Saudi Dental Journal (2022) **34**, 647–660

King Saud University

Saudi Dental Journal

www.ksu.edu.sa
www.sciencedirect.com

REVIEW ARTICLE

Nanocrystalline hydroxyapatite in periodontal bone regeneration: A systematic review

Marwa Y. Shaheen

Department of Periodontics and Community Dentistry, College of Dentistry, King Saud University, Riyadh, Saudi Arabia

Received 23 June 2022; revised 28 September 2022; accepted 29 September 2022
Available online 7 October 2022

KEYWORDS

Periodontal diseases;
Periodontal bony defects;
Periodontal regeneration;
Nanocrystalline hydroxyapatite

Abstract *Background:* Periodontal diseases when persistent, results in periodontal pockets, attachment loss and progressive destruction of the alveolar bone. Grafting periodontal bone defects with bone substitute biomaterials has proven clinical success for accomplishing reconstruction of lost attachment apparatus, especially in deep intra-bony defects. Nanoparticles (NPs) have been considered indispensable in the future of health sciences and NP based alloplastic graft materials such as nanocrystalline hydroxyapatite (NCHA) hold great promise for regeneration of periodontal defects. Therefore the aim of this review is to evaluate the role of NCHA as an effective substitute for periodontal bone regeneration.

Material & methods: Popular scientific databases such as PubMed (Medline), Cochrane database of clinical trials, Scopus (Elsevier), Web of science (Clarivate Analytics) and Google Scholar, were searched. The literature search was restricted to published reports in English, between January 2000 and December 2021. Database search returned 1227 results which were screened based on title, author names and publication dates.

Results: Data from the 14 included studies were reviewed and tabulated. In the present review, all the studies reported using commercially available NCHA for periodontal bone regeneration.

Conclusion: NCHA is a suitable bone substitute material for periodontal bone regeneration, with outcomes comparable to that of conventionally used graft materials such as bovine xenograft and other synthetic alloplastic materials. While grafting with NCHA in intrabony periodontal defects, after any form of periodontal flap surgery or debridement, significantly improves bone regeneration by 6 months, addition of adjuncts like EMD and PRF further enhance the outcomes.

E-mail address: mashaheen@ksu.edu.sa
Peer review under responsibility of King Saud University. Production and hosting by Elsevier.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sdentj.2022.09.005

Contents

1. Introduction

1.1. Background

Chronic periodontal diseases result in periodontal pockets, attachment loss and progressive destruction of the alveolar bone (Nickles et al. 2009). Periodontal bony defects often require long term management and pose greater clinical challenge. Grafting with bone substitute biomaterials has proven clinical success for accomplishing reconstruction of lost attachment apparatus in deep intra-bony defects (Retzepi and Donos 2010). Guided bone regeneration GBR associated with bone grafting, inhibits the invasion of the rapidly growing fibrous capsule facilitating the localization of the host bone-originated osteoblasts (Fujihara et al. 2005). Biocompatibility, improved qualities and functionalities are primary requisites of the emerging materials involved in bone grafting and regeneration (Yang et al. 2009). Commonly used bone grafting material consists of autogenous grafts, allografts, xenografts and alloplasts (Piattelli et al. 1996). Amongst these, inorganic, biocompatible and bioactive alloplastic materials are widely used due to their availability. In particular, clinically significant results have been achieved with calcium phosphate ceramics used in the form of hydroxyapatite (HA) and tricalcium Phosphate (TCP) (Cao et al. 2005).

Nanotechnology and Nanoparticles have gained more scientific relevance and have been largely researched upon in the past decades (Jarudilokkul et al. 2007). Nanoparticles (NPs) have been considered indispensable in the future of health sciences and have wide range of medical implications in the field of cancer therapy, drug delivery, tissue engineering, regenerative medicine, biomolecules detection, and also as antimicrobial agents (Rudramurthy and Swamy 2018). NPs have been developed in several forms such as dendrimers, micelles, liposomes or polymers which are organic in nature, and graphene or carbon nanotubes or electro-spun tubes comprising the inorganic forms (Anu Mary Ealia and Saravanakumar 2017). However, developing biologically sustainable and biocompatible NPs that could survive in the oral environment has always remained a challenge. The superior properties of NPs in terms of size, charge, large surface area, strength, solubility, chemical and surface reactivity, color, high stability and thermal conductivity have resulted in their increased usage in dental research (Davar et al. 2010). Despite these innumerable advantages, use of NPs in clinical scenarios is still a matter of concern owing to the toxicity involved, limited delivery options and technique sensitivity (Davar et al. 2010). Evidence based studies reveal that the physicochemical and biological characteristics of the dental implants and removable prostheses are enhanced in association with NPs (Sambhy et al. 2006). Further, asymmetric membranes produced through Nano-technology act as an inhibitory barrier against pathogens and facilitates bone regeneration (Otunola et al. 2017).

Implants and their concomitant prosthetic replacements focus on synthetic materials mimicking natural bone in their properties. Interestingly, improvement on the surface characteristics, through cell adhesion, proliferation, differentiation, and their integration with surrounding tissues have greater implications on the clinical success of titanium implants (Menezes et al. 2018). Based on an in vitro study, coating titanium implant surfaces with gold and silver nanoparticles resulted in better osteogenic differentiation of stem cells and notable influence on the osseous interface formation, based on in vitro an (Heo et al. 2016). On the other hand, HA nanocrystals based treatment of titanium surfaces enhanced cell proliferation and differentiation, with further spread, thereby contributing to the synthesis of bone matrix, and accentuated osseointegration, even under an in vivo scenario (Suo et al. 2019). Biomaterials like HA have mineral components similar to natural bone and are osteoconductive in nature. Reconstruction of mandibular and osteoporotic bone defects prior to fixation are some of the prevalent clinical applications of nanocrystalline HA (Liao et al. 2005). Amongst NPs, the most widely reported biomaterial for clinical tissue regeneration is nanocrystalline hydroxyapatite (NCHA) (Kokubo 1998). Literature reveals that nanoparticulate NCHA enhances osseointegration and osteoblastic adhesion in comparison to their micro-particulate HA with the same chemical composition. It has further been reported that modification of the composition and crystal structure enables

amplification of the physicochemical and biological properties of HA particles (Rouahi et al. 2006). According to de Lima Cavalcanti et al. (2019) the high cell adhesion properties, osteoconductivity and osteoblast viability inherent with NCHA renders it as an excellent scaffold for bone defect regeneration. Additionally, when combined with chitosan and graphene oxide, NCHA has greatly improved in vitro cell-material interactions and enhanced osseointegration, in vivo (Suo et al. 2019).

Expanding their applications clinically, sinus floor elevation and augmentation with NCHA was shown to result in adequate bone formation supporting implant placement and without any signs of inflammation (Bosshardt et al. 2014). Similarly, implants placed at sites augmented with NCHA displayed better implant stability than defects treated using a graftless tenting technique (Khaled et al. 2019). Nevertheless, the management of periodontal bone defects, conventionally done through mechanical debridement and guided tissue regeneration (GTR), still poses a clinical challenge and necessitates the need for advanced biomaterials and grafts (Nickles et al. 2009). Although guide bone regeneration (GBR) using alloplastic graft materials has shown sufficient promise in healing refractory periodontal bone defects, the role of alloplastic NPs in the form of NCHA requires further insight, in spite of its reported clinical use (Rudramurthy and Swamy 2018; Ramalingam et al. 2019; Ramalingam et al. 2020).

1.2. Aim of the study

In line with the recent advances in general clinical implications of nanoparticles in periodontal regeneration, and more specifically the role of NCHA in treating periodontal bone defects, a systematic review of research articles published from 2001 until 2021 was conducted. The present review primarily aimed to summarize the various potential clinical applications of NCHA as a graft material for the regeneration of periodontal bone defects. Secondarily, this review also attempts to shed light on the novel methods involving NPs for the treatment of periodontal pathogenesis with particular emphasis on bone regeneration.

2. Material & methods

Institutional ethical approval was not obtained for the study as the protocol only involved a systematic review of literature, performed in accordance with Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines (Fig. 1). The present review addressed the focused question, ''Is nanocrystalline hydroxyapatite (NCHA) an effective bone substitute material for periodontal bone regeneration?''.

2.1. Selection criteria

Clinical studies, including prospective and retrospective data collection, randomized controlled trials and case series with a minimum of 10 patients, encompassing the following criteria were selected for the review.

