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REVIEW ARTICLE

Role of Synthetic Hydroxyapatite—In Socket Preservation: A Systematic Review and Meta-analysis

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Abstract

Since a long time, the preservation of the socket is emphasized for various reasons. Many studies have suggested the ridge preservation through socket grafting using various bone graft substitute materials (GSMs). But none of the studies suggested the material of choice for the grafting. So, the systematic review was planned to analyze the outcomes of synthetic hydroxyapatite (SHA) graft material for socket preservation. The review was aimed to determine the existing evidence for the use of SHA GSM for grafting and its usefulness.

Materials and methods: The literature search was performed for the studies published in the English language independently by all four authors (search team) in the Medline database through the PubMed search engine for the past 5 years. The study involved predetermined inclusion and exclusion criteria for the search. The final lists of clinical trials were analyzed to determine the existing evidence and suggested the mechanism of action.

Review results: The search resulted in 117 titles. After application of inclusion and exclusion criteria, a total of seven studies were found eligible for this systematic review. Out of seven, two studies were found eligible for meta-analysis whereas remaining included for the systematic review.

Conclusion: The meta-analysis favors socket grafting compared to control in terms of preservation of existing bone height and width. The SHA grafting showed successful bone regeneration with less connective tissue component. The histomorphometric evaluation showed a good bone regeneration associated with SHA than xenograft. Within the limitations of this meta-analysis, the synthetic GSM can be used for socket grafting.

Clinical significance: In the wake of increasing graft materials in the market and different origin raw material sources for the preparation of graft materials, clinicians are in dilemma for selection and its use. The success of grafting depends on the selection of appropriate material with a suitable calcium/phosphate (Ca/P) ratio. The review provided available evidence for the use of SHA.

Keywords: Bone, Extraction, Healing, Implant, Regeneration, Restoration.

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Introduction

Extraction is the most common procedure performed in routine dental practice because of caries, periodontal disease, and so on. Bony defects secondary to extraction if left untreated may lead to further bone loss.[1–3] Eventually, the fixed restoration of the missing tooth may be a nightmare for the patient and difficult for the clinician to restore without the sound alveolar bone using either implant-supported restoration or fixed partial denture using natural tooth as an abutment.[4–7] The bone loss followed by extraction requires socket grafting to prevent bone resorption or enhance earlier bone formation.[8–11] Various techniques have been demonstrated, developed, and published as successful means for the preservation of the alveolar bone.[4,9,12–25] But none of the techniques claimed the superiority over the other.[5,20,26–29]

Many GSMs are available commercially for grafting and showed varying success rates. The published literature has shown the use of different origin synthetic substitute materials for grafting but none of them have advised single material as an ideal substitute.[9–11,30] Many systematic reviews performed till date concluded with the uncertainty of recommendation because of heterogeneous study material, use of different origin GSMs, etc.[5,26–29,31–44] Changing trends in the mechanism of action[7,45] fascinated researchers to develop newer materials with the advent of production technology, and the clinicians to use it for enhancement ofbone regeneration.[46–49]

In the light of changing the mechanism of action, synthetic GSMs are becoming more versatile, as these reduce the morbidity of the second surgery, time, and the skill required for harvesting autogenous graft.[45,50–53] Because of the disadvantages associated with autogenous grafting, the paradigm shift happened toward processed graft substitutes. The processed graft substitute of different origins requiresbone-banking facilities which are not economical and have a chance of disease transfer risk.[54] This led to the pursuit of synthetic materials.

To the best of our knowledge, no systematic reviews are available till date exclusively assessed the use of synthetic graft

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substitute for socket preservation. So, this systematic review was planned to delineate the suggested mechanism of action and analyze critically the existing literature to discuss the level of evidence for the use of SHAGSM for socket grafting.

Material and Methods

The literature search was performed for the studies published in the English language independently by all four authors (VSK, PSR, KR, and AAK) in the Medline database through the PubMed search engine for the past 5 years (January 2014–December 2018). The search for cross-reference articles was performed. The study involved predetermined inclusion and exclusion criteria for the search. The final lists of clinical trials were analyzed to determine the evidence and suggested the mechanism of action.

