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The Effect of Hydroxyapatite on Alveolar Bone Regeneration in Various Dental Procedure: Systematic Review and Meta-Analysis

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Abstract: The effect of hydroxyapatite (HA) bone substitute on alveolar bone regeneration has been analyzed in various dental procedures including ridge preservation, sinus augmentation, and periodontal bone defect treatment. The objective on this study was to determine and analyze the structural effect of the HA bone substitute in these dental applications. The systematic review was conducted using electronic databases from PUBMED, EMBASE, and COCHRANE. The search covered articles published from 1998 up to November 2023. The primary outcome measures were radiographic (intraoral periapical, CT long cone-paralleling technique, computer-assisted densitometry image analysis), histologic/histomorphometry, and other radiographic methods. The secondary outcome measures related to bone regeneration were assessed, including clinical, radiographic/histologic, and histological evaluations. The present systematic review focused on randomized controlled trials (RCTs) and prospective controlled clinical trials (CCTs). The results showed that HA and ß-TCP were found to be safe and clinically acceptable compared to other treatments.

Keywords: Bone defect; Bone regeneration; Hydroxyapatite.

Introduction

Several grafting materials are commonly used during bone surgery to generate lost bone and restore the alveolar ridge contour (Ajami et al., 2021). One such materials is hydroxyapatite (HA) bone substitute. The four categories of bone grafting materials are autograft, allograft, xenograft, and alloplastic graft. Autograft is considered the gold standard as it provides a good scaffolding for osteoconduction, contains growth factors for osteoinduction, and progenitor cells for osteogenesis (Chamrad et al., 2021). However, autograft procedures have the risk of donor site morbidity and can be limited by graft availability. Allografts and xenografts carry the risk of disease transmission and can evoke an immunologic reaction. Due to these problems, there is increasing interest in the use of alloplastic (synthetic) grafting materials (Ajami et al., 2021; Gaddam et al., 2022).

The first documented use of a synthetic bone graft was indeed reported in 1892 by Van Meekeren, who treated a large bone defect with calcium sulfate. Since then, bioceramics such as hydroxyapatite (HA) have been extensively used as bone grafting materials in humans (Chopra et al., 2020). HA has a chemical composition and crystalline structure similar to that of bone, making it an ideal substitute. However, recent studies have shown that the use of HA may interfere with the normal healing process. Therefore, there is a

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need to develop a bone substitute with optimal bone regenerative properties for various dental procedures (Kazimierczak et al., 2023).

Hydroxyapatite (HA) and other calcium-based ceramic materials are considered bioactive because they have shown the ability to support bone ingrowth (Li et al., 2019). These materials have osteoconductive properties, which mean they can promote the attachment and migration of osteoblasts (bone-forming cells) on their surface. HA is particularly known for its ability to directly bond with bone (Muthusamy et al., 2021). In dentistry and maxillofacial surgery, HA has been used alone or in combination with auto/allo/xenografts to successfully regenerate alveolar bone. HA is available in various forms, including powders, porous blocks, and beads, providing versatility for different clinical applications (Popescu et al., 2020; Wang et al., 2021).

The effect of hydroxyapatite (HA) bone substitute on alveolar bone regeneration has been analyzed in various dental procedures including ridge preservation, sinus augmentation, and periodontal bone defect treatment (Sun et al., 2022; Youseflee et al., 2023). Several reviews have been conducted, but none have specifically focused on the bone regenerative effect of HA. Therefore, the question of whether HA has a significant clinical effect on alveolar bone regeneration remains unclear. The objective on this study was to determine and analyze the structural effect of HA bone substitute on alveolar bone regeneration in these dental applications. All clinical HA applications for ridge preservation, sinus augmentation, and periodontal bone defect treatment were considered for analysis (Ren et al., 2022; Schorn et al., 2021).

Methods

The systematic review mentioned in followed the guidelines of the Preferred Reporting of Systematic Review and Meta-Analysis (PRISMA) statement and used the Population, Intervention, Comparison, and Outcomes (PICO) format to structure the research question. The focused question of the study was "is HA bone substitute effective in alveolar bone regeneration? "The study clearly defined their research design and method, conducting a literature search and analyzing 24 studies that met their inclusion criteria to determine the effect of HA on different types of bone defects (Rethlefsen et al., 2021; Xiao et al., 2023).

Population, intervention, comparison, and outcomes

The systematic review included studies that involved healthy individuals of any age who underwent various dental procedures The studies focused on comparing the use of an alloplastic material based on hydroxyapatite (HA) with other treatment options such as autograft, allograft, xenograft, socket sealing techniques, and biological active agents. Only studies that assessed the outcomes of alveolar bone regeneration through clinical, radiographic, histological, and histomorphometric evaluations were included in the review (Kylmaoja et al., 2022).