Problem – Periodontal bone defects including peri-implantitis defects and alveolar ridge augmentation

Intervention – Alloplastic NCHA as the bone substitute material for grafting periodontal bone defects

Comparison – Other bone substitutes (autograft, allograft, xenograft) and periodontal surgical procedures without bone grafting

Outcome – Comprehensive clinical, radiographic and/or histological evidence of new bone formation including, but not limited to reduction in probing depth, gain in clinical attachment level, bone defect fill level (both clinical and radiographic), bone density, residual bone defect area and new bone area (histology only).

2.2. Search strategy

Popular scientific databases such as PubMed (Medline), Cochrane database of clinical trials, Scopus (Elsevier), Web of science (Clarivate Analytics) and Google Scholar, were searched using a combination of free text search terms, and Boolean operators (AND/OR). The search terms included, nanocrystalline, hydroxyapatite, ''nanocrystalline hydroxyapatite'', periodontitis, peri-implantitis, periodontal, ''periodontal pocket'', ''intrabony defect'', ''alveolar bone'', ''alveolar ridge'', ''bone regeneration'', and ''ridge augmentation''. The literature search was restricted to published reports in English, between January 2000 and December 2021. In addition studies with less than 10 patients per group, follow-up period less than 6 months and incomplete reporting of PICO characteristics were excluded.

2.3. Review process

Two independent observers verified the quality of the review process in terms of the review protocol, inclusion and exclusion criteria, and data extraction. Selected article titles based on the search strategy, and criteria for inclusion/exclusion were documented in a reference management software (EndNote X7, Clarivate Analytics, Philadelphia, USA). The titles were screened for duplicates and suitability for inclusion in the review. This was followed by abstract screening and selection, based on their relevance identified by at least one of the reviewers. Selected abstracts were assessed for full text selection, based on agreement by both reviewers and any disagreement which was resolved through discussion and re-evaluation. Full-texts of all selected articles were obtained from databases and repositories or through personal communication with the author. The manuscripts were read thoroughly, with special emphasis on the reported methods and results. Furthermore, the bibliographies were scrutinized to identify studies which may have otherwise been missed out during literature search. Data from selected articles were tabulated using a data-extraction spreadsheet to summarize author information, study design, patient demographics, methodology, results, conclusions and limitations (Table 1).

3. Results

3.1. Literature search

Database search returned 1227 results (PubMed – 607; ScienceDirect – 415; Web of Science – 194; Cochrane database – 11), which were screened based on title, author names and publication dates. After removal of duplicates, 864 articles

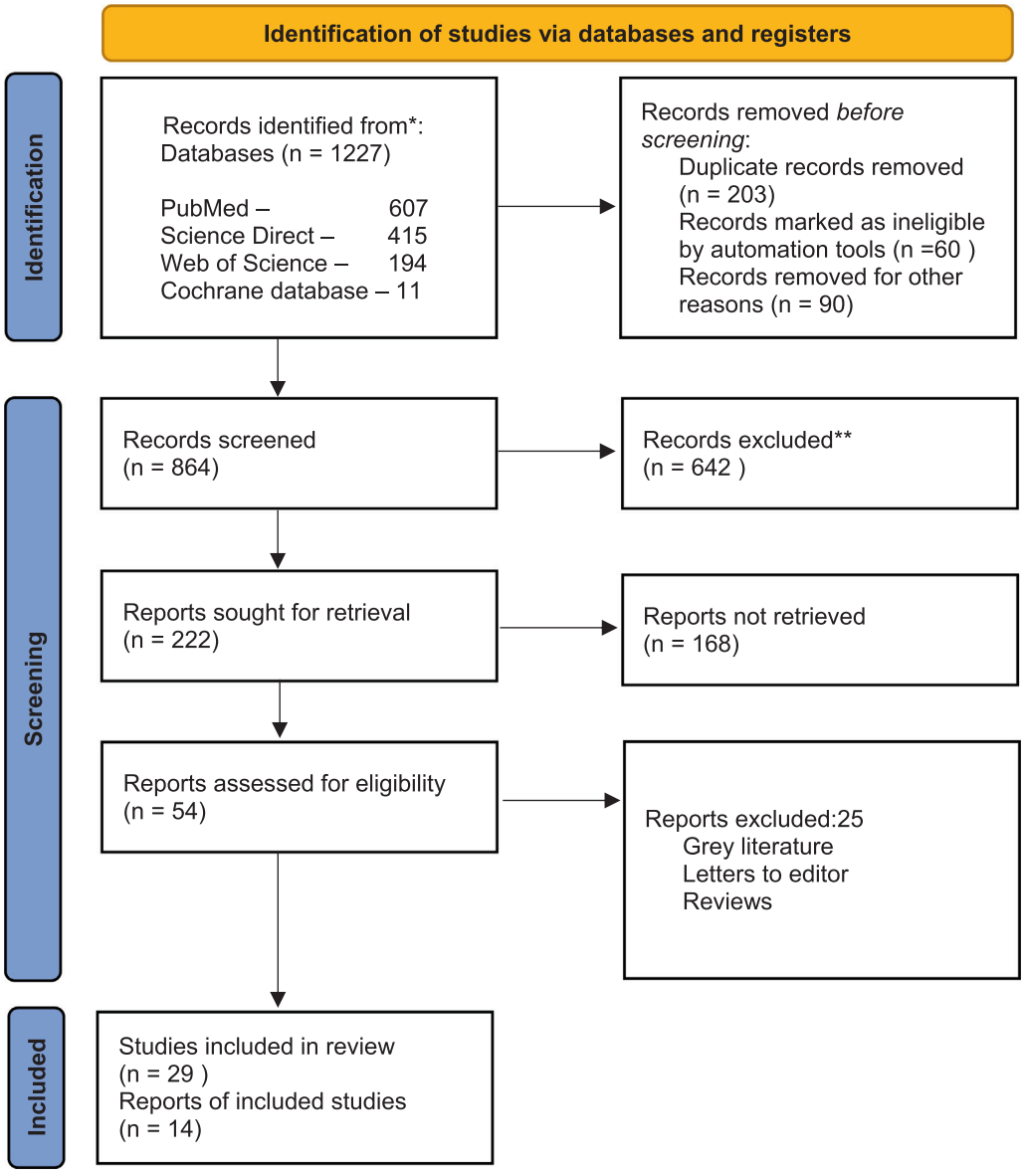

Fig. 1 PRISMA CHART.

were selected for abstract screening and selection, by the independent reviewers. A total of 54 abstracts were identified for full text review. Upon perusal of the full texts, 22 articles describing studies conducted in animal models and 3 articles reporting in-vitro experiments were excluded. Out of the remaining 29 articles reporting clinical data, 3 studies using non-NCHA nanocrystalline bone substitute material (Kumari et al. 2014; Pandit et al. 2015; Stevanović et al. 2015), and 3 studies with small sample size ($n < 10$) and short follow-up (< 6 months) (Checchi et al. 2011; Canuto et al. 2013; Horváth et al. 2013), were excluded.

3.2. Review results

Since the present review was based on a focused question pertaining to periodontal bone regeneration, a further 6 clinical studies evaluating maxillary sinus lift were excluded (Canullo and Dellavia 2009; Heinemann et al. 2009; Canullo et al. 2012; El Hage et al. 2012; Ghanaati et al. 2014; Wolf et al. 2014). Within the remaining 17 articles for final review, two articles were identified with the same sample and dataset (Singh et al. 2012a, 2012b), and three articles reported continuous data for the sample at differing timelines (6 months, 2 years and 4 years) (Schwarz et al. 2006, 2008, 2009), and these were considered only as two studies for the final review. Data from the 14 included studies were reviewed and tabulated (Table 1).

a. *Study design and patient demographics*

In all the reviewed studies, clinical data was collected prospectively, except for one study which reported retrospective data (Pilloni et al. 2014). There was one multicenter study reporting data from two centers (Strietzel et al. 2007), and three studies involving a split-mouth study design (Heinz et al. 2010; Gholami et al. 2012; Elgendy and Abo Shady

Table 1 Summary of study characteristics of the reviewed articles.

