World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Osteoconductivity of biphasic calcium phosphate as a bone graft in bone regeneration process: Scoping review

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World Journal of Advanced Research and Reviews, 2025, 25(01), 987-998

Publication history: Received on 30 November 2024; revised on 08 January 2025; accepted on 10 January 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.25.1.4044

Abstract

Introduction: Currently, various biomaterials in the biomedical field have been developed to be utilized as bone grafts. Bone graft is a living tissue that is transplanted into bone defects and thus help the bone healing process. One of the bone grafts that has been developed and has many advantages is Biphasic Calcium Phosphate (BCP). BCP is a combination of Beta-Tricalcium Phosphate (β-TCP) and Hydroxyapatite (HA). HA has strong osteoconductive properties but has the disadvantage of low tensile stress and very slow resorbability, while β-TCP is known as a material with fast resorbability. The rate of bone regeneration produced by BCP is faster than the use of HA or β-TCP alone because it has been shown to have strong osteoconductive property. The purpose of this scoping review is to review the literature to determine the osteoconductive properties of BCP as a bone graft in the bone regeneration process.

Method: To obtain journal data, a search was conducted using three databases: PubMed, ScienceDirect, and Scopus. Of the three found 239 journals. Data were selected based on inclusion and exclusion criteria. The title, abstract and full text of each study were carefully analysed. Data extraction was made based on histology, histomorphometry, micro-CT, and bone regeneration osteogenic gene expression.

Result: There were 40 selected articles and the results showed the osteoconductivity of BCP in accelerating the process of bone regeneration through histology, histomorphometry, micro-CT, and osteogenic gene expression.

Conclusion: Osteoconductivity of BCP can be used as bone graft in bone regeneration process.

Keywords: Biphasic Calcium Phosphate; Bone Graft; Bone Regeneration; Medicine; Osteoconductivity

1. Introduction

Until now, synthetic materials are growing rapidly in the biomedical field to replace human organs, or what are known as biomaterials. Biomaterial is a material used to replace or repair the function of damaged or degenerated tissues and organs and is expected to improve the patient's quality of life.[1]Based on the type, there are 5 types of biomaterials, including polymers, metals, natural materials, composites, and bioceramics.[2]

Bioceramics are inorganic biomaterials with a combination of ionic and covalent bonds that play an important role in biomedical engineering applications. In general, bioceramics are divided into four parts, oxide ceramics, glass and glass-ceramics, calcium phosphate ceramics, and bone cements and substitutes.[3] Several types of calcium phosphate ceramics are often used in the biomedical field, including Hydroxyapatite (HA), Tricalcium phosphate, and Biphasic

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calcium phosphate.[4] Bioceramic is osteoconductive and biocompatible, therefore it can be used as bone graft material for bone tissue regeneration because the mineral elements have similarities to human bone, which can induce cell infiltration, cell proliferation, and new bone formation.[4–6] Bone graft can be transplanted into damaged bone because it has mineral elements that resemble bone, thus it can accelerate the process of bone regeneration. Bone grafts are classified into two categories, including natural and synthetic bone grafts.[7]

Biphasic Calcium Phosphate (BCP) is a type of synthetic bone graft consisting of a combination of β-Tricalcium Phosphate (β-TCP) and Hydroxyapatite (HA).[8] Hydroxyapatite has strong osteoconductive properties and excellent biocompatibility, because its chemical structure is similar to the bone mineralization phase, but HA has the disadvantages of low tensile stress and very slow resorbability. β-TCP is generally known as a bioceramic with fast resorbability, therefore it can replace bone tissue quickly.[9] Hence, the rate of bone regeneration produced by BCP is faster compared to the use of HA or β-TCP alone.[7] This is because BCP is proven to be strong osteoconductive and biocompatible, its composition is ideal for use as a bone regeneration material. HA provides volume stability, while β-TCP promotes a bioactive response with faster degradation.[10] Osteoconduction is very important in the process of bone regeneration because it maintains space for new bone growth, which in turn will occur in the process of osteogenesis to produce bone-forming cells.[11]

The ideal design of BCP in accelerating the bone regeneration process can be achieved by modifying the ratio, particle size, and microstructure of HA and β-TCP.[12] BCP can be used as a gold standard in the use of bone grafts due to better bioactive and osteoconductive properties compared to other bone grafts.[10, 12] Considering BCP is able to form bone simultaneously, which has evidenced by a number of in vitro and in vivo studies.[13]

Based on the above background, this scoping review aims to examine the literature in order to determine the osteoconductive properties of BCP as a bone graft in the bone regeneration process.