Search Strategy

The search was performed using MeSH keywords. Various Boolean operators were used and the search string was formed to focus the research question. The search words included "extraction" and "graft", "extraction" and "synthetic graft", "socket preservation", "ridge augmentation" and "extraction", "tooth extraction" and "hydroxyapatite" or "tooth extraction" and "bioceramic material" or "tooth extraction" and "post-extraction." The search included title, abstract, and keywords fields. Various filters like year of publication, human, and clinical trials were applied as appropriate to derive the desired output. To broaden the understanding of the subject, the review articles were thoroughly screened for cross-reference studies. The review articles gave insights for the future directions and the lacunae noted by previous researchers were considered to deepen the understanding of the present review.

Inclusion and Exclusion Criteria

The randomized clinical trials (RCTs) which used asynthetic graft material for socket grafting have been considered with a minimum of 10 patients assessed for the nature of bone regeneration using histomorphometry and available in the Medline database (searched through PubMed). Case reports and case series of fewer than 10 patients and non-English language publications were excluded.

The Type of Patients

The patients requiring grafting after extraction for socket preservation followed by microscopic examination for bone characterization during implant placement were considered for review.

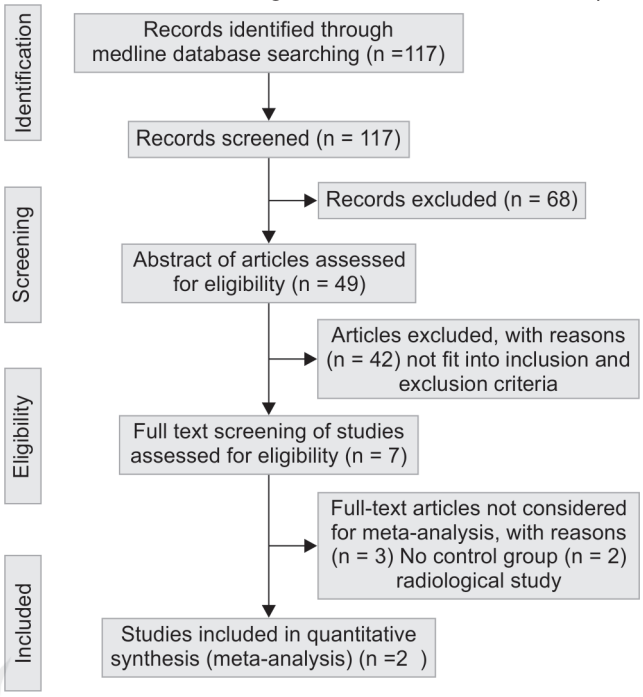
Type of Intervention and Outcome Measures

Synthetic hydroxyapatite from different origins compared with any of other graft substitutes or control (no intervention/natural healing) groups. The outcome variable considered was the bone level and the nature of bone formed irrespective of various methods opted for assessment.

Data Extraction and Analysis

The screening was performed individually by all authors (team 1—VSK and RSP; team 2—KR and AAK) along with cross-reference resources. Both groups of authors prepared the PRISMA flow diagram that was used for final screening (Flowchart 1). The bibliography was created using the Mendeley desktop app (version 1.19.3) and was used to check for duplicates. The Review Manager 5.3 (Version: 5.3.5) used to extract data from eligible studies (Tables 1 to 3). If there is any confusion in the inclusion and the exclusion of the studies, it was sorted out through discussion. The data extracted were validated by another team for accuracy and for any missing data from the studies (AJ and MAK). The corresponding authors of selected studies were consulted through e-mail for further clarification and the necessary data required for meta-analysis in case of missing observations in the published article. The studies included for meta-analysis were assessed for the quality using Maurits van Tulder et al.'s criteria for risk of bias[55] (Tables 4 and 5).

Flowchart 1: PRISMA flow diagram for the review and meta-analysis



Results

The search resulted in a total of 117 titles. After the application of inclusion and exclusion criteria, a total of 49 clinical trials were included for abstract review. The abstract review resulted in seven eligible studies for a full-length study assessment. Seven studies were found eligible for full-article review.[56–62] Only two studies (Mayer[56] and Machtei[57]) were found eligible for a quantitative analysis among seven studies (Table 1 and Flowchart 1). Whereas remaining five studies were considered for systematic review; among them, three had (Mozzati,[58] El-Chaar,[61] and Canullo[62]) no control group and two studies (Oliveira[59] and Cavdar[60]) used the radiographic analysis. So, only two studies were considered for meta-analysis[56,57] (Tables 2 and 3).