For further consideration provide additional details for the systematic review. Including a variety of outcome measures will help assess the effectiveness of HA-based materials for alveolar bone regeneration comprehensively (Cuozzo et al., 2020). The primary outcome measures radio graphic assessment and histologic/ histomorphometry assessment, are crucial in evaluating changes in bone density, volume, and the formation of new alveolar bone (Basyuni et al., 2020; Brum et al., 2019).

By incorporating these outcome measures, the systematic review will be able to provide a comprehensive analysis of the structural effect of HA bone substitutes on alveolar bone regeneration in different dental applications, considering both radiographic, histologic, and clinical parameters (Chamrad et al., 2021).

Search strategy

The search for literature was conducted using electronic databases from PUBMED, EMBASE, and COCHRANE. The search covered articles published from 2000 up to November 2023. To identify relevant studies, a combination of search terms (key words and MeSH terms) was used to identify the proper studies, including hydroxyapatite OR apatite OR calcium hydroxyapatite OR nano-hydroxyapatite AND bone regeneration OR bone healing OR bone response OR osseointegration (Chugh et al., 2021).

Eligibility criteria

The study focused on English-language human studies related to alveolar bone treatment. Longitudinal prospective studies, including randomized controlled trials (RCTs) and clinical controlled trials (CCTs) were included. The aim was to determine the effect of hydroxyapatite (HA) bone substitute on alveolar bone regeneration. The search strategy involved the use of electronic databases and specific search terms. The review assessed outcomes such as changes in bone density, volume, and the formation of new alveolar bone. Secondary outcome measures related to periodontal health and soft tissue healing were also considered (Cann et al., 2020; Wang et al., 2022).

Moreover, the study established inclusion and exclusion criteria. Inclusion criteria encompassed human trials involving healthy individuals without any age restrictions who underwent treatments associated with alveolar bone, including ridge or socket preservation, sinus augmentation, and periodontal bony defect (Muller et al., 2020). Studies with a minimum of six patients and a follow-up period of at least three months were considered. Outcome measures related to bone regeneration were assessed, including clinical, radiographic/histologic, and histomorphometric evaluations (Ren et al., 2022). On the other hand, case reports, case series, and case control analyses were excluded, as well as studies lacking a control group or a comparison between the use of alloplastic material and other treatments. In vitro, animal, and non-clinical control studies were also excluded from the review (Vignesh et al., 2019; Wu et al., 2022).

Data extraction and statistical analysis

Each study was evaluated independently by two readers (WFB and DEW). Disagreements were resolved by SA. The level of agreement between the reviewers was determined by k value. The data were extracted based on general characteristics (treatment modality, study design, and outcome measure). Means and standard deviations (SD) from each study were used to calculate 95% confidence intervals (CI). Statistical analysis was performed with SPSS for window v.15 (SPSS. Inc, Chicago, IL, USA). Furthermore, results of studies that used the same methods of evaluation and similar outcome measurements were combined and the data were presented in a statistical graph.

The study established inclusion and exclusion criteria focused on human trials involving healthy individuals of any age who underwent treatments related to alveolar bone, such as ridge or socket preservation, sinus augmentation, and periodontal Bony defects. The selected studies had to include a minimum of six patients and have a follow-up period of at least three months (Youseflee et al., 2023). Various outcome measures related to bone regeneration, including clinical, radiographic/histologic, and histomorphometric evaluations were assessed. On the other hand, case reports, case series, and case control analyses were excluded, as well as studies without a control group or a comparison between the use of alloplastic material and other treatments, in vitro, animal, and non-clinical control studies where non-control studies were also excluded from the review (Brum et al., 2019; Campodoni et al., 2021)

Quality assessment

The study assessed the methodological quality and risk of bias using parameters derived from the Cochrane Collaboration, Consolidated Standards of Reporting Trials (CONSORT) statement, and previous studies (Yu & Wei, 2021). The parameters evaluated in the studies, including randomized controlled trials (RCTs) and clinical controlled trials (CCTs), included adequate sequence generation, allocation concealment, randomization method, masking, statement of eligibility criteria (inclusion and exclusion), follow up, method of statistic (sample size calculation/power of statistic), and risk of bias category (low/moderate/high) (Al-Hamoudi et al., 2022; Hassani et al., 2022).

The accepted methods of generating a random allocation sequence include using a random-umbers table or a computer software program. Adequate randomization was considered when the case allocation sequence was generated by referring to a random table or using random methods like tossing a coin or shuffling cards or envelopes. Inadequate randomization methods included generating the sequence based on odds or using factors like the date of birth, date of admission, or hospital/clinical record number. Adequate allocation concealment was achieved when the participant and investigator could not foresee the assignment before assigning before assigning the subject to a group. Adequate concealment methods included using central telephone, web-based systems, pharmacy-controlled systems, and/or sequentially numbered drug containers in sealed opaque envelopes (Bajuri et al., 2021; Pearson et al., 2020).