2. Methods

2.1. Searching and selection studies

In the beginning of the study, the author made a research question whether BCP supports osteoconduction in bone regeneration. Electronic journal searches used the Pubmed, ScienceDirect, and Scopus databases. The search process to get the results according to the purpose using the keywords BCP, bone regeneration, and osteoconductivity using the Boolean "AND". Modification of the search on the database was done to get more relevant results (Table 1). The literature search process was carried out for two months.

Journal collection was carried out based on topics and research objectives that are in accordance with predefined keywords. All journals collected were then selected, if there were the same journal title, the duplicate journal will be deleted. The inclusion criteria used were studies involving an unlimited number of BCPs, data on general BCP exposure, osteoconduction, histologic features, histomorphometry, micro-CT, and gene expression of osteogenic bone regeneration, clinical trial study design, journal publications in the last 5 years, and journals are experimental studies in vivo. Exclusion criteria included BCP not being an intervention in the study and data in the form of article reviews, clinical case studies, qualitative studies, and case reports.

This study used a scoping review by adapting the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-analyses) for journal search strategies.

2.2. Data extraction and synthesis

The data extraction process was taken from journals with titles and abstracts that match the topics and keywords. In the final step, 40 studies were selected for data extraction. Characteristics of research data in selected journals were extracted based on the osteoconductive properties of BCP in the bone regeneration process seen from histology, histomorphometry, micro-CT, and osteogenic gene expression. Data included author and year of publication.

The next strategy for synthesizing data, this review used tables to describe the most discussion of the findings. The most studies on the findings are about the osteoconductivity of BCP in in vivo studies by displaying data on histology, histomorphometry, micro-CT, and osteogenic gene expression in bone regeneration. The 40 journals were then read carefully in full paper. See Table 1.

Table 1 Search keywords

Keywords	Synonyms
BCP	*"BCP", "biphasic calcium phosphate", "biphasic calcium phosphate ceramics", "HAp/betaTCP" , "HA/β-TCP" , "HA/beta-TCP" "HA/beta TCP" "β-tri-Calcium phosphate" "HA/β tricalcium phosphate"*
Osteoconduction	*"osteoconductivity", "osteoconductive", "osteoconduction"*
Bone regeneration	*"bone generation", "bone remodeling", "bone healing","bone tissue engineering", "osteogenesis", "bone integration", "bone substitute","bone graft", "osteogenic differentiation", "bone tissue regeneration", "bone graft", "bone graft substitutes"*

3. Result

3.1. Study Selection and Data Collection Process

The author divided 3 groups with the stages of finding journals, distributing journals and extracting journals based on the inclusion and exclusion criteria at PICO, with P (Problem) in the form of bone graft, I (Intervention) in the form of a group with BCP, C (Comparison) in the form of a group without BCP treatment. or with other material treatment, and O (Outcome) in the form of bone regeneration. In the initial journal search of all databases, PubMed 7 journals, Scopus 10 journals, and ScienceDirect 222 journals were found. The total number of journal searches is 239 journals. Among them, 204 journals were excluded because after reviewing the titles and abstracts the journals did not meet the criteria. The eligible journals are 40 journals that meet the inclusion criteria (Figure 1). The results of the journal search found 4 parameters, including journals that evaluated histology (Table 2), histomorphometry (Table 3), micro-CT (Table 4), and the expression of the osteogenic osteoconductivity gene (Table 5). The author used these 4 parameters due to the findings of most studies and can represent qualitative and quantitative data that show the process of bone regeneration.