Author (year)	Study Design	Objectives/Aims	Patient Demographics	Material Used	Methodology	Outcomes	Conclusions	Limitations (as reported by the authors)
Strietzel et al (2007)	Two-centre prospective clinical study	Evaluation of lateral alveolar ridge augmentation sites grafted with nanocrystalline hydroxyapatite (NCHA).	14 patients (male – 7/ female – 7/mean age – 50.6 ± 11.5 years) indicated for lateral alveolar ridge augmentation.	NCHA paste (Ostim®, Heraeus Kulzer, Hanau, Germany) + Titanium mesh (TioMeshs, Dentaurum, Ispringen, Germany)	Deficient alveolar ridges were grafted with NCHA + titanium mesh. Clinical alveolar ridge gain was evaluated with pre and post treatment models. Bone biopsies (3.5 mm × 2.5 mm × 8 mm) were obtained from the grafted sites after 6 months (during implant placement) and analyzed histomorphometrically.	After 6 months there was statistitcally significant median alveolar ridge width gain of 2 mm (range 1–4 mm/ p = 0011). Histomorphometric mean bone area was 52.3%, with no significant difference in remnant NCHA between the peripheral (23.4%) and central (15.1%) parts of the regenerated alveolar ridge. Implants were placed in all sites and loaded after 4 months, and no implants were lost until 24 months.	Significant quantitative and qualitative alveolar bone regeneration with NCHA, suitable for implant placement with sufficient primary stability. Small amounts of remnant NCHA in the grafted sites at 6 months, indicating continuous bone regenerative process.	Extent of alveolar ridge width gain reported was minimal, and 60% of patients required additional lateral augmentation during implant placement.
Kasaj et al. (2008)	Prospective clinical RCT	Compare clinical outcomes of intrabony periodontal defects treated by OFD only or OFD with NCHA grafting (OFD + NCHA).	28 patients (n = 14 per group/male – 14/ female – 14) with a mean age of 52.6 ± 7.7 years.	NCHA paste (Ostim®, Heraeus Kulzer, Hanau, Germany)	Intrabony periodontal defects with clinical PD ≥ 6 mm and radiographic depth ≥ 3 mm were treated with OFD and were either left ungrafted or grafted withNCHA paste. Clinical parameters (PD, CAL and GR) were assessed after 2 months, 4 months and 6 months.	In both groups, there was significant reduction in mean PD (OFD – 2.6 ± 1.3 mm/ OFD + NCHA – 3.9 ± 1.2 mm) and significant gain in mean CAL (OFD – 1.8 ± 1.2 mm/OFD + NCHA – 3.6 ± 1.6). The differece between the groups was also significant for PD and CAL. While GR increased significantly in OFD group (0.8 ± 0.8 mm), than OFD + NCHA group (0.4 ± 0.4 mm), the difference between groups was not significant.	Grafting intrabony periodontal defects with NCHA paste resulted in significantly better clinical outcomes (PD and CAL), than with OFD alone..	Uncertainity over the relationship between CAL gain and periodontal regeneration, short follow up period and absence of radiographic records.
Schwarz et al. (2009)	Prospective randomized clinical case-series	Evaluation of intrabony *peri*-implantitis defect regeneration with either NCHA or a combination of bovine xenograft + CM.	20 patients (n = 10 per group/male – 7/ female – 13) with a mean age of 54.4 ± 12.5 years.	NCHA paste (Ostim®, Heraeus Kulzer, Hanau, Germany), Bovine xenograft (BioOss®, Geistlich, Wolhusen, Switzerland) and CM (BioGide®,Geistlich, Wolhusen, Switzerland).	Moderate intrabony *peri*-implanitis defects were treated with OFD followed by grafting with NCHA paste or bovine xenograft + CM. Clinical parameters (PD, CAL and GR) were assessed after 6 months, 2 years and 4 years.	Although not statistically compared, at 6 months, grafting with bovine xenograft + CM resulted in greater reduction in PD (2.6 ± 0.4 mm/NCHA – 2.1 ± 0.5 mm) and gain in CAL (2.3 ± 0.6 mm/NCHA – 1.8 ± 0.6 mm). The increase in GR was similar (0.3 ± 0.2 mm). Similar clinical outcomes were observed after 2 years - PD reduction (NCHA – 1.5 ± 0.6 mm/ Bovine xenograft + CM – 2.4 ± 0.8 mm); CAL gain (NCHA – 1.0 ± 0.4 mm/ Bovine xenograft + CM – 2.0 ± 0.8 mm); and after 4 years - PD reduction (NCHA – 1.1 ± 0.3 mm/ Bovine xenograft + CM – 2.5 ± 0.9 mm); CAL gain (NCHA – 0.6 ± 0.5 mm/ Bovine xenograft + CM – 2.0 ± 1.0 mm).	Favorable clinical regeneration of intrabony *peri*-implantitis defects in terms of PD and CAL were evidenced with NCHA and bovine xenograft + CM. However, the use of natural bone graft with CM yieled better results.	Small sample size, non standardized study design, absence of histological or radiographic assessment and no statistical comparison.

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Study Design	Objectives/Aims	Patient Demographics	Material Used	Methodology	Outcomes	Conclusions	Limitations (as reported by the authors)
Heinz et al. (2010)	Prospective clinical RCT (split-mouth design)	Compare clinical outcomes of intrabony periodontal defects treated by PPFS only or PPFS with NCHA grafting (PPFS + NCHA).	14 patients (male − 7/ female − 7) in the age range of 38–50 years with paired intrabony periodontal defects.	NCHA paste (Ostim®, Heraeus Kulzer, Hanau, Germany)	Intrabony periodontal defects $\geq$ 4 mm, were treated by PPFS and were either grafted with NCHA paster or left ungrafted. Clinical PD and PBL were assessed after 6 months.	In both groups, there was reduction in mean PD and PBL after 6 months. The reduction of clinical parameters in PPFS + NCHA group (PD − 4.3 ± 1.6 mm/PBL − 4.3 ± 1.4 mm) were significantly higher than that of PPFS group (PD − 2.9 ± 1.1 mm/ PBL − 2.6 ± 1.4 mm).	Significantly better clinical outcomes with intrabony periodontal defect regeneration following PPFS and NCHA grafting.	Small sample size and absence of histological assessment.
Gholami et al. (2012)	Prospective clinical RCT (split-mouth design)	Compare horizontal ridge width alteration following extraction and socket grafting with either NCHA or bovine xenograft.	12 patients (male − 4/ female − 8) with a mean age of 44.6 ± 11.4 years (range 21–60 years), having 28 symmetrical, non-molar, extraction sockets (n = 14 per group).	NCHA (NanoBone®, Artoss GmbH, Rostock, Germany), Bovine xenograft (BioOss®, Geistlich, Wolhusen, Switzerland) and CM (BioGide®,Geistlich, Wolhusen, Switzerland).	Following extraction, sockets were grafted with either NCHA or bovine xenograft and covered by CM in both groups. After 6–8 months, at the time of implant placement, clinical horizontal ridge width alteration was assessed and 2 × 6 mm bone cores were obtained for histological/ histomorphometric assessement.	In both groups, there was a significant reduction in mean horizontal ridge width (NCHA − 0.93 ± 0.57 mm/ bovine xenograft − 1.07 ± 0.97), without any statistical difference between the groups. Also, histologic bone area was not significantly different between both groups (NCHA − 28.63 ± 12.53%/bovine xenograft − 27.35 ± 12.39%).	Socket grafting and regeneration with either NCHA or bovine xenograft, along with CM, yieled comparable results. There was no statistically valid evidence of the superiority of one particular material over the other.	Small sample size.
Pietruska et al. (2012)	Prospective clinical RCT	Compare clinical and radiographic outcomes of intrabony periodontal defects treated by OFD only or OFD with NCHA grafting (OFD + NCHA).	30 patients (n = 15 per group/male-13/ female-17) in the age range of 38–55 years.	NCHA embedded in silica (NanoBone®, Artoss GmbH, Rostock, Germany)	Following OFD, intrabony periodontal defects (at least 3 mm deep and 2 mm wide) were either left ungrafted or grafted with NCHA. Clinical (PD, CAL and GR) and radiographic (Defect depth and width) parameters were assessed after 6 months and 12 months.	After 6 months, both groups showed significant reduction in mean PD (OFD − 2.9 ± 1.0 mm/OFD + NCHA − 3.3 ± 1.7 mm) and significant gain in mean CAL (OFD − 2.3 ± 0.9 mm/ OFD + NCHA − 2.5 ± 2.3 mm) after 6 months. Mean GR increased significantly in both groups (OFD − 0.5 ± 0.5 mm/OFD + NCHA − 0.8 ± 1.3 mm). There was no statistically significant difference between the groups for any parameters. Similar radiographic findings were observed in terms of defect depth and width. No significant difference between the parameters observed at 6 months and 12 months	Use of NCHA as a bone substitue material for intrabony periodontal defect regeneration following OFD, does not significantly improve clinical or radiographic parameters when compared to OFD alone.	Absence of histological assessment.