Studies were considered qualified if they applied adequate statistical analysis and had low risk of bias. Adequate statistical analysis was determined by factors such as the reported group number, sample size, data distribution) parametric or nonparametric), and statistical power (*P-value*). The risk of bias was categorized as low, moderate, or high based on the quality assessment. A low risk of bias was assigned if the study clearly met criteria such as adequate sequence generation, adequate allocation concealment, and implemented masking for participants and examiners, along with reported eligibility criteria and detailed follow-up reports. A moderate or high risk of bias was considered if one or more criteria for bias were lacking (Popescu et al., 2020; Xiao et al., 2023).

Results and Discussion

Results

A literature search on PubMed and initially retrieved 500 articles. They then proceeded with a stepwise selection process, which involved screening based on title, abstract, and inclusion criteria. The inter-reader agreement, measured using the kappa statistic, was high throughout the selection process. Out of the initial 500 articles, 32 studies were included in the final analysis. Table 3. present the quality assessment of the included studies, specifically focusing on treatment modalities such as alveolar ridge or socket preservation, sinus augmentation, and periodontal bone defect. The table also indicates the outcomes of the study quality assessment for randomized controlled trails (RCTs) and Controlled Clinical Trials (CCTs) study designs. Among the 32 included studies, three were classified as having a low risk of bias, one had a moderate risk of bias, and 28 were categorized as having a high risk of bias. The risk of bias assessment is likely based on the authors' evaluation of factors such as methodological quality, randomization, allocation concealment, blinding, and other potential sources of bias (Prabakaran et al., 2020; Sato et al., 2020).

Table 1. Selection of publications.

Steps	Number of articles note
Searched by PUBMED, EMBASE and COCHRANE Database	504 articles published by August 2015
Applied first selection: Human trials	239 k value: 0.968
Screened by abstract	74 k value: 0.910
Included by inclusion criteria	32 k value: 0.864
Excluded by exclusion criteria	42
Used for further analysis	32
With similar outcome measures to be analyzed statistically	17
Without similar outcome measures; Not allowing statistical analysis	25

Table 2. Alveolar ridge or socket preservation with primary outcome measure related to new bone formation (mean ± SD, 95% CI, and *P* value).

Studies	Intervention group	N	Measurement methods	Follow-up (month)	Control group	Test group	Power of statistic
	T1: Bio-Oss + gelatin sponge T2: NanoBone + gelatin sponge	11 11	3D DVT (bone density)	10	352 ± 29.3	T1: 699 ± 13.3 T2: 399 ± 15.6	NA
Luczyszyn et al. (2005) (RCT)	T: Resorbable HA (Algipore) + Acellular dermal matrix graft (ADMG) C: ADMG	NA NA	Histology (newly formed bone)	6	46%	1%	NA
Mendez et al. (2017) (RCT)	T1: Deproteinized cancellous bovine bone xenograft + 10% collagen matrix C: Demineralized freeze-dried cortical bone allograft	10 10	Histomorphometric	6	25.5 ± 10.1%	35,3 ± 16.8%	NA

Table 3. Sinus augmentation with primary outcome measure related to new bone formation (mean ± SD, 95% CI, and *P* value).

Studies	Intervention group	N	Measurement methods	Follow-up (month)	Control group	Test group	Power of statistic
Lindgren et al. (2010) (RCT)	T: Biphasic calcium phosphate (BCP) C: Deproteinized bovine bone (DBB)	5 5	Histomorphometric (newly formed bone	8	31.7 ± 18.0%	28.6 ± 14.3% T2: 399 ± 15.6	*P* = 0.67 (P_{val}<0.05)
Baena et al. (2013) (RCT)	T : Polyacid-HA (PLGA/HA) C: Deproteinized bovine bone	4 4	Radiographic by CT (bone density)	6	946 ± 161.9	286 ± 134.4	*P* = 0.002 (P_{val} < 0.05
Kühl et al. (2013) (CCT)	T_1 : Blood + Autogenous Bone (PAB) + ß-TCP T_2: Blood + PAB + ß-TCP/HA C: Blood + PAB	10 10 10	Radiographic by µ-CT (bone density)	NA	18.5%	T1: 17.1% T2: 21.7%	*P* = 0.578
Tosta et al. (2013) (RCT)	T: Biphasic calcium phosphate (with 60% HA and 40% ß-TCP) + Membrane collagen C: Particulate autogenous + Membrane collagen	15 15	Histomorphometric (area fraction of mineralized bone)	9	Area 1: 41.03 ± 4.62% Area 2: 38.63 ± 7.52%	Area 1: 33.70 ± 8.08% Area 2: 26.68 ± 3.92%	*P1*= 0.008 *P2*<0.001 (P_{val} < 0.05)
Ghanaati et al. (2013)(RCT)	T: Synthetic HA (NanoBone) C: Deproteinized bovine bone (Bio-Oss)	4 4	Histomorphometric (newly formed bone)	6	C: 25.73 ± 7.94%	T: 21.85 ± 5.96	*P*>0.05 (*P_{val}* < 0.05)
Pang et al (2017) (RCT)	T: Auto BT C: Bio-Oss	21 12	Histomorphometric	6	C: 31.24 ±13.87%	T: 35.0 ± 19.33%	NA

