Synthetic Bone Substitutes in Combination with Growth Factors for Maxillary Sinus Floor Augmentation: A Mini-review

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Authors’ contributions

This work was carried out in collaboration between all authors. Author CCN wrote the initial graft and performed the literature search. Author ID had the idea and revised the draft. Authors EC, LK, IT and NP revised the draft. Author AMV contributed to the literature search. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Growth factors have been applied in maxillary sinus augmentation with clinically successful results. The purpose of this article is to evaluate the effectiveness of growth factors in combination with various synthetic scaffolds.
Methods and Materials: A systematic review of studies examining the effects of synthetic materials in combination with growth factors were performed.

Results: Twelve (1 human and 11 animal) studies were eligible for inclusion. Due to the great heterogeneity of the studies regarding design, materials and outcomes, a meta-analysis was not performed. The majority of the studies show a reduction in healing time and enhancement of bone formation within the subantral environment. Bone Morphogenetic Protein-2 and GDF-5 were the two most common osteoinductive factors studied, showing a significant effect on new bone formation. Moreover, initial outcomes of trials with stem cells genetic transformation, that results in increased production of growth factors, are positive and justify further research.

Conclusion: The incorporation of growth factors into the synthetic scaffold may be beneficial regarding the healing process.

Keywords: Sinus augmentation; synthetic materials; PRF; growth factors.

1. INTRODUCTION

Maxillary sinus augmentation technique is a common surgical procedure for creating adequate bone volume before implant placement [1]. During the maxillary sinus floor elevation procedure, the space created between the residual maxillary ridge and the elevated Schneiderian membrane is usually filled with grafting material [2,3]. This membrane is periosteum that acts as a major carrier of bone-regeneration [4-9], whereas the various grafting materials do not provide the cellular elements necessary for osteogenesis and are only osteoconductive [10].

Osteoconductiveness has long been recognized as an important mechanism in bone regeneration. It occurs in the presence of a scaffold that allows for vascular and cellular migration, attachment, and distribution [11]. Factors that accelerate angiogenesis