Table 1 (*continued*)

Author (year)	Study Design	Objectives/Aims	Patient Demographics	Material Used	Methodology	Outcomes	Conclusions	Limitations (as reported by the authors)
Singh et al. (2012a, 2012b)	Prospective clinical RCT	Compare clinical outcomes of intrabony periodontal defects treated by OFD only or OFD with NCHA grafting and collagen membrane (OFD + NCHA + CM).	16 patients (male-9/female-7) in the age rane of 25–65 years, with 20 intrabony periodontal defects (n = 10 per group).	NCHA (Sybograf®, Eucare Pharma. Pvt. ltd., Chennai, India) + Type I collagen membrane (PerioCol®, Eucare Pharma. Pvt. ltd., Chennai, India)	Following OFD, intrabony periodontal defects were either left ungrafted or grafted with NCHA and covered by collagen membrane. Clinical parameters (PD, CAL and GR) were assessed after 1 month, 3 months and 6 months.	In both groups, after 6 months, there was significant reduction in mean PD (OFD − 3.22 ± 1.09 mm/OFD + NCHA + CM − 4.33 ± 0.50 mm) and significant gain in mean CAL (OFD − 2.78 ± 1.09 mm/OFD + NCHA + CM − 3.78 ± 0.66 mm). The difference in PD and CAL was statistically significant between the groups There was significant increase in mean GR in both groups (OFD − 0.44 ± 0.52 mm/OFD + NCHA + CM − 0.55 ± 0.52 mm), without any statistical difference between the groups.	Combined use of NCHA with collagen membrane for grafting OFD treated intrabony periodontal defects, resulted in clinically significant PD reduction and CAL gain, than with OFD alone.	Inability to obtain histological evidence of periodontal defect regeneration.
Al Machot et al. (2014)	Prospective clinical RCT	Compare clinical outcomes of intrabony periodontal defect regeneration using either NCHA or EMD.	38 patients (n = 19 per group/male-20/female-18) in the age range of 30–65 years.	NCHA paste (Ostim, Heraeus Kulzer, Hanau, Germany) and EMD (Straumann Emdogain, Straumann, Basel, Switzerland)	Following periodontal flap surgery, deep (≥4mm) and wide (≥2mm) intrabony pockets were either grafted with NCHA or EMD. Clinical parameters (PD, CAL and GR) were assessed after 6 months and 12 months.	In both groups, after 6 months, there was significant reduction in mean PD (NCHA − 2.7 ± 1.8 mm/EMD − 3.2 ± 1.6 mm), significant gain in mean CAL (NCHA − 1.5 ± 2.0 mm/EMD − 2.0 ± 1.6 mm) and sifnificantly increased mean GR (NCHA − 1.2 ± 1.2 mm/EMD − 1.2 ± 1.1 mm). There was no signficant difference between the groups, and between the parameters observed at 6 months and 12 months.	Clinical outcomes of intrabony periodontal defect regeneration were similar with both NCHA and EMD. Although not statistically significant, the use of EMD yielded slightly better clinical parameters than NCHA.	Small sample size and absence of histological analysis of periodontal regeneration.
Pilloni et al. (2014)	Retrospective clinical study	Compare the clinical efficacy of four different treatment strategies (OFD only, OFD + EMD, OFD + NCHA, OFD + EMD + NCHA) for intrabony periodontal defect regeneration.	64 patients (male-30/female-34) with a mean age of 37.7 years.	NCHA (NeoActive Ghimas, Casalecchio di Reno, Italy) and EMD (Straumann Emdogain, Straumann, Basel, Switzerland)	Patients with intrabony periodontal defects greater than 3 mm in depth were retrospectively identified into four treatment groups (OFD only, OFD + EMD, OFD + NCHA, OFD + EMD + NCHA). Clinical parameters (PD, CAL and GR) recorded at 12 months, 18 months and 24 months were analyzed statistically.	In all groups, there was reduction in PD, increase in CAL and GR, at 12 months. While OFD + EMD + NCHA group had the greatest reduction in mean PD (5.75 mm), the OFD + NCHA group had the poorest clinical outcomes among all groups. No statistical comparison were made between the groups.	Combination of EMD + NCHA following OFD, has a synergistic role in regeneration of intrabony periodontal defects.	Only clinical parameters were evaluated retrospectively.

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Study Design	Objectives/Aims	Patient Demographics	Material Used	Methodology	Outcomes	Conclusions	Limitations (as reported by the authors)
Elgendy and Abo Shady (2015)	Prospective clinical RCT (split-mouth design)	Compare clinical and radiographic outcomes of intrabony periodontal defects grafted with NCHA alone or with a combination of NCHA + PRF.	20 patients with a mean age of 41.98 ± 7.73 years, and each patient having 2 identical intrabony periodontal defects (n = 20 defects per group).	NCHA (Nano–bone®, ARTOSS GmbH, Rostock, Germany) and Autologous PRF	Intrabony periodontal defects with clinical PD $\geq$ 6 mm, were treated through OFD and randomly divided into two treatment groups based on graft material (Group 1 - NCHA + PRF; Group 2 - NCHA). Clinical (PD and CAL) and radiographic (BD) parameters were assessed at 3 months and 6 months.	In both groups, there was a significant reduction in mean PD (NCHA + PRF − 3.33 ± 0.31 mm; NCHA − 3.30 ± 0.29 mm) and significant gain in mean CAL (NCHA + PRF − 3.55 ± 0.26 mm; NCHA − 3.50 ± 0.21 mm) and radiographic BD (NCHA + PRF − 34.45 ± 3.60%; NCHA − 16.86 ± 3.41%), after 6 months. All the three evaluated parameters were significantly higher in the group treated with NCHA + PRF.	Adjunct PRF along with NCHA for intrabony periodontal defect regeneration resulted in signficantly enhanced clinical and radiographic outcomes than with NCHA alone.	Autologus PRF harvesting procedure and equipment.
Koduru et al. (2019)	Prospective clinical RCT	Compare clinical and radiographic outcomes of intrabony periodontal defects grafted with either NCHA or synthetic bioactive glass putty.	20 patients (n = 10 per group) in the age range of 25–55 years.	NCHA (Sybograf®, Eucare Pharma. Pvt. ltd., Chennai, India) and Synthetic bioactive glass putty (NovaBone® Dental Putty, Osteogenics, Lubbock, Texas, USA)	Intrabony periodontal defects with clinical PD $\geq$ 5 mm and radiographic BL $\geq$ 3 mm, were treated through OFD and randomly divided into two treatment groups based on graft material (Group 1 - NCHA; Group 2 - Bioactive glass putty). Clinical (PD, CAL and GR) and radiographic (BL) parameters were assessed after 3 months, 6 months and 9 months.	In both groups, mean PD, CAL and BL changed significantly at 3, 6 and 9 months when compared to the baseline. The change in GR was significant only at 3 months. After 6 months, mean reduction in PD - Group 1 (3.0 ± 0.92 mm)/ Group 2 (3.5 ± 0.83 mm); mean gain in CAL - Group 1 (4.7 ± 0.54 mm)/Group 2 (5.0 ± 0.57 mm); mean gain in BL - Group 1 (5.9 ± 0.55 mm)/Group 2 (5.6 ± 0.42 mm). There was no significant difference between the groups for all assessed parameters across all time periods of assessment.	Both graft materials (NCHA and syntehtic bioactive glass putty) have comparable outcomes for intrabony periodontal defect regeneration. In terms of clinical parameters, grafting with NCHA yielded slightly superior results, than with bioactive glass.	Study conducted in a single-center and was of short duration.
Bahammam and Attia (2021)	Prospective clinical RCT	Compare expression of VEGF in intrabony periodontal defects treated with OFD and application of either PRF alone or a combination of PRF along with NCHA graft.	60 patients (n = 15 per group/male-33/ female-27) in the age range of 27–48 years.	NCHA and autologous PRF	Intrabony periodontal defects with clinical PD $\geq$ 6 mm, were randomly divided into four treatment groups (Group 1 - OFD + PRF; Group 2 - OFD + NCHA; Group 3 - OFD + PRF + NCHA; Group 4 - OFD). Clinical (PD and CAL) and radiographic (BD and BL) parameters were assessed after 6 months. GCF samples were obtained at 3, 7 and 14 days in all groups to assess VEGF expression.	In all the groups, reduction in mean PD and BL was significant after 6 months. With respect to mean gain CAL, it was significant in all groups except group 4. Increase in BD was only significant in group 3. There was no significant difference between the groups. After 6 months, mean reduction in PD – Group 1 (2.7 ± 0.89 mm)/Group 2 (2.4 ± 1.17 mm)/Group 3 (3.0 ± 0.94 mm)/Group 4 (0.90 ± 1.10 mm); mean gain in CAL - Group 1 (1.17 ± 1.21 mm)/Group 2 (1.7 ± 1.03 mm)/Group 3 (2.1	PRF with NCHA is a succesful alternative for regeneration of intrabony periodontal defects. VEGF expression was identified in all treatment groups, confirming its role in angiogenesis and osteogenesis during early bone healing.	Evaluation of four different treatment modalities in different patients without a split-mouth design.