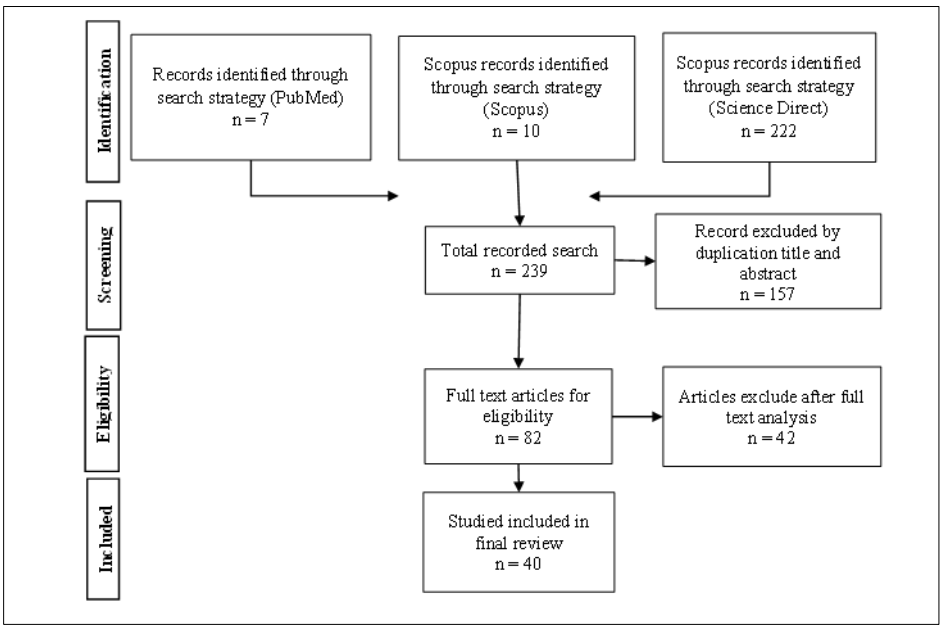

Figure 1 Flow chart of literature adapted from PRISMA method: from identification and screening inclusion of studies.

4. Histology

Of the 40 selected articles, there were 30 articles that evaluated the qualitative data obtained from the formation of new bone after BCP bone grafting which was seen through histology with bone-forming cell parameters. See Table 2.

Table 2 Histological results on the use of previously performed BCP**.**

No.	Authors	Journal Name, Volume, Year	Histological results
1.	Danesh-Sani *et al*	Wolters Kluwer Health, Inc, 25(5), 2016. [14]	New bone is formed on BCP particles that are associated with each other, marked by osteocyte proliferation.
2.	Pripatnanont *et al.*	International Journal of Oral and Maxillofacial Implants, 31(2), 2016.[9]	There is an increase in new bone formation which is characterized by the presence of osteoblasts fused with BCP at week 8.
3.	Rustom *et al.*	Acta Biomater, 44, 2016.[15]	The presence of osteocytes in the lacunae of new bone tissue was seen in BCP scaffolds.
4.	Jelusic *et al.*	Clinical Oral Implants Research, 28(10), 2017.[16]	New bone, osteoclasts and osteoblasts are formed after 6 months.
5.	Jensen *et al.*	Clinical Oral Implants Research, 18(6), 2017.[17]	Osseous healing occurred at week 24 with the formation of osteoblast cells around the BCP material.
6.	Shim *et al.*	Journal of Industrial and Engineering Chemistry (55), 2017.[18]	On day 10, the BCP group showed ALP activity which is an early marker of immature osteoblast activity.
7.	Tang *et al.*	Materials science & engineering. C, Materials for biological applications, 70, 2017.[19]	There is a picture of new bone formation at week 16 which is characterized by the formation of fibrous tissue around the BCP material.
8.	Zhang *et al.*	Materials Science and Engineering, 147, 2017. [19]	At week 12 found new bone formation with good integration of host bone and accompanied by proliferation of osteocytes and osteoblasts.
9.	Gjerde *et al.*	Stem Cell Research and Therapy, 9(1), 2018.[20]	There is an increase in the width and volume of the alveolar ridge. New bone and osteoblasts form on the surface after 5 months.
10.	Hameed *et al.*	Biochemical and Cellular Archives, 18(1), 2018. [21]	There was an increase in bone density accompanied by many osteocytes formed until day 60.
11.	Taz *et al.*	Journal of Biomaterials Applications, 32(10), 2018.[22]	There is new bone formation and increased osteocyte activity.
12.	Touri *et al.*	Materials Science & Engineering C, (84) 2018.[23]	There is an increase in the viability and proliferation of osteoblasts.
13.	Wang *et al.*	Ceramics International, 44(2), 2018.[24]	Visible formation of osteoblast cells around the BCP material after 7 days.
14.	Zhang *et al.*	The International journal of oral & maxillofacial implants, 33(3), 2018.[25]	In the 6th week there is proliferation of osteoblast cells.
15.	Neto *et al.*	Pesquisa Brasileira em Odontopediatria e Clinica Integrada, 19(1), 2019.[26]	There is proliferation of osteoblasts, osteoclasts, and osteocytes in bone defects.
16.	Oh *et al.*	International Journal of Oral and Maxillofacial Implants, 34(1), 2019.[12]	New bone formation is seen based on the number of osteoclasts.
17.	Prem *et al.*	The International Journal Periodontics Restorative Dent, 39(3), 2019.[27]	New bone is formed which is characterized by the presence of osteons consisting of Haversian canals and surrounded by lamellae and canaliculi.