The study by Mayer et al. used the biphasic calcium sulfate (BCS) with β tri-calcium phosphate (β-TCP) and hydroxyapatite (HA)compared with the control group.[56] The study by Machtei et al. included 11 patients each in the test and the control group[57] and compared BCS/HA with control and xenograft. Whereas Mozzati et al.[58] used RegenOss [equine collagen I and magnesium (Mg)–hydroxyapatite (ratio: 40–60%)] and Canullo et al.[62] used Mg-enriched nanohydroxyapatite powder in their study. All of them used synthetic GSM and performed the histomorphometric analysis. El-Chaar et al. study assessed less than 10 patients because of dropouts and had no control group.[61] In Cavdar and Oliveira studies, only radiological assessment was performed.[59,60] In both the studies, different synthetic GSMs were used.

Table 1: Sample size and intervention of included studies in the meta-analysis

S no	*Author name*	*Study set up and region of study origin*	*Sample size—control*	*Sample size—test group/s*	*Intervention*	*Type of study*	*Inclusion/exclusion*
1	Mayer[56]	Department of Dental School, Israel	15	14	BCS with TCP and HA	RCT	Included
2	Machtei[57]	Department of Dental School, Israel	11	11	BCS/HA	RCT	Included

Table 2: Characteristics of included studies in the systematic review with reasons for not considering in meta-analysis

S no	*Author name*	*Study set up and region of study origin*	*Sample size—control and test*		*Intervention*	*Type of study*	*Reasons for not considering in meta-analysis*
1	Oliveira[59]	University Department, Brazil	26 patients divided into four groups, not mentioned the number of patients allotment to each		Deproteinized bovinebone mineral with 10% collagen (DBBM-C), poly(d,l-lactide-coglycolide) with hydroxyapatite/b-TCP scaffold (PLGA/HA), PLGA/HA/b-TCP with 2.0% simvastatin scaffold (PLGA/HA/S)	RCT	Only radiographic study
2	Cavdar[60]	University Department, Turkey	11	41	Demineralized bone matrix + collagen membrane (CM)(N =14), hydroxyapatite bone substitute (HBS) + CM (N =14), CM (N =13), or left empty (N = 11)	RCT	Only radiographic study
3	Mozzati[58]	University Department, Italy	00	32	Equine collagen I and Mg–hydroxyapatite	Single arm study no control group	No control group
4	El-Chaar[61]	Private office, New York	00	8	15% hydroxyapatite, 85% b-TCP complex	Case series, single arm study, no control	No control group
5	Luigi Canullo[62]	Private office, Italy	00	20	Mg-enriched hydroxy-apatite (MgHA)	Case series, no control	No control group

Discussion

The use of SHA graft substitutes for bone formation has changed its mechanism of action from the scaffold[63–65] to osteo induction.[66–70] The synthetic graft material, in the beginning, was used as a scaffold. The clinicians still think that it acts as a scaffold and bone defect-filling material. With evolution, synthetic GSM acted as an osteoconductive material.[30,54,71] The mechanism of osteoconduction depends on the nature of origin, particle size, porosity, resorption rate, etc.[68,69,72] The published literature showed the structure of HA is an important factor for an osteoinductive property. A few studies have shown osteoinductivity of HA in heterotrophic sites.[66,73] The nanotechnology-assisted production made the clinicians dream for an artificial bone. The dream has come to a part reality for bone reconstruction. A few case reports emphasized the bone formation using block grafts for larger bone defects reconstruction in both animal and humans.[66,73–75] The changing scenario has been well documented in the published literature.[66,73–75]

Table 3: Quantity of bone formation in test groups among all the studies eligible for systematic review

S no	*Author name*	*Total bone area in %*	*Connective tissue/marrow space in %*	*Residual graft in %*
1	Mayer[56]	47.7 ± 10.6	36.3 ± 19.4	15.99 ± 11.4
2	Machtei[57]	44.15 ± 18.8	NF* and NR**	16.51 ± 16.2
3	El-Chaar[61]	40.25	49.25	10.38
4	Luigi Canullo[62] at 4th and 12th month	31.85 ± 6.99 41.32 ± 9.37	27.33 ± 17.72 32.40 ± 9.87	40.82 ± 6.71 26.28 ± 11.49
5	Oliveira[59]	NA#	NA#	NA#
6	Cavdar[60]	NA#	NA#	NA#
7	Mozzati[58]	$NQ	$NQ	$NQ