Table 4. Periodontal bony pocket with primary outcome measure related to new bone formation (mean ± SD, 95% CI and *P* value)

Studies	Intervention group	N	Measurement methods	Follow-up (month)	Control group	Test group	Power of statistic
Debnath T et al., 2014 (RCT)	T1: HA-BG (bioactive glass) + biodegradable membrane T2: HAP + biodegradable membrane C: OFD + biodegradable membrane	10 10	Radiographic by intra oral periapical/IOPA (bone defect fill)	6	0.9 ± 0.7%	T1: 2.6 ± 0.66% T2: 1.6 ± 0.66%	NA
(Lal & Dixit) (CCT)	T : OFD + HA + own blood C1: OFD + Cissus Quadrangu laris (CQ) + saline C2: Oxidized regenerated + OFD C3: OFD	5 5 5 5	Radiographic (defect fill)	1 3 6	C1: 1.6 mm³ C2: 3 mm³ C3: 0.60 mm³	T: 3 mm³	NA
Mistry S et al., 2012	T1 : OFD + HA T2: OFD + BG (Bioactive Glass) T3: OFD + BG + HA C: OFD	8 8 8 8	Radiographic (Depth of the defect)	6 #0-6	9.20 ± 0.44 3.00 ± 0.71	T1: 9.40 ± 0.44 T2: 8.80 ± 0.83 T3: 9.40 ±1.51 T1: 3.00 ± 0.71 T2: 4.40 ± 1.14 T3: 4.20 ± 0.44	$P < 0.01$
Deepika et al.,2023	T: HA+Crystal Collagen+L-PRF C: HA+Crystal collagen+ PLA-PGA membrane	14 14	Clinical and Radiographic	6	0.35 ±1.90 mm	0.28 ± 1.85 mm	NA

Discussion

According to the studies reviewed, hydroxyapatite (HA) bone substitute was examined in various treatment modalities including ridge or socket preservation, sinus augmentation, and periodontal bone defects (Shang et al., 2022). The studies compared HA to other graft sources such as autologous bone, allograft (DFBA or mineralized freeze-dried bone allograft), xenogeneic (organic bovine, porcine, caprine, or coral-derived HA), replicating (morphogenetic proteins), and alloplastic (bioglass, bioceramics) graft materials or combinations. The aim was to determine the effect of HA on alveolar bone regeneration. While significant differences were found in sinus augmentation, no significant difference was observed in the treatment of periodontal bone defects.

The present systematic review focused on randomized controlled trials (RCTs) and prospective controlled clinical trials (CCTs) that examined the effect of hydroxyapatite (HA) bone substitute on alveolar bone regeneration. The control groups in these studies included patients who received autogenous, allogenic, xenogenic, and barrier membrane treatments, such as enamel matrix derivative (EMD), collagen, open flap debridement (OFD), or an untreated socket. The test groups received synthetic HA, HA containing biphasic calcium phosphate (BCP), or nanocrystalline HA (NC-HA) (Radulescu et al., 2023). Various outcome measures were used to evaluate the healing of hand and soft tissues, including radiographic (intraoral periapical, computer -assisted densitometry image analysis), histologic, and histomorphometric analyses (Mumith et al., 2020). The quality assessment of the studies classified as having a low risk of bias in most cases, wih only three studies classified as having a low risk of bias. Insufficient data were reported in many studies, making it difficult to determine the validity of the outcomes and estimates. Measures of new bone regeneration after HA bone substitute grafting included newly formed bone presence (histomorphometric analysis), bone density (radiographic analysis), and bone defect fill (radiographic or bone sounding methods). Clinical measurements, such as probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), and gingival index (GI) were also used to evaluate the soft tissue around the defect area. Histologic sections were assessed descriptively without statistical analysis.

According to a systematic review, the effectiveness of hydroxyapatite (HA) bone substitute varied depending on the treatment modality and case NanoBone was found to be effective in sinus augmentation but not suitable for socket preservation in organic bovine material containing collagen (Bio-Oss) showed significantly better preservation in alveola ridge cases compared to a synthetic bone substitute composed of HA and silicone dioxide (NanoBone) (Table 2 and 3). Autogenous grafts were considered the gold standard for grafting procedures, resulting in a high rate of new bone regeneration. The combination of autograft or allograft with platelet-rich plasma (PRP) showed higher rates of newly formed bone compared to synthetic bone substitutes like NovaBone (Tan et al., 2022). Several randomized controlled trials have established the usefulness of PRP in tissue regeneration, facilitating and accelerating bone formation (Li et al., 2022).