18.	Kang *et al.*	Materials Science and Engineering C, 110, 2020.[28]	There was an increase in the formation of new bone which was seen in the 6th month accompanied by an increase in the proliferation of osteoblasts.
19.	Lee *et al.*	Materials, 13(6), 2020.[29]	Bone neoformations were seen extending from the inside of the BCP at weeks 4 and 12 with marked osteocyte proliferation.
20.	Lima *et al.*	Carbohydrate Polymers, 245, 2020.[30]	Thin, irregular and immature bone trabeculae are formed bone tissue by reactive osteoblasts and osteocytes on day 30.
21.	Prem *et al.*	Ceramics International (46) 2020.[27]	There is an increase in the growth of osteoblasts on bone-implant applications.
22.	Uetanabaro *et al.*	The International Journal of Oral & Maxillofacial Implants, 35(1), 2020.[31]	After 90 days, new bone formation was seen, accompanied by proliferation of osteocytes and osteoblasts.
23.	Ventura *et al.*	Materials and Design (192) 2020.[29]	At week 8, there was an increase in new bone formation and an increase in osteoblast cells.
24.	Ventura*et al.*	Materials Science & Engineering C (110) 2020.[32]	Cartilage formation occurs in the damaged area which is characterized by the presence of a high number of osteoblasts.
25.	Brito *et al.*	Brazilian Dental Journal, 32(1), 2021.[33]	On day 45 there was an increase in the amount of new bone in the bone defect and a high number of osteoclasts was found.
26.	Junior *et al.*	Scientific Reports (11), 2021.[13]	On day 90 there is an increase in bone formation and proliferation of osteocytes and osteoblasts.
27.	Lezzi *et al.*	Materials, 14(9), 2021.[34]	There is new bone formation which is characterized by the presence of osteoblasts which are deposited into osteoid after 2 months.
28.	Li *et al.*	Bioactive Materials, 2021.[35]	New bone is formed in the rib defect by osteoblasts after 90 days.
29.	Tang *et al.*	Acta Biomater (129) 2021.[36]	There was new bone formation in each group after 12 weeks due to activation of cellular NKA which favoured viability and osteogenic differentiation of osteoblasts.
30.	Zhi *et al.*	Bioactive Materials, 2021.[37]	Osteoblast cells appeared in the fibrous bone tissue after 18 months.

Previous research conducted by Junior *et al* and Li *et al* proved that BCP can accelerate the process of new bone formation.[13, 35] Uetanabaro *et al* also concluded that BCP can increase the process of new bone formation which is characterized by an increase in the proliferation of osteocytes and osteoblasts. New bone is formed characterized by the presence of osteons consisting of Haversian canals and surrounded by lamellae and canaliculi.[31]

5. Histomorphometry

Out of the 40 selected articles, 9 articles evaluated quantitative data obtained from histomorphometry results after BCP administration with parameters of percentage and surface area of new bone formation. See Table 3.

Table 3 Histomorphometry results on the use of BCP that have been done previously.

No.	Authors	Journal Name, Volume, Number, Year	Histomorphometry results
1.	Danesh-Sani *et al*	Wolters Kluwer Health, Inc, 25(5), 2016.[14]	The average percentage of new bone formation was 29.2%.
2.	Bedeloglu *et al.*	Journal of Dental Sciences 12, 2017.[38]	New bone formation was 55.6 ± 14.1%.
3.	Jensen *et al.*	Clinical Oral Implants Research, 18(6), 2017.[17]	New bone formation occurred up to 51.6% until the 24th week.
4.	Hameed *et al.*	Biochemical and Cellular Archives, 18(1), 2018.[21]	New bone was formed with a surface area of 58.5 mm2 ± 0.1 mm2 on day 60.
5.	Puigpelat *et al.*	The International Journal Periodontics Restorative Dent, 39(3), 2019.[29]	New bone formation was 83% ± 27.0%.
6.	Lee *et al.*	Materials, 13(6), 2020.[39]	The percentage of new bone particles was 34.99% ± 1.71% and mineralized bone was 43.19% ± 5.03%.
7.	Brito *et al.*	Brazilian Dental Journal, 32(1), 2021.[33]	The percentage of bone volume on day 45 eas 25%.
8.	Han *et al.*	Biomaterials, 272, 2021.[40]	New bone was formed up to a surface area of 2.55 mm2 ± 1.89 mm2 at the 4th week.
9.	Nascimento *et al.*	International Journal of Environmental Research and Public Health, 18(2), 2021.[41]	At month 6, the percentage of new bone formation was 27% ± 4.3%.