Table 1 (*continued*)

Author (year)	Study Design	Objectives/Aims	Patient Demographics	Material Used	Methodology	Outcomes	Conclusions	Limitations (as reported by the authors)
						± 1.04 mm)/Group 4 (1.0 ± 1.13 mm); mean reduction in BL - Group 1 (2.2 ± 0.09 mm)/Group 2 (1.49 ± 0.65 mm)/Group 3 (2.31 ± 1.50 mm)/Group 4 (1.1 ± 0.57 mm); mean increase in BD - Group 1 (17.25%)/ Group 2 (14.39%)/Group 3 (46.78%)/Group 4 (11.55%).		
Deshpande et al. (2021)	Prospective clinical RCT	Compare clinical and radiographic outcomes of intrabony periodontal defects grafted with either NCHA or a composite of NCHA + ECM (natural collagen).	40 patients (male-24/ female-16) with a mean age of 33.5 years (range 21–56 years), having atleast one intrabony defect (maxilla-27/mandible-13/ n = 20 per group).	NCHA (Sybograf®, Eucare Pharma. Pvt. ltd., Chennai, India) and NCHA with natural collagen (ECM) (Sybograf-C®, Eucare Pharma. Pvt. ltd., Chennai, India)	Intrabony periodontal defects with clinical PD greater than 5 mm were treated through OFD and randomly divided into two treatment groups based on graft material (Group 1 - NCHA + ECM collagen composite; Group 2 - NCHA). Clinical (PD and CAL) and radiographic (BL) parameters were assessed after 3 months and 6 months.	In both groups, mean PD, CAL and BL changed significantly at 3 months and 6 months when compared to the baseline. After 6 months, mean reduction in PD - Group 1 (5.0 ± 0.28 mm)/ Group 2 (4.85 ± 0.30 mm); mean gain in CAL - Group 1 (4.15 ± 0.17 mm)/Group 2 (3.95 ± 0.22 mm); mean gain in BL - Group 1 (3.86 ± 0.78 mm)/Group 2 (4.18 ± 0.69 mm). While there was significant difference between the groups in terms of PD reduction and CAL gain at 3 months (NCHA + ECM better than NCHA alone), there was no statistical difference for all assessed parameters at 6 months.	Inclusion of natural collagen (ECM with NCHA resulted in better outcomes in the early phase (after 3 months). However, after 6 months the results with both NCHA and NCHA + ECM were comparable.	Small sample size with short follow up, absence of split-mouth design and non availability of advanced radiographic modalities like CBCT.
Elbattawy and Ahmed (2021)	Prospective clinical study (non-randomized)	Compare clinical and radiographic outcomes of intrabony periodontal defects treated by OFD only or OFD with NCHA grafting (OFD + NCHA).	20 patients (n = 10 per group/male-9/ female-11) in the age range of 36–56 years.	NCHA (Nano–bone®, ARTOSS GmbH, Rostock, Germany)	Following OFD, intrabony periodontal defects with clinical PD $\geq$ 6 mm and radiographic BL $\geq$ 3 mm, were either left ungrafted or grafted with NCHA and covered by collagen membrane. Clinical (PD, CAL and GR) and radiographic (BDA) parameters were assessed after 6 months.	In both groups, there was a significant reduction in mean PD (OFD − 2.4 ± 0.5 mm; NCHA − 3.2 ± 1.1 mm), significant gain in mean CAL (OFD − 1.2 ± 0.8 mm; NCHA − 2.7 ± 1.3 mm) and significant reduction in radiographic BDA (OFD − 1.7 ± 1.0 mm^2; NCHA − 3.4 ± 2.2 mm^2). There was no significant difference between the groups.	Both OFD and OFD + NCHA resulted in comparable intrabony periodontal defect regeneration after 6 months.	Non-randomized study

NCHA – Nanocrystalline hydroxyapatite; RCT – Randomized controlled trial; OFD – Open flap debridement; PD – Probing depth; CAL – Clinical attachment level; GR – Gingival recession; CM – Collagen membrane; PPFS – Papilla preservation flap surgery; PBL – Probing bone level; EMD – Emdogain; PRF – Platelet rich fibrin; BD – Bone density; BL – Bone level; VEGF – Vascular endothelial growth factor; ECM – Extracellular matrix; CBCT – Cone-beam computed tomography; BDA – Bone defect area.

2015). Randomization of clinical samples was reported in all the studies except for one non-comparative study by Strietzel et al. (2007), and one comparative study by Elbattawy and Ahmed (2021). All the studies were reported based on an adult population, with reasonable male to female distribution and age ranging from 21 years to 65 years. The lowest sample size in any interventional group was 10 patients and the greatest was 20 patients. While all studies had an equal ratio of the number of defects regenerated to the number of patients treated per group, two studies respectively reported 12 and 16 patients with 28 and 20 defects which were regenerated using NCHA (Gholami et al. 2012; Singh et al. 2012a, 2012b). These studies were included in the review as they reported a minimum number of 10 defects which were clinically treated and followed up, per group. Although, the minimum follow up required as per inclusion criteria was 6 months, studies also reported post-treatment follow up period as early as 2 weeks to 1 month, and as long as after 1, 2 and 4 years. In order to maintain homogeneity of reviewed clinical data, only outcomes after 6 months of follow up were considered for the present review. None of the studies reported significant differences in outcomes based on demographic characteristics.

b. *Biomaterials used and their clinical applications*

Since the present review was about the use of NCHA as a bone substitute material for periodontal defect regeneration, all the studies reported usage of NCHA in one form or the other. While NCHA paste was predominantly used (Ostim®, Heraeus Kulzer, Hanau, Germany), particulate NCHA (Nano bone®, ARTOSS GmbH, Rostock, Germany/Sybograf®, Eucare Pharma. Pvt. Ltd., Chennai, India), NCHA embedded in amorphous silica matrix and a composite graft comprising NCHA and extracellular-matrix (ECM) collagen (Sybograf-C®, Eucare Pharma. Pvt. Ltd., Chennai, India) were also use. In addition, titanium mesh, bovine xenograft, collagen membrane, enamel matrix derivative (EMD/Emdogain), and autologous PRF have reportedly been used for comparative interventions (Table 1). Interestingly, only one study reported direct comparison between two different types of NCHA (with or without ECM collagen), for periodontal defect regeneration (Deshpande et al. 2021). While they reported early clinical gains with the use of NCHA + ECM composite, after 6 months there were no significant differences in the clinical and radiographic outcomes with both variants of NCHA graft used.

c. *Nature of periodontal bone defect regeneration and variables assessed*

Except three studies, all the other reviewed studies evaluated the role of NCHA for intrabony periodontal defect regeneration. Among these three studies, Strietzel et al. (2007) reported about lateral alveolar ridge augmentation using NCHA and titanium mesh, Schwarz et al. (2009) evaluated the long-term effects of NCHA versus bovine xenograft, for peri-implantitis bone defect regeneration, and Gholami et al. (2012) compared NCHA and bovine xenograft for socket preservation after extraction. In all studies reporting about intrabony defect regeneration using NCHA, the defect site was clinically prepared for grafting through complete mucoperiosteal open flap debridement (OFD), excepting the study by Heinz et al. (2010), wherein a papilla preservation flap surgery (PPFS) was used for debridement. Interestingly, in seven out of the eleven reviewed studies, only OFD or PPFS debridement was one comparative variable, against debridement with NCHA grafting. In addition, Pilloni et al. (2014) and Bahammam and Attia (2021), compared the roles of EMD and PRF as adjuncts to NCHA for bone regeneration. The roles of EMD and PRF were also respectively evaluated by the studies of Al Machot et al. (2014) and Elgendy and Abo Shady (2015). While the use of CM as a means of guided bone regeneration with NCHA was reported in one study (Singh et al. 2012a, 2012b), only one study used a synthetic bioactive glass putty graft as a comparison variable (Koduru et al. 2019). The outcomes of bone regeneration with NCHA were predominantly evaluated based on clinical and radiographic parameters. Additionally, histological assessment was reported in two studies which evaluated alveolar ridge augmentation (Strietzel et al. 2007; Gholami et al. 2012). Quantitative outcomes in each reviewed study, after 6 months, following bone regeneration with NCHA are presented in Tables 2 and 3.