According to the studies reviewed, inorganic bovine-derived HA or deproteinized bovine bone (DBB) were found to be significantly more effective in osteoconduction compared to other materials such as ß-TCP alone, synthetic HA, or biphasic synthetic materilas (Opris et al., 2020; Pan et al., 2020). The histomorphometric analysis showed similar new bone formation around graft particles for BCP and inorganic bovine bone (ABB) or DBB. In sinus augmentation, DFDBA and HA combined with autogenous bone showed similar values for new bone formation. PLGA/HA had lower bone regeneration density compared to DBB. HA and ß-TCP were found to be safe and clinically acceptable in periodontal defect filling compared to other treatments. DFDBA was found to be appropriate for regenerating periodontal tissue, while HA and DFDBA showed similar effects on defect fill. The use of NC-HA bone graft with a collagen membrane demonstrated clinical and radiographic advantages over other treatments (Lin et al., 2020).

The combination of platelet-rich plasma (PRP) with a barrier membrane (Goretex) or a synthetic bone substitute composed of biphasic porous calcium phosphate (BCP) with 60% hydroxyapatite (HA) and 40% beta tricalcium phosphate (beta TCP) with enamel matrix derivative (EMD) or hydroxyapatite cement (HAC) with a no bioabsorbable e PTFE membrane led to greater attachment gain and bone fill compared to synthetic HA alone or a conventional flap (Makishi et al., 2023). These combinations achieved increased bone fill in the defect site, although the results were not significantly different after 6 months of follow-up (Table 4).

Conclusion

HA bone substitute is a good bone graft candidate to reduce the high risk of donor morbidity and evoke less pain, but no significant results were found in the studies. Thus, to overcome the problem in grafting procedures, superior bone substitute in the ideal properties for the treatment of bone defect must be developed

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References

Ajami, E., Fu, C., Wen, H., Bassett, J., Park, S., & Pollaed, M. (2021). Early bone healing on hydroxyapatite-coated and chemically-modified hydrophilic implant surfaces in an ovine model. *Int J Mol Sci*, *22*(17), 9361. https://doi.org/10.3390/ijms22179361.

Al-Hamoudi, F., Rehman, H., Almoshawan, Y., Talari, A., Chaudhry, AA.,, Reilly, G., & Rehman, I. (2022). Bioactive composite for orbital floor repair and regeneration. *Int J Mol Sci*, *23*(18), 10333. https://doi.org/10.3390/ijms231810333

Baena, R., Lupi, S., Pastorino, R., Maiorona, C., Lucchese, A., & Rizzo, S. (2013). Radiographic evaluation of regenerated bone following poly(lactic-co-glycolic) acid/hydroxyapatite and deproteinized bovine bone graft in sinus lifting. *J. Craniofac. Surg*, *24*(3), 845-848. https://doi.org/10.1097/SCS.0b013e31827ca01a.

Bajuri, M., Selvanathan, N., Schaff, F., Suki, M., & Ng, A. (2021). Tissue-engineered hydroxyapatite bone scaffold impregnated with osteoprogenitor cells promotes bone regeneration in sheep moel. *Tissue Eng Regen Med*, *18*(3), 377-385. https://doi.org/10.1007/s13770-021-00343-2.

Basyuni, S., Ferro, A., Santhanam, V., Birch, M., & McCaskie, A. (2020). Systematic scoping review of mandibular bone tissue engineering. *Br J Oral Maxillofac Surg*, *58*(6), 632-642. https://doi.org/10.1016/j.bjoms.2020.03.016.

Brum, I., Carvalho, J., Pires, J., Carvalho, M., Santos, L., & Elias, C. (2019). Nanosized hydroxyapatite and B-tricalsium phosphate coposite: Physico-chemical, cytotoxicity, morphological properties and in vivo trial. *Sci Rep*, *9*(1), 19602. https://doi.org/10.1038/s41598-019-56124-4.

Campodoni, E., Velez, M., Fragogeorgi, E., Morales, I., Presa PDL., Stanicki, D., Dozio, S., Xanthopoulos, S., Bouziotis, P., Dermisiadou, E., Rouchota, M., Loudos, G., Marin, P., Laurent, S., Boutry, S., Pamseri, S., Montesi, M., Tampieri, A., & Sandri, M.

(2021). Magnetic and radio-labeled bio-hybrid scaffolds to promote and track in vivo the progress of bone regeneration. *Biomater Sci*, *9*(22), 7575-7590. https://doi.org/10.1039/d1bm00858g.

Cann, S., Tornquist, E., Barreto, I., Faulob, M., Lomami, H., Verezhak, M., Guizar-Sicairos, M., Isaksson, H., & Haiat, G. (2020). Spatio-temporal evolution of hydroxyapatite crystal thickness at the bone-implant interface. *Acta Biomater*, *116*, 391-399. https://doi.org/10.1016/j.actbio.2020.09.021.

Chamrad, J., Marcian, P., & Cizek, J. (2021). Beneficial osseointegration effect of hydroxyapatite coating on cranial implant-FEM investigation. *Plos one*, *16*(7), e0254837. https://doi.org/10.1371/journal.pone.0254837.