The percentage of new bone formation produced by BCP is 83% ± 27.0% (Puigpelat *et al*, 2019). Another study with similar results conducted by Hameed *et al.* (2018) In vivo new bone formation occurs with a surface area of 58.5 mm2 ± 0.1 mm^2 on day 60.

6. Micro-CT

Out of the 40 selected articles, there were 11 articles that evaluate new bone formation after BCP administration as seen through Micro-CT results with the parameter of bone volume percentage compared to tissue volume (% Bone Volume / Tissue Volume) (Zhi *et al.*, 2021). See Table 4

Table 4 Micro-CT results on previous use of BCP.

No.	Authors	Journal Name, Volume, Year	Micro-CT results
1.	Pripatnanont *et al.*	International Journal of Oral and Maxillofacial Implants 31(2) 2016.[9]	The percentage of new bone volume formed in BCP1 (8:2) by 20.70% ± 2.76% and BCP2 (9:1) by 20.72% ± 3.97%
2.	Rustom *et al.*	Acta Biomaterialia, (44) 2016.[15]	The percentage of new bone volume formed by 83% ± 3%
3.	Jelusic *et al.*	Clinical Oral Implants Research, 28(10), 2017.[16]	The percentage of new bone volume formed by 38.42% ± 12.61%.
4.	Gjerde *et al.*	Stem Cell Research and Therapy, 9(1), 2018.[20]	The percentage of new bone volume formed by 13,34 %
5.	Oh *et al.*	International Journal of Oral and Maxillofacial Implants, 34(1), 2019.[12]	The percentage of new bone volume formed by 35,21 % ± 6,93 %

6.	Kang *et al.*	Materials Science and Engineering C, 110, 2020.[28]	The percentage of new bone volume formed by 30% ± 1.1%
7.	Lee *et al.*	Materials, 13(6), 2020.[28]	The percentage of new bone volume formed by 53.12% ±10.73%
8.	Uetanabaro *et al*.	The International Journal of Oral & Maxillofacial Implants, 35(1), 2020.[31]	The percentage of new bone volume formed by 37 %
9.	Ventura *et al.*	Materials Science & Engineering C (110) 2020.[29]	The percentage of new bone volume formed by 34.98% ± 6.95%
10.	Li *et al.*	Bioactive Materials, 2021.[42]	The percentage of new bone volume formed by 43 % ± 3%
11.	Zhi *et al.*	Bioactive Materials, 2021.[37]	The percentage of new bone volume formed by 90%

Previous research conducted by Rustom and Lee indicated a good BV/TV presentation after BCP administration for bone defects was 83% ± 3% and 53.12%±10.73%.[15]

7. Osteogenic Gene Expression

From 40 selected articles, there are 10 articles that discuss about new bone formation after BCP administration as seen through the results of gene expression that effected the process of osteogenesis and each journal uses different parameters in their research. See Table 5.

Table 5 Osteogenic gene expression result on the use of previously performed BCP.

