

Recently, calcium silicate-based materials have gained acceptance for dental application due to their resemblance to MTA. One of the products which have been widely accepted is 'Biodentin™', the dentin replacement material, and it is commercially available since 2009 by Septodont (<http://www.septodontusa.com/products/biodentin>). The main components of Biodentin are tricalcium silicate, dicalcium silicate, calcium carbonate, and zirconium oxide. Calcium chloride and hydrosoluble polymer are the liquid components¹⁶⁸.

CONCLUSION

It is concluded from this review that the use of bioceramics in dentistry has gained interest in the last decade and it is an example of the evolution in dental resin-based restorative materials. However, it was found to be mostly added to dental adhesives as compared to direct restorative filling composites. Among these, ACP was used the most frequently followed by HA, BAG, DCP, and MCPM. Few studies were however based on TCP and TTCP. The trend of using nano-particles/fibers was also discussed in this review and 25% of studies showed the usage of nano-materials (NACP and nano-HA) in dental resin restorative materials. Although the effects of bioceramics have been investigated since 1988, only two human trials and three *in vivo* (rat models) studies have been conducted. *In vitro* studies were mainly focused on mechanical properties followed by physical, chemical and biological properties to evaluate the performance of these restorative materials. Recently, ACTIVA BioACTIVE-RESTORATIVE (Pulpdent) has been introduced as a bioactive RBC, but still this material needs further thorough investigation as only nine studies have been found to date. With the advent of bioceramics-based restorative materials, dental professionals will be able to produce sophisticated restorations, bonding elements, and effective interfacial adhesion. By understanding the chemical, physical and biological nature of these restorative materials, the clinician will be able to choose the appropriate materials as needed and produce a high-quality product to satisfy the patient's dental needs.

FUTURE DIRECTIONS

It is well established that bioceramics (*i.e.* HA, ACPs and BAG) have excellent biological, exceptional biocompatible and bioactive properties due to similarity with human hard tissues. The restorative materials based on these bioceramics have shown their potential to be used in clinical dentistry. However, concern has been noticed in

terms of their mechanical properties. Therefore, in future, more research is required to improve their physical and mechanical properties without decreasing the biological potential. A further need is to improvise their design and processing parameters to limit their brittleness, so it can be used in load bearing (masticatory load) area. Ionic substitution in bioceramics can improve the biological and mechanical properties; as an ionic-covalent structural model of the CP family seems ready to accept both cationic and anionic substituents. These substitutions may induce modifications in the lattice parameters as well as in the crystallinity of the materials, both of which are responsible for influencing the solubility of these materials under physiological conditions. Surface modification during the *in situ* synthesis and doping with amine, bromine, and with metal ions can also lead to the improvement in the properties of fillers, and subsequently as well as dental restorative composites. A new challenge will be to increase the toughness and it is anticipated that co-precipitation with ceramics such as zirconia, titania, alumina can enhance the physical and mechanical properties of restorative composites. The reported studies on bioceramics-based restorative materials are mainly based on *in vitro* testing and little attention has been paid to their *in vivo* and clinical applications. Therefore, it will be required to evaluate the clinical application of these materials within the physiological limits of masticatory loads. This review has shown that bioceramics-based dental restorative composites have produced tremendous results, however, further research is required to fully investigate the potential performance of these composites in clinical applications.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Maria Khan for her assistance in reviewing the final data and Dr. Steph Smith for helping in proof reading. Further report that no financial funding and support was received in the preparation of this manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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