Chopra, V., Thomas, J., Sharma, A., Panwar, V., Kaushik, S., Sharma, S., Porwal, K., Kulkarni, C., Rajput, S., Singh, H., Jagavelu, K., Chattopadhyay, N., & Ghosh, D. (2020). Synthesis and evaluation of a zinc eluting rGo/hydroxyapatite nanocomposite optimized for bone augmentation. *ACS Biomater Sci Eng*, *6*(12), 6710-6725. https://doi.org/10.1021/acsbiomaterials.0c00370.

Chugh, A., Mehrotra, D., & Yadav, P. (2021). A systematic review on the outcoe of distraction osteogenesis in TMJ ankylosis. *J Oral Biol Craniofac Res*, *11*(4), 581-595. https://doi.org/10.1016/j.jobcr.2021.07.007

Cuozzo, R., Ssatoretto, S., Resende, R., Alves, A., Mavropoulos, E., Da Silva, M., & Calasans-Maia, M. (2020). Biological evaluation of zinc-containing calcium alginate-hydeoxyapatite composite microspheres for bone regeneration. *J Biomed Mater Res B Appl Biomater*, *108*(6), 2610-2620. https://doi.org/10.1002/jbm.b.34593.

Gaddam, V., Podarala, V., Venkata, S., Mukku, S., Devalam, R., & Kundu, B. (2022). Multi-ion-doped nano-hydroxyapatite-coated titanium intramedulalry pins for long bone fracture repair in dogs-clinical evaluation. *J Biomed Mater Res B Appl Biomater*, *110*(4), 806-816. https://doi.org/10.1002/jbm.b.34960.

Ghanaati, S., Barbeck, M., Lorenz, j., Stuebinger, S., Seitz, O., Landes, c., Kaviacs, A., Kirpatrick, C., & Sader, R. (2013). Synthetic bone substitute material comparable with xenogeneic material for bone tissue regeneration in oral cancer patients: first and preliminary histological, histomorphometrical and clinical results. *Ann. Maxillofac. Surg.*, *3*(2), 126-138. https://doi.org/10.4103/2231-0746.119221

Hassani, A., Khoshfetrat, A., Rahbarghazi, R., & Sakai, S. (2022). Collagen and nano-hydroxyapatite interaction in alginate-based microcapsule provide an appropriate osteogenic microenvironment for modular bone tissue formation. *Carbohydr Polym*, *277*, 118807. https://doi.org/10.1016/j.carbpol.2021.118807.

Kazimierczak, P., Wessely-Szponder, J., Palka, K., Barylyak, A., Zinchenko, V., & Przekora, A. (2023). Hydroxyapatite of fluorapite-which bioceramic is better as a base for the production of bone scaffold? A comprehensive comparative study. *Int J Mol Sci*, *24*(6), 5576. https://doi.org/10.3390/ijms24065576.

Kühl, S., Brochhausen, C., Götz, H., Filippi, A., Payer M., d'Hoedt, B., & Kreisler, M. (2013). The influence of bone substitute materials on the bone volume after maxillary sinus augmentation: a microcomputerized tomography *Clin. Oral Investig*, *17*(2), 543-551.

Kylmaoja, E., Holopainen, J., Abushahba, F., Ritala, M., & Tuukkanen, J. (2022). Osteoblast attachment on titanium coated with hydroxyapatite by atomic layer deposition. *Biomolecules*, *12*(5), 654. https://doi.org/10.3390/biom12050654.

Lal, N., & Dixit, J. Biomaterials in periodontal osseous defects. *J. Oral Biol. Craniofac. Res.*, *2*(1), 36-40. https://doi.org/10.1016/S2212-4268(12)60009-8

Li, L., Li, J., Zuo, Q., Zuo, Y., Lin, L., Cai, B., & Li, Y. (2022). Lotus root and osteon-inspired channel structural scaffold mediate cell biomineralization and vascularized bone tissue regeneration. *J Biomed Mater Res B Appl Biomater*, *110*(5), 1178-1191. https://doi.org/10.1002/jbm.b.34991.

Li, Y., Li, B., Song, Y., Ma, A., Li, C., Zhang, X., Li, H., Zhang, Q., & Zhang, K. (2019). Improved osteoblast adhesion and osseointegration on TiO2 nanotubes surface with hydroxyapatite coating. *Dent Mater J*, *38*(2), 278-286. https://doi.org/10.4012/dmj.2018-118.

Lin, W., Chuang, C., Yao, C., & Tang, C. (2020). Effect of cobalt precursors on cobalt-hydroxyapatite used in bone regeneration and MRI. *J. Dent Res*, *99*(3), 277-284. https://doi.org/10.1177/0022034519897006.

Lindgren, C., Hallman, M., Sennerby, L., & Sammons, R. (2010). Back-scattered electron imaging and elemental analysis of retrieved bone tissue following sinus augmentation with deproteinized bovine bone or biphasic calcium phosphate. *Clin Orak Implants Res*, *21*(9), 924-930. https://doi.org/10.1111/j.1600-0501.2010.01933.x

Luczyszyn, S., Paplexiou, V., Novaes, A., Grisi, M., Souza, S., & Taba, M. (2005). Acellular dermal matrix and hydroxyapatite in prevention of ridge deformities after tooth extraction. *Implant Dent*, *14*(2), 176-184. https://doi.org/10.1097/01.id.0000165082.77499.41.