No.	Authors	Journal Name, Volume, Year	Osteogenic gene expression result
1.	Garai dan Sinha	Materials Science and Engineering C, 59, 2016.[43]	The ALP assay showed an increase enzyme at day 21.
2.	Huang *et al.*	Materials Science and Engineering C 70, 2017.[44]	There was an increase in ALP osteogenic gene expression activity.
3.	Li *et al.*	Materials Science and Engineering C, 80, 2017.[28]	Increased osteogenic genes BSP, Bglap, Alp, BMP-2 and COL-1
4.	Shim *et al.*	Journal of Industrial and Engineering Chemistry, 68, 2018.[18]	There was increased of Runx2, ALP, OCN and OPN expression
5.	Sayed *et al.*	Materials Science & Engineering C, 105, 2019.[45]	On day 7 and 14, earlystage markers, ALP and OPN significantly expressed the heat shock effect on osteogenic activity.
6.	Gu *et al.*	Journal of biomedical materials research. Part B, Applied biomaterials, 108(4), 2020.[46]	There is an increase in the osteogenic ALP and COL-1. genes expression on the 7th day.
7.	Kang *et al.*	Materials Science and Engineering C, 110, 2020.[28]	There is a protein Osteopontin (OPN), Osteocalcin (OCN), Alkaline phosphatase (ALP), Collagen-1(COL-1) expression at BCP scaffold after incubation on 7th and 14th days
8.	Ventura *et al.*	Materials Science & Engineering C, 110, 2020.[29]	ALP and BSP expression increased after the third day of incubation in osteogenic media
9.	Li *et al.*	Bioactive Materials, 2021.[42]	COL-I, BSP, OPN and OCN expressions were found in BCP-nano, and osteogenic differentiation of MC3T3 occurs.

10.	Tang *et al.*	Acta Biomaterialia, 129, 2021.[36]	BCP-induced NKA activation is beneficial for viability and osteogenic differentiation of osteoblasts.

Administration of BCP in bone defects can increase genes expression such as Alkaline Phosphatase (ALP), Osteopontin (OPN), Collagen-1 (COL-1), Osteocalcin (OCN), as well as others various genes that signal an early osteogenic process.[8, 28, 42]

8. Discussion

The latest evolution in the medical field is the use of synthetic or natural bone grafts as an alternative to bone substitution therapy. The requirements for synthetic bone graft materials include: must have similar physical and chemical properties with the original tissue, biocompatible, its application is simple and can be fixed to the tissue, osteoconductive, and speed of biodegradation similar to natural bone.[12] Commonly used synthetic bone grafts are: calcium phosphate (CaP) based biomaterials, such as Biphasic Calcium Phosphate (BCP). BCP consists of more stable hydroxyapatite [HA, Ca10(PO4)6(OH)2] with strong osteoconductive properties and excellent biocompatibility and Beta-Tricalcium Phosphate with fast resorbability [β-TCP, Ca3(PO4)2] in different ratios. Therefore, the rate of bone regeneration produced by BCP is faster than using HA or -TCP alone.[7, 47]

BCP has significant advantages over autografts, allografts, and another materials CaP, because BCP is biocompatible, osteoconductive, safe to use as a treatment in vitro, in vivo, and clinical models, lower morbidity, and less cost-effectiveness. Kim and Park (2020) stated that BCP has the potential to become the gold standard for bone graft material and as an alternative material or additive in bone regeneration processes in various applications in the field of dentistry and orthopedics, such as dental implants, periodontal disease treatment, defect treatment and bone fracture. The study also proved that BCP has osteoconductive properties in specific HA/β-TCP ratio, and leads to increased osteoblast proliferation and osteogenic differentiation that can accelerate the process of new bone formation.[47]

Previous studies have proven that BCP can be used as a material to support bone regeneration. BCP has been proven to be used as a substitute bone material in cases of bone defects.[40] BCP can release calcium and phosphate ions and increase bone apatite-like crystals, which induce bone formation. BCP Structure which is porous provides a place for blood vessels to penetrate into the bone and provide nutrients in bone cells.[48] The osteoconductivity property makes BCP suitable used as a graft material that can induce bone formation.[49] One of factors that affect BCP osteoconductivity in the process of bone regeneration are size particle. Micro-sized BCPs are proven to increased bone regeneration than with macro size, by increasing the homogeneity of bone distribution.[15] Osteoconductivity property that promotes bone formation can also be increased by increasing ratio of β-TCP/HA that formed BCP, by increasing the rate of bioresorption, so the release of Ca and P ions can advance to trigger osteogenic differentiation.

A number of studies conducted in vivo have shown that BCP has high levels of better osteoconductivity to bone regeneration when compared to other bone grafts. Various tests in in vivo studies were carried out to prove the osteoconductivity of the BCP. Histological picture shows the formation of new bone which is characterized by the presence of osteocytes and osteoblasts.[23, 26, 31] Osteoblasts are described as cuboidal or columnar cells with a nucleus round cells and located in the center of the cell. Osteocytes are described as flat or oval shaped cells with an oval-shaped nucleus. Osteoblasts are located around the bone structure row, whereas osteocytes are located osteocytes spread out in narrow spaces known as lacunae.[50, 51].