4. Discussion

Clinical regeneration of periodontal and alveolar bone is of paramount importance for the success of periodontitis treatment and dental implant rehabilitation. Periodontal bone is liable to resorption following extraction and due to disease processes involving the gingiva, periodontal ligament and peri-implant tissue (Ramalingam et al. 2020). While a key element of periodontal bone healing is the removal of the pathological determinants of resorption, the cornerstone lies in the ability to regenerate hard and soft tissue support structures. The earliest modality of periodontal regeneration was through guided tissue regeneration (GTR) using barrier membranes. This was later extrapolated to bone defect regeneration, socket preservation and alveolar ridge augmentation through guided bone regeneration (Ramalingam et al. 2016; Sivolella et al. 2018; Ramalingam et al. 2019). Placement of a suitable bone substitute material is needed for all forms of bone regeneration.

The growing clinical facets of guided bone regeneration opened avenues for the research, identification and use of several bone substitutes or grafts from autologous, allogenous, xenogenous and alloplastic origins, with each form having its own merits and demerits (Badwelan et al. 2020). Synthetic alloplastic bone substitutes are inorganic and biocompatible, and over the last two decades have been used successfully in orthopedics and dentistry for bone defect healing and regeneration. Additionally, they are not associated with any donor site morbidity, risk of infection or immunogenicity (Cheah et al. 2021). With the advent of nanotechnology, several biocompatible nanoparticles have been evaluated for their potential roles in bone regeneration. NCHA is one such potential bone substitute which combines the benefits of nanotechnology and calcium phosphate bioceramics. Furthermore, as a bioceramic nanoparticle, NCHA exerts biomimetic properties for bone regeneration and healing by increasing the surface area of action and through increased availability of calcium and phosphorus ions (Pepla et al. 2014).

In the present review, all the studies reported using commercially available NCHA for periodontal bone regeneration.

Table 2 Quantitative outcomes after 6 months following periodontal bone regeneration with nanocrystalline hydroxyapatite as a bone substitute material.

Author (Year)	Quantitative outcomes *(mean ± S.D.)*			
	Clinical *(in mm)*			Radiographic
	PD reduction	*CAL gain*	*GR increase*	
Kasaj et al. (2008)	3.9 ± 1.2	3.6 ± 1.6	0.4 ± 0.4	–
Schwarz et al. (2009)	2.1 ± 0.5	1.8 ± 0.6	0.3 ± 0.2	–
Heinz et al. (2010)	4.3 ± 1.6	4.3 ± 1.4	–	–
Pietruska et al. (2012)	3.3 ± 1.7	2.5 ± 2.3	0.8 ± 1.3	–
Singh et al. (2012a, 2012b)	4.33 ± 0.50	3.78 ± 0.66	0.55 ± 0.52	–
Al Machot et al. (2014)	2.7 ± 1.8	1.5 ± 2.0	1.2 ± 1.2	–
Pilloni et al. (2014)	5.75*	–	–	–
Elgendy and Abo Shady (2015)	3.30 ± 0.29	3.50 ± 0.21	–	16.86 ± 3.41% (BD↑)
	3.33 ± 0.31#	3.55 ± 0.26#		34.45 ± 3.60% (BD↑)#
Koduru et al. (2019)	3.0 ± 0.92	4.7 ± 0.54	–	5.9 ± 0.55 mm (BL↑)
Bahammam and Attia (2021)	2.4 ± 1.17	1.7 ± 1.03	–	1.49 ± 0.65 mm (BL↑)/14.39% (BD↑)
	3.0 ± 0.94#	2.1 ± 1.04#		2.31 ± 1.50 mm (BL↑)/46.78% (BD↑)#
Deshpande et al. (2021)	4.85 ± 0.30	3.95 ± 0.22	–	4.18 ± 0.69 mm (BL↑)
	5.0 ± 0.28$	4.15 ± 0.17$		3.86 ± 0.78 mm (BL↑)$
Elbattawy and Ahmed (2021)	3.2 ± 1.1	2.7 ± 1.3	–	3.4 ± 2.2 mm^2 (BDA↓)

PD – Probing depth; CAL – Clinical attachment level; GR – Gingival recession; BD – Bone density; BL – Bone level; BDA – Bone defect area.
* Adjunct EMD (Enamel matrix derivative).
\# Adjunct PRF (Platelet rich fibrin).
$ Adjunct ECM (Extracellular matrix collagen).

Although, the biomaterial characterization were not described in any study, the product monographs of each type of material used was verified to confirm the nanoscale nature of the graft material used (Table 1). Being a nanoceramic, the defining characteristic of NCHA is the number of available active surface molecules which are capable of stimulating osteoblasts and thereby accentuating bone healing (Schnettler et al. 2004). This is further enhanced the extremely small, amorphous particle size of NCHA along with a chemical composition similar to that of bone mineral matrix (Strietzel et al. 2007). This is clearly seen from the outcomes of the present review, wherein all studies reported significant bone formation with NCHA as early as 6 months, as evidenced by reduction in PD, gain in CAL and increase in alveolar ridge dimensions (Tables 1–3). Additionally, NCHA has also been shown to increase the potential for osseointegration through increasing osteoconductivity (Pepla et al. 2014).

While none of the reviewed studies evaluated osseointegration, Schwarz and colleagues reported successful regeneration of peri-implant bone defects over a long-term follow up period ranging from 3 months to 4 years (Schwarz et al. 2006, 2008, 2009). They observed clinically relevant bone formation around implants, post peri-implantitis treatment and NCHA grafting, which was similar if not better than the routinely used GBR with bovine xenograft and collagen membrane. Interestingly, their study also demonstrated a clear advantage of the NCHA paste, which could be used to graft intrabony defects without the need for a collagen membrane. Similar findings were also reported by 5 more reviewed studies which either used NCHA paste or NCHA along with plasticizer like silica gel (Strietzel et al. 2007; Kasaj et al. 2008; Heinz et al. 2010; Pietruska et al. 2012; Al Machot et al. 2014). Although the use of a barrier membrane has been considered imperative in GBR of intrabony defects (Alauddin et al. 2022), only 3 out of the 14 reviewed studies used a collagen barrier membrane along with NCHA (Gholami et al. 2012; Singh et al. 2012a, 2012b; Elbattawy and Ahmed 2021). All of these studies reported significantly improved bone formation after 6 months of grafting. Nevertheless, none of them compared the role of barrier membrane as a variable. The only reviewed study which used collagen matrix as a determinant was by Deshpande et al. (2021), who compared intrabony defect regeneration with either NCHA or a composite of NCHA and extracellular matrix (ECM) collagen. While it was reported that the addition of ECM to NCHA improved early outcomes by 3 months, after 6 months of healing there was no significant difference. These evidences make it alluring to hypothesize that NCHA as a graft material has physical and biological properties which bestow in it the ability to be used for bone regeneration without a barrier membrane. While these could be due to their extremely small and amorphous particle size, capable of packing more active molecules and

Table 3 Quantitative outcomes after 6 months following alveolar bone regeneration with nanocrystalline hydroxyapatite as a bone substitute material.

Author (Year)	Nature of bone defect	Quantitative outcomes	
		Clinical ridge width gain	Histological bone area
Strietzel et al. (2007)	Lateral ridge augmentation	2 mm (median)	52.3% (median)
Gholami et al. (2012)	Socket preservation	–	28.63 ± 12.53% (mean)

surface area within a given volume, future studies to evaluate the same would lend further credence (Pepla et al. 2014).

NCHA has been reported as capable of stimulating cell proliferation, especially within periodontal tissues and osteogenic progenitors (Al Machot et al. 2014). The biological mechanism behind this stimulant effect of NCHA has been linked to the epidermal growth factor receptor pathway (Pepla et al. 2014). Nonetheless, the role of specific adjuncts such as enamel matrix derivative (EMD) and platelet rich fibrin (PRF), specifically for their angiogenic and osteogenic effects, were also reported in the present review (Al Machot et al. 2014; Pilloni et al. 2014; Elgendy and Abo Shady 2015; Bahammam and Attia 2021). EMD is a protein rich in amelogenins which possess the potential to stimulate fibroblasts and osteoblasts in periodontal tissue (Pilloni et al. 2014). Moreover, EMD has been shown to be a potent enhancer of angiogenesis and neovascularization, when placed in the vicinity of healing tissue (Al Machot et al. 2014). Although Al Machot et al. (2014), reported that the use of EMD alone in intrabony defects yielded better results than using NCHA alone, Pilloni et al. (2014) observed synergistic effects when combining EMD with NCHA graft, for intrabony defects treated by OFD. Similarly, PRF is a rich source of several growth factors such as platelet derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) (Elgendy and Abo Shady 2015; Bahammam and Attia 2021). As a result of which, PRF when combined with graft materials stimulates cellular chemotaxis, neovascularization and osteogenic differentiation. Elgendy and Abo Shady (2015), observed significantly enhanced regeneration of intrabony periodontal defects with a combination of NCHA and PRF, than with NCHA alone. On the contrary, Bahammam and Attia (2021) reported similar bone regeneration with NCHA alone, as with NCHA and PRF. Nevertheless, reported enhanced expression of VEGF with PRF, indicating a beneficial role for PRF as an adjunct to NCHA.