Makishi, S., Watanabe, T., Saito, K., & Ohshima, H. (2023). Effect of hydroxyapatite/B-Tricalcium Phosphate on Osseointegration after implantation into mouse maxilla. *Int J Mol Sci*, *24*(4), 3124. https://doi.org/10.3390/ijms24043124.

Mendez, C., Lang, N., Caneva, M., Lemus GR., Solano, G., & Botticelli, D. (2017). Comparison of allograft and xenograft used for alveolar ridge preservation. A clinical and histomorphometric RCT in humans. *Randomized Contrlled Trial*, *19*(4), 608-615. https://doi.org/10.1111/cid.12490.

Muller, W., Ackermann, M., Al-Nawas, B., Righesso, L., Munoz-Espi, R., Tolba, E., Neufurth, M., Schroder, H., & Wang, X. (2020). Amplified morphogenetic and bone forming activity of amorphous versus crystalline calcium phosphate/polyphosphate. *Acta Biomater*, *118*, 233-247. https://doi.org/10.1016/j.actbio.2020.10.023.

Mumith, A., Cheong, V., Fromme, P., Coathup, M., & Blunn, G. (2020). The effect of strontum and silicon substituted hydroxyapatite electrochemical on bone ingrowth and osseointegration of selective laser sintered porous metal implants. *Plos one*, *15*(1), e0227232. https://doi.org/10.1371/journal.pone.0227232.

Muthusamy, S., Mahendiran, B., Sampath, S., Jaisankar, S., Anandasadagopan, S., & Krishnakumar, G. (2021). Hydroxyapatite nanophases augmented with selenium and manganese ions for bone regeneration: Physiochemical, microstructural and biological characterization. *Mater Sci Eng C Mater Biol Appl*, *126*, 112149. https://doi.org/10.1016/j.msec.2021.112149.

Opris, H., Bran, S., Dinu, C., Baciut, M., Prodan, D., Mester, A., & Baciut, G. (2020). Clinical applications of avian eggshell-derived hydroxyapatite. *Bosn J Basic Med Sci*, *20*(4), 430-437. https://doi.org/10.17305/bjbms.2020.4888.

Pan, Y., Zhao, Y., Kuang, R., Liu, H., Sun, D., Mao, T., Jiang, K., Yang, X., Watanabe, N., Mayo, K., Lin, Q., & Li, J. (2020). Injectable hydrogel-loaded nano-hydroxyapatite that improves bone regeneration and alveolar ridge promotion. *Mater Sci Eng C Mater Biol Appl*, *116*, 111158. https://doi.org/10.1016/j.msec.2020.111158

Pearson, J., Gerken, N., Bae, C., Lee, K., Satsangi, A., McBride, S., Appleford, M., Dean, D., Hollinger, J., Ong, J., & Guda, T. (2020). In vivo hydroxyapatite scaffold performance in infected bone defects. *J Biomed Mater Res B Appl Biomater*, *108*(3), 1157-1166. https://doi.org/10.1002/jbm.b.34466.

Popescu, R., Tabaran, F., Farcasanu, A., Purdoiu, R., Magyari, K., Vulpoi, A., Dreanca, A., Sevastre, B., Simon, S., Popuc, I., & Baia, L. (2020). Bone regeneration response in an experimental long bone defect orthotopically implanted with alginate-pullulan-glass-ceramic composite scaffolds. *J Biomed Mater Res B Appl Biomater*, *108*(3), 1129-1140. https://doi.org/10.1002/jbm.b.34464.

Prabakaran, S., Rajan, M., Lv, C., & Meng, G. (2020). Lanthanides-substituted hydroxyapatite/aloe vera composite coated titanium plate for bone tissue regeneration. *Int J Nanomedicine*, *15*, 8261-8279. https://doi.org/ 10.2147/IJN.S267632.

Radulescu, D., Vasile, O., Andronescu, E., & Ficai, A. (2023). Latest research of doped hydroxyapatite for bone tissue engineering. *Int J Mol Sci*, *24*(17), 13157. https://doi.org/10.3390/ijms241713157.

Ren, M., Wang, X., Hu, M., Jiang, Y., Xu, D., Xiang, H., Lin, J., & Yu, B. (2022). Enhanced bone foration in rat critical-size tibia defect by a novel quersetin-containing alpha-calcium sulphate hemihydrate/nano-hydroxyapatite composite. *Biomed Pharmacother*, *146*, 112570. https://doi.org/10.1016/j.biopha.2021.112570.