According to Lezzi *et al.* (2021), in a study of the use of BCP for sinus augmentation maxillary in sheep experimental animals, the most prominent osteoblasts were formed position around the BCP material after 3 months.[52] The formation of new bone that occurs is clearly depicted in the gaps between the particles as well as in the pores of the BCP material.[22] Histologically there is also a picture of osteons around the BCP material consisting of the Haversian canal, and surrounded by lamellae and canaliculi structures. Another study using BCP material for bone marrow stem cells showed increased proliferation after 7 days. [53]The study of Tang *et al.* (2017) who compared BCP materials with HA and B-TCP alone showed that BCP was better at inducing new bone formation after being observed for 16 weeks.[24]

In vivo studies on the osteoconductivity of BCP to bone regeneration are also described through histomorphometry, which is based on the area of new bone formed around the BCP in mm2 or percent (%). Histomorphometry test aims to determine and evaluate quantitative rate of new bone formation and bone remodeling, which are widely used in the study of the use of biomaterials.[54] Some studies show that there are progressive increases in the area of new formation around the BCP material.[14, 33, 40]

The results of micro-CT can also be used to see the osteoconductivity properties of BCP, by looking at the ratio of bone volume to tissue volume. Various studies have demonstrated that BCP was more effective in increasing new bone volume compared to other bone graft materials. The study conducted by Oh *et al,* proves that mineralized new bone volume after administration of calcium phosphate group (35.21±6.93%) was higher compared with the bovine bone group (31.06±8.27%).[12] Jelusic *et al* also found significant difference in the rate of new bone formation after 6 months of BCP (38.42% ± 12.61%), which is faster than monophasic B-TCP (36.16±19.37%).[16] Pripatnanont *et al* proved an increase in % BV/TV after being given BCP starting from the 2nd week until the 8th week. The new bone volume formation at week 8 when compared to defects not given BCP had lower % BV/TV scores than the BCP group. The study also showed no significant difference in bone volume formed when the composition of HA: TCP was different [BCP1 (8:2) = 20,70 % ± 2,76%; BCP2 (9:1) = 20.72% ±3.97%].[9] Another study proving the osteoconductivity of BCP in forming new bone through BCP values.[15, 20, 31, 42]

Gene expression can be used to show bone osteogenic activity after being given BCP. One of the most frequently used osteogenic markers is alkaline phosphatase (ALP). ALP expression, may exhibit immature osteoblast activity and osteogenic differentiation. After differentiation osteogenic, cells will secrete mineral matrix which will cause calcium deposition, which is an osteogenic marker for mature osteoblasts. The study conducted by Shim *et al* (2018), demonstrated that BCP administration could increase the expression of ALP, and Runx2 also known as Cbfa1.[8] Runx2 plays an important role in the transcriptional control of osteoblast differentiation, an early stage of bone calcification and maturation of osteoblasts. Runx2 can be induced by BMP to stimulate the expression of other osteogenic markers.[8, 44]

Type 1 Collagen (COL-1) which is also an osteogenic differentiation marker detected on post-administration qRT-PCR analysis BCP.[28, 44] Increased expression of other genes after being given BCP include OCN, OPN, and BSP. Apart from expression gene, the osteoinductive nature of BCP can also be demonstrated through the activation of NKA (Na+, K+-ATPase). NKA plays an important role in the process of bone osteogenesis and when NKA is increased the expression of ALP, BMP2, and OCN (osteogenic expression gene) were also increased. Besides that, NKA is also profitable viability and osteogenic differentiation of osteoporotic osteoblasts.[36]

Based on the search results, it was found that BCP was able to stimulate bone formation cell differentiation, new bone formation, and bone attachment because it can induce growth factors such as bone morphogenetic protein (BMP).[40] BCP has a disadvantage that is at 1 days after transplantation will trigger excessive BMP release, which can cause clinical complications such as severe swelling, neoplasm, cyst-like tissue formation, and osteoclastic bone resorption.[55] To overcome this complication, modifications can be made to the surface of the BCP so as to inhibit the release of excessive BMP when transplanted. Some materials that may be used for these modifications are alginate, chitosan, collagen, and heparin.[56]

9. Conclusion

On histology, histomorphometry, micro-CT, and osteogenic gene expression of BCP showed that BCP has osteoconductivity properties as a bone graft in the bone regeneration process.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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