Evolution of nanotechnology in the realm of bone substitute materials like NCHA, while reducing the particle size from micro scale to nano scale, have also increased the surface area and bioactivity (Cheah et al. 2021). The outcomes of the present review and the individual included studies, further point to the versatility of NCHA as a bone substitute material for periodontal bone regeneration in general and intrabony defects in particular (Table 1). While the role of NCHA in ridge augmentation was identified through histology, it was not done as a routine in the case of studies evaluating intrabony defect grafting and regeneration. This was a major limitation mentioned by the authors of these reviewed studies too. Other than that, most studies also claimed the absence of radiographic records and split mouth design, as another major limitation. On the whole, the heterogeneity of the reviewed studies, in terms of randomization, patient selection and outcome variables assessed was a factor to be considered while deciphering the results of this review. Paucity of quality randomized controlled trials evaluating NCHA for regenerating periodontal bone was yet another limiting factor. Methodologically, this was eliminated through inclusion of outcome variables which could only be standardized across all the included studies, as shown in Table 1.

5. Conclusion

Within the limits of the present review, it might be concluded that NCHA is a suitable bone substitute material for periodontal bone regeneration, with outcomes comparable to that of conventionally used graft materials such as bovine xenograft and other synthetic alloplastic materials. While grafting with NCHA in intrabony periodontal defects, after any form of periodontal flap surgery and debridement, significantly improves bone regeneration by 6 months, addition of adjuncts like EMD and PRF enhance the same. Future long term randomized studies utilizing a split mouth design and evaluation clinical, radiographic and histological outcomes after NCHA grafting are to be recommended. Similarly, studies comparing the NCHA with allografts and autografts, for periodontal bone regeneration shall also add value to the existing available evidence.

6. Conflict of Interest Statement

The authors declare no conflicts of interest.

Acknowledgement

The author acknowledges Department of Periodontology, College of Dentistry, King Saud University, and its Teaching Staff, Colleagues, Patients, Participants, Technicians and any member help to pursue and finish this study. The author expresses sincere gratitude to Dr. Amani Mohammed Basudan for supporting in the review process.

References

Al Machot, E., Hoffmann, T., et al, 2014. Clinical outcomes after treatment of periodontal intrabony defects with nanocrystalline hydroxyapatite (Ostim) or enamel matrix derivatives (Emdogain): a randomized controlled clinical trial. Biomed. Res. Int 2014, 786353.

Alauddin, M.S., Abdul Hayei, N.A., et al, 2022. Barrier Membrane in Regenerative Therapy: A Narrative Review. Membranes 12 (5), 444.

Anu Mary Ealia, S., Saravanakumar, M.P., 2017. A review on the classification, characterisation, synthesis of nanoparticles and their application. IOP Conf. Ser.: Mater. Sci. Eng. 263, 032019.

Badwelan, M., Alkindi, M., et al, 2020. The Efficacy of Recombinant Platelet-Derived Growth Factor on Beta-Tricalcium Phosphate to Regenerate Femoral Critical Sized Segmental Defects: Longitudinal In Vivo Micro-CT Study in a Rat Model. J. Invest. Surg. 33 (5), 476–488.

Bahammam, M.A., Attia, M.S., 2021. Expression of Vascular Endothelial Growth Factor Using Platelet Rich Fibrin (PRF) and Nanohydroxyapatite (nano-HA) in Treatment of Periodontal Intra-Bony Defects - A Randomized Controlled Trial. Saudi J. Biol. Sci. 28 (1), 870–878.

Bosshardt, D.D., Bornstein, M.M., et al, 2014. Maxillary sinus grafting with a synthetic, nanocrystalline hydroxyapatite-silica gel in humans: histologic and histomorphometric results. Int. J. Periodont. Restorat. Dent. 34 (2), 259–267.

Canullo, L., Dellavia, C., 2009. Sinus lift using a nanocrystalline hydroxyapatite silica gel in severely resorbed maxillae: histological preliminary study. Clin. Implant Dent. Relat. Res. 11 (Suppl 1), e7–e13.

Canullo, L., Patacchia, O., et al, 2012. Implant restoration 3 months after one stage sinus lift surgery in severely resorbed maxillae: 2-