*NF—not found in the article
**NR—no response from corresponding author
#NA—not applicable, radiological assessment only
$NQ—no quantitative analysis performed

There are many clinical reports, case series, and few original research, and RCTsthat presented the benefits of synthetic GSM.[5,29,30,54,56,57] But none of the systematic reviews nor the RCTs advised single material as an ideal graft substitute. This inconsistency in the conclusion might be due to a variety of commercially available GSMs and clinical scenarios which cannot be standardized like animal study defect models for conclusive remarks. The size and the nature of the lesion, along with patient factors, might be the reason for this inconclusiveness. So, this review addressed the focused question of SHAGSM use for socket grafting

Table 4: Internal quality assessment of included studies for meta-analysis

S no	*Characteristics examined according to Maurits van Tulder et al.*[55]*	*Mayer*[56]	*Machtei*[57]
A	Was the method of randomization adequate?	Yes	Yes
B	Was the treatment allocation concealed?	No	Yes
C	Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes
D	Was the patient blinded to the intervention?	No	Yes
E	Was the care provider blinded to the intervention?	No	Yes
F	Was the outcome assessor blinded to the intervention?	No	Yes
G	Were co-interventions avoided or similar?	No	Yes
H	Was the compliance acceptable in all groups?	Yes	Yes
I	Was the drop-out rate described and acceptable?	Yes	No
J	Was the timing of the outcome assessment in all groups similar?	Yes	No
K	Did the analysis include an intention-to-treat analysis?	Don't know	Yes

*It includes only the internal validity criteria ($n = 11$) that refer to characteristics of the study that might be related to selection bias (criteria a and b), performance bias (criteria d, e, g, and h), attrition bias (criteria i and k), and detection bias (criteria f and j)
A to K—scored as—yes/no/don't know

Table 5: Risk of bias assessment in the included studies for meta-analysis

Type bias	*Points to be considered*	*Mayer*[56]	*Machtei*[57]
Selection bias	Criteria a and b	Partly	No
Performance bias	Criteria d, e, g, and h	Significantly	No
Attrition bias	Criteria i and k	Partly	Partly
Detection bias	Criteria f and j	Partly	No

and emphasized on the histomorphometry of bone regeneration. The systematic review ascertained the objectives of the study. However, seven studies found eligible for systematic review; out of seven studies, four have discussed histomorphometry. One study exclusively described the effect of the synthetic graft substitute for bone regeneration pattern using various assays.[76]

Mayer et al. study included BCS with b-TCP and HA for grafting.[56] The study assessed a combination of two alloplastic materials in comparison to natural socket healing in 40 extraction sites of 36 patients. The final assessment included 15 extraction sites in the control group and 14 in the test group.[56] The study did not mention the tooth number, instead mentioned anterior and posterior teeth in the mandible and the maxilla. The study involved the premolar and the molar region in both controls (12/15 sockets) and graft (14/14 sockets).[56] The graft group showed minimal bone loss compared to the control group. The histological evaluation revealed the mature lamellar bone in both groups.[56] But, the study had not mentioned how many bony specimens were taken for assessment. The study showed more connective tissue in natural healing compared to the test group.[56] The study used a combination of materials but not the individual material, so it is difficult to comment on the effect of each component as both materials have different resorption kinetics. The author claims that the combination improved the quality of the material.[56]

The study of Machtei et al. included 11 patients each in the test and the control group.[57] The study compared BCS/HA with control and xenograft. The study group involved premolars, canine, and incisors evenly presented both in the mandible and the maxilla.[57] The study showed a similar percentage of bone (44.15 ± 18.8%) as that of Mayer et al.'s study (47.7 ± 10.6%) but it was less compared with the control group. The study didnot reveal the connective tissue component as mentioned in Mayer et al.'s study for comparison. Both studies consist of a similar sample size of 10 in Mayer et al.[56] and 11 in Machtei et al.[57]