Rethlefsen, M., Kirtley, s., Waffenschmidt, S., Ayala, A., & Moher, D. (2021). PRISMA-S: an extension to the PRISMA statement for Reporting Literature Searches in Systematic Review. *Sys Rev*, *10*(1), 39. https://doi.org/10.1186/s13643-020-01542-z

Sato, N., Handa, K., Venkataiah, V., Hasegawa, T., Njuguna, M., Yahata, Y., & Saito, M. (2020). Comparison of the vertical bone defect healing abilities of carbonate apatite, B-tricalcium phosphate, hydroxyapatite and bovine-derived heterogenous bone. *Dent Mater J*, *39*(2), 309-318. https://doi.org/10.4012/dmj.2019-084.

Schorn, L., Fienitz, T., Gerstenberg, F., Sterner-Kock, A., Maul, A., Lommen, J., Holtmann, H., & Rothamel, D. (2021). Influence of different carrier materials on biphasic calcium phosphate induced bone regeneration. *Clin Oral Invest*, *25*(6), 3729-3737. https://doi.org/10.1007/s00784-020-03700-y.

Shang, L., Shao, J., & Ge., S. (2022). Immunomodulatory properties: the accelerant of hydroxyapatite-based materials for bone regeneration. *Tissue Eng Part C Methods*, *28*(8), 377-392. https://doi.org/10.1089/ten.TEC.2022.00111112.

Sun, C., Weng, P., Chang, J., Lin, Y., Tsunag, F., Lin, F., Tsai, T., & Sun, J. (2022). Metformin-incorporated gelatin/hydroxyapatite nanofiber scaffold for bone regeneration. *Tissue Eng part A*, *28*(1-2), 1-12. https://doi.org/10.1089/ten.TEA.2021.0038.

Tan, X., Gerhard, E., Wang, Y., Tran, R., Xu, H., Yan, S., Rizk, E., Armstrong, A., Zhou, Y., Du, J., Bai, X., & Yang, J. (2022). Development of biodegradable osteopromotive citrate-based bone putty. *Small*, *18*(36), e2203003. https://doi.org/10.1002/smll.202203003.

Tosta, M., Cortes, A. R., Corrêa, L., Pinto, S., Jr., , Tumenas, I., & Katchburian, E. (2013). Histologic and histomorphometric evaluation of a synthetic bone substitute for maxillary sinus grafting in humans. . *Clin. Oral Implants Res.*, *24*(8), 866-870. https://doi.org/10.1111/j.1600-0501. 2011. 02384. x

Vignesh, U., Mehrotra, D., Howlader, D., Kumar, S., & Anand, V. (2019). Bone marrow aspirate in cystic maxillofacial bony defects. *Randomized Controlled Trial*, *30*(3), e247-e251. https://doi.org/10.1097/SCS.0000000000005200.

Wang, B., Liu, J., Niu, D., Wu, N., Yun, W., Wang, W., Zhang, K., Li, G., Yan, S., Xu, G., & Yin, J. (2021). Mussel-Inspired Bisphosphonated Injectable Nanocomposite Hydrogels With Adhesive, Self-Healing, And Osteogenic Properties For Bone Regeneration. *ACS Appl Mater Interfaces*, *13*(28), 32673-32689. https://doi.org/10.1021/acsami.1c06058.

Wang, H., Hu, B., Li, H., Feng, G., Pan, S., Chen, Z., Li, B., & Song, J. (2022). Biomimetic Mineralized Hydeoxyapatite Nanofiber-Oncorporated Methacrylated Gelatin Hydrogel With Improved Mechanical And Osteoinductive performances for bone regeneration. *Int J Nanomedicine*, *17*, 1511-1529. https://doi.org/10.2147/IJN.S354127.

Wu, Y., Yang, L., Chen, L., Geng, M., Xing, Z., Chen, S., Zeng, Y., Zhou, J., Sun, K., Yang, X., & Shen, B. (2022). Core-Shell Structured Porous Calcium Phosphate Bioceramic Spheres For Enhanced Bone Regeneration. *ACS Appl Mater Interfaces*, *14*(42), 47491-47506. https://doi.org/10.1021/acsami.2c15614.

Xiao, X., Liu, Z., Shu, R., Wang, J., Zhu, X., Bai, D., & Lin, H. (2023). Periodontal bone regeneration with a degradable thermoplastic HA/PLCL bone graft. *J Mater Chem B*, *11*(4), 772-786. https://doi.org/10.1039/d2tb02123d.

Youseflee, P., Ranjbar, F., Bahraminasab, M., Ghanbari, A., Faradonbeh, D., Arab, S., Alizadeh, A., & Nooshabadi, V. (2023). Exosome loaded hydroxyapatite (HA) scaffold promotes bone regeneration calvarial defect: an in vivo study. *Cell Tissue Bank*, *24*(2), 389-400. https://doi.org/10.1007/s10561-022-10042-4.

Yu, L., & Wei, M. (2021). Biomineralization of collagen-based materials for hard tissue repair. *Int J Mol Sci*, *22*(2), 944. https://doi.org/10.33990/ijms22020944