year results of a multicenter prospective clinical study. Clin. Implant Dent. Relat. Res. 14 (3), 412–420.
Canuto, R.A., Pol, R., et al, 2013. Hydroxyapatite paste Ostim, without elevation of full-thickness flaps, improves alveolar healing stimulating BMP- and VEGF-mediated signal pathways: an experimental study in humans. Clin. Oral Implants Res. 24 (Suppl A100), 42–48.
Cao, L.-Y., Zhang, C.-B., et al, 2005. Synthesis of hydroxyapatite nanoparticles in ultrasonic precipitation. Ceram. Int. 31 (8), 1041–1044.
Cheah, C.W., Al-Namnam, N.M., et al, 2021. Synthetic Material for Bone, Periodontal, and Dental Tissue Regeneration: Where Are We Now, and Where Are We Heading Next? Materials (Basel) 14 (20), 6123.
Checchi, V., Savarino, L., et al, 2011. Clinical-radiographic and histological evaluation of two hydroxyapatites in human extraction sockets: a pilot study. Int. J. Oral Maxillofac. Surg. 40 (5), 526–532.
Davar, F., Salavati-Niasari, M., et al, 2010. Thermal decomposition route for synthesis of Mn3O4 nanoparticles in presence of a novel precursor. Polyhedron 29 (7), 1747–1753.
de Lima Cavalcanti, J.H., Matos, P.C., et al, 2019. In Vitro Assessment of the Functional Dynamics of Titanium with Surface Coating of Hydroxyapatite Nanoparticles. Materials (Basel) 12 (5).
Deshpande, A.P., Baburaj, M.D., et al, 2021. Extracellular matrix containing nanocomposite bone graft in periodontal regeneration - A randomized controlled clinical and radiographic evaluation. J. Indian Soc. Periodontol. 25 (4), 313–319.
El Hage, M., Abi Najm, S., et al, 2012. Graft shrinkage and survival rate of implants after sinus floor elevation using a nanocrystalline hydroxyapatite embedded in silica gel matrix: a 1-year prospective study. Implant Dent 21 (3), 213–219.
Elbattawy, W., Ahmed, D., 2021. Clinical and radiographic evaluation of open flap debridement with or without Nanocrystalline Hydroxyapatite bone graft in management of periodontal intrabony defects. Egypt. Dent. J. 67 (Issue 1 – January (Oral Medicine, X-Ray, Oral Biology & Oral Pathology)), 433–446.
Elgendy, E.A., Abo Shady, T.E., 2015. Clinical and radiographic evaluation of nanocrystalline hydroxyapatite with or without platelet-rich fibrin membrane in the treatment of periodontal intrabony defects. J. Indian Soc. Periodontol. 19 (1), 61–65.
Fujihara, K., Kotaki, M., et al, 2005. Guided bone regeneration membrane made of polycaprolactone/calcium carbonate composite nano-fibers. Biomaterials 26 (19), 4139–4147.
Ghanaati, S., Lorenz, J., et al, 2014. Nanocrystalline hydroxyapatite-based material already contributes to implant stability after 3 months: a clinical and radiologic 3-year follow-up investigation. J. Oral Implantol. 40 (1), 103–109.
Gholami, G.A., Najafi, B., et al, 2012. Clinical, histologic and histomorphometric evaluation of socket preservation using a synthetic nanocrystalline hydroxyapatite in comparison with a bovine xenograft: a randomized clinical trial. Clin. Oral Implants Res. 23 (10), 1198–1204.
Heinemann, F., Mundt, T., et al, 2009. A 3-year clinical and radiographic study of implants placed simultaneously with maxillary sinus floor augmentations using a new nanocrystalline hydroxyapatite. J. Physiol. Pharmacol. 60 (Suppl 8), 91–97.
Heinz, B., Kasaj, A., et al, 2010. Clinical effects of nanocrystalline hydroxyapatite paste in the treatment of intrabony periodontal defects: a randomized controlled clinical study. Clin. Oral Investig. 14 (5), 525–531.
Heo, D.N., Ko, W.K., et al, 2016. Titanium dental implants surface-immobilized with gold nanoparticles as osteoinductive agents for rapid osseointegration. J. Colloid Interface Sci. 469, 129–137.
Horváth, A., Stavropoulos, A., et al, 2013. Histological evaluation of human intrabony periodontal defects treated with an unsintered nanocrystalline hydroxyapatite paste. Clin. Oral Investig. 17 (2), 423–430.
Jarudilokkul, S., Tanthapanichakoon, W., et al, 2007. Synthesis of hydroxyapatite nanoparticles using an emulsion liquid membrane system. Colloids Surf., A 296 (1), 149–153.
Kasaj, A., Röhrig, B., et al, 2008. Clinical evaluation of nanocrystalline hydroxyapatite paste in the treatment of human periodontal bony defects–a randomized controlled clinical trial: 6-month results. J. Periodontol. 79 (3), 394–400.
Khaled, H., Atef, M., et al, 2019. Maxillary sinus floor elevation using hydroxyapatite nano particles vs tenting technique with simultaneous implant placement: A randomized clinical trial. Clin. Implant Dent. Relat. Res. 21 (6), 1241–1252.
Koduru, S., Aghanashini, S., et al, 2019. A Clinical and Radiographic Evaluation of the Efficacy of Nanohydroxyapatite (Sybograf™) versus Bioactive Calcium Phosphosilicate Putty (Novabone(®)) in the Treatment of Human Periodontal Infrabony Defects: A Randomized Clinical Trial. Contemp. Clin. Dent. 10 (1), 16–23.
Kokubo, T., 1998. Apatite formation on surfaces of ceramics, metals and polymers in body environment. Acta Mater. 46 (7), 2519–2527.
Kumari, B., Gautam, D.K., et al, 2014. An evaluation and comparison of the efficacy of nanocrystalline calcium sulfate bone grafts (NanoGen) and medical-grade calcium sulfate bone grafts (DentoGen) in human extraction sockets. Compend. Contin. Educ. Dent. 35 (10), e36–e41.
Liao, S., Wang, W., et al, 2005. A three-layered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. Biomaterials 26 (36), 7564–7571.
Menezes, H.H.M., Naves, M.M., et al, 2018. Effect of Surgical Installation of Dental Implants on Surface Topography and Its Influence on Osteoblast Proliferation. Int. J. Dent. 2018, 4089274.
Nickles, K., Ratka-Kruger, P., et al, 2009. Open flap debridement and guided tissue regeneration after 10 years in infrabony defects. J. Clin. Periodontol. 36 (11), 976–983.
Otunola, G.A., Afolayan, A.J., et al, 2017. Characterization, Antibacterial and Antioxidant Properties of Silver Nanoparticles Synthesized from Aqueous Extracts of Allium sativum, Zingiber officinale, and Capsicum frutescens. Pharmacogn. Mag. 13 (Suppl 2), S201–S208.
Pandit, N., Sharma, A., et al, 2015. The use of nanocrystalline and two other forms of calcium sulfate in the treatment of infrabony defects: A clinical and radiographic study. J. Indian Soc. Periodontol. 19 (5), 545–553.
Pepla, E., Besharat, L.K., et al, 2014. Nano-hydroxyapatite and its applications in preventive, restorative and regenerative dentistry: a review of literature. Annali di stomatologia 5 (3), 108–114.
Piattelli, A., Scarano, A., et al, 1996. Evaluation of guided bone regeneration in rabbit tibia using bioresorbable and non-resorbable membranes. Biomaterials 17 (8), 791–796.
Pietruska, M., Skurska, A., et al, 2012. Clinical and radiographic evaluation of intrabony periodontal defect treatment by open flap debridement alone or in combination with nanocrystalline hydroxyapatite bone substitute. Ann. Anatomy – Anatomischer Anzeiger 194 (6), 533–537.
Pilloni, A., Saccucci, M., et al, 2014. Clinical evaluation of the regenerative potential of EMD and NanoHA in periodontal infrabony defects: a 2-year follow-up. Biomed. Res. Int. 2014, 492725.
Ramalingam, S., Al-Rasheed, A., et al, 2016. Guided bone regeneration in standardized calvarial defects using beta-tricalcium phosphate and collagen membrane: a real-time in vivo micro-computed tomographic experiment in rats. Odontology 104 (2), 199–210.
Ramalingam, S., Alrayyes, Y.F., et al, 2019. Lateral Periodontal Cyst Treated with Enucleation and Guided Bone Regeneration: A Report of a Case and a Review of Pertinent Literature. Case Rep. Dent. 2019, 4591019.
Ramalingam, S., Sundar, C., et al, 2020. Chapter 1 - Alveolar bone science: Structural characteristics and pathological changes. In: Alghamdi, H., Jansen, J. (Eds.), Dental Implants and Bone Grafts. Woodhead Publishing, pp. 1–22.

Retzepi, M., Donos, N., 2010. Guided Bone Regeneration: biological principle and therapeutic applications. Clin. Oral Implants Res. 21 (6), 567–576.

Rouahi, M., Champion, E., et al, 2006. Physico-chemical characteristics and protein adsorption potential of hydroxyapatite particles: influence on in vitro biocompatibility of ceramics after sintering. Colloids Surf. B: Biointerfaces 47 (1), 10–19.

Rudramurthy, G.R., Swamy, M.K., 2018. Potential applications of engineered nanoparticles in medicine and biology: an update. J. Biol. Inorg. Chem. 23, 1185–1204.

Sambhy, V., MacBride, M.M., et al, 2006. Silver Bromide Nanoparticle/Polymer Composites: Dual Action Tunable Antimicrobial Materials. J. Am. Chem. Soc. 128 (30), 9798–9808.

Schnettler, R., Stahl, J.P., et al, 2004. Calcium Phosphate-Based Bone Substitutes. Eur. J. Trauma 30 (4), 219–229.

Schwarz, F., Bieling, K., et al, 2006. Healing of intrabony periimplantitis defects following application of a nanocrystalline hydroxyapatite (Ostim) or a bovine-derived xenograft (Bio-Oss) in combination with a collagen membrane (Bio-Gide). A case series. J. Clin. Periodontol. 33 (7), 491–499.

Schwarz, F., Sahm, N., et al, 2009. Surgical regenerative treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane: a four-year clinical follow-up report. J. Clin. Periodontol. 36 (9), 807–814.

Schwarz, F., Sculean, A., et al, 2008. Two-year clinical results following treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane. J. Clin. Periodontol. 35 (1), 80–87.

Singh, V.P., Nayak, D.G., et al, 2012a. Clinical and radiographic evaluation of Nano-crystalline hydroxyapatite bone graft (Sybograf) in combination with bioresorbable collagen membrane (Periocol) in periodontal intrabony defects. Dent. Res. J. 9 (1), 60–67.

Singh, V.P., Nayak, D.G., et al, 2012b. Nano-crystalline hydroxyapatite bone graft combined with bioresorbable collagen membrane in the treatment of periodontal intrabony defects: A randomized controlled clinical trial. J. Indian Soc. Periodontol. 16 (4), 562–568.

Sivolella, S., Perin, C., et al, 2018. Guided Bone Regeneration in the Treatment of a Lateral Periodontal Cyst: 2-Year Clinical and Radiologic Follow-up. Int. J. Periodontics Restorative Dent. 38 (5), 747–754.

Stevanović, M., Biočanin, V., et al, 2015. Efficacy of nanocrystalline bone substitute biphasic calcium phosphate/poly-DL-lactide-co-glycolide for periodontal intrabony defects filling. Vojnosanit. Pregl. 72 (8), 689–695.

Strietzel, F.P., Reichart, P.A., et al, 2007. Lateral alveolar ridge augmentation using a synthetic nano-crystalline hydroxyapatite bone substitution material (Ostim): preliminary clinical and histological results. Clin. Oral Implants Res. 18 (6), 743–751.

Suo, L., Jiang, N., et al, 2019. The enhancement of osseointegration using a graphene oxide/chitosan/hydroxyapatite composite coating on titanium fabricated by electrophoretic deposition. J. Biomed. Mater. Res. B Appl. Biomater. 107 (3), 635–645.

Wolf, M., Wurm, A., et al, 2014. The effect of patient age on bone formation using a fully synthetic nanocrystalline bone augmentation material in maxillary sinus grafting. Int. J. Oral Maxillofac. Implants 29 (4), 976–983.

Yang, F., Both, S.K., et al, 2009. Development of an electrospun nano-apatite/PCL composite membrane for GTR/GBR application. Acta Biomater. 5 (9), 3295–3304.