Histomorphometric analysis showed more of bone in the control group (81.72 ± 4.3%) than that in the BCS/HA group (44.15 ± 18.8%) which, in turn, was greater than in the xenograft group (22.50 ± 24.72%)in Machtei et al.'s[57] study. Residual scaffold material was significantly greater in the xenograft group (40.18%) than the BCS/HA group (16.51%). The BCS/HA group (44.15%) showed bone twice that of the xenograft group (22.50%).[57]

The meta-analysis favors the use of SHAGSM over the control/natural healing group in terms of clinical and radiological outcomes. The histomorphometric analysis favored the grafting procedure compared to control (Fig. 1). Even though meta-analysis involved only two studies, the quantitative analysis favors grafting of the socket for the preservation of bone (Fig. 2). Advances in tissue-engineering techniques might soon provide novel biomaterials which are currently evaluated worldwide and will soon be introduced into the clinical

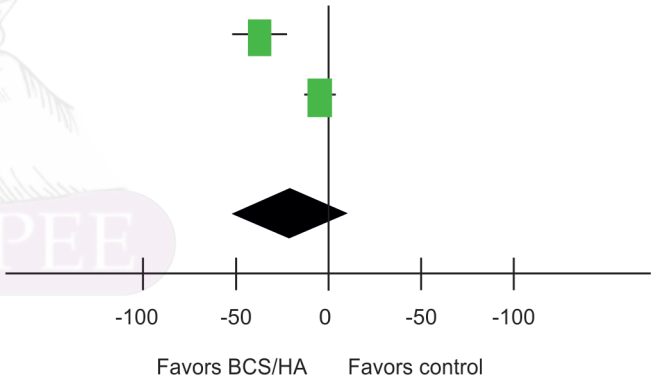


Fig. 1: Showing comparison of total bone formed among BCS/HA group and control. Comparison 1: BCS/HA vs control. Outcome changes 1.1 total bone area

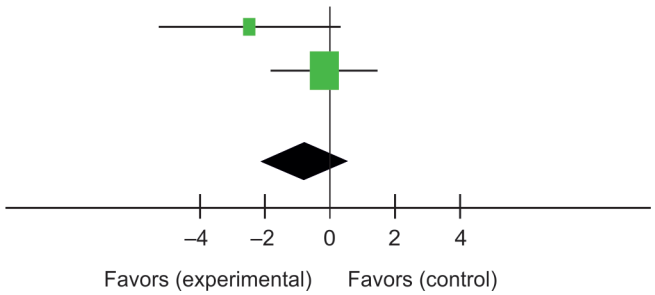


Fig. 2: Showing comparison of vertical ridge changes among BCS/HA group and control. Comparison 1: BCS/HA vs control. Outcome changes 1. 2: vertical ridge

practice.[77] The newer GSM falls into the category of biomimetic scaffolds, as they stimulate bone formation, not only chemically but also structurally through micropores which connect each other. The osteoinductivity of these materials has been shown by published literature.[66,76,78] The changing scenario and improved production technology may make the dream of artificial bone formation for grafting in the near future. The recent systematic reviews showed that the SHAGSM improved the bone regeneration along with the preservation of resorption.[33,37,38,71] Long-term follow-up data are mandatory to elucidate the presence of grafted particles which would eventually interfere with the longevity of implant function.

Conclusion

Socket preservation using synthetic HA showed beneficial results compared to control group within the limitation of available studies for meta analysis. The use of GSM prevented alveolar bone resorption. The histomorphometric evaluation showed less residual graft material associated with SHA. Ridge preservation should become the standard of care for every extraction, so that healthy bone can be retained for successful restoration. To derive more robust evidence, we may need more number of RCTs with similar methodology and the same material for grafting in an economical way.

Author Contribution

VSK and PSR drafted the protocol; VSK, PSR and KR developed a search strategy; VSK, PSR, KR and AAK searched for trials; VSK, AJ, MAK and KR obtained copies of trials; VSK, PSR, AJ, MAK, KR and AAK selected trials to include; VSK, AJ, AAK and KR extracted data from trials; VSK, AJ and AAK entered data into RevMan; RK, Specialist-Cochrane South Asia carried out the analyses; VSK, KR and AAK interpreted the analysis; VSK, PSR, AJ, MAK, KR and AAK drafted the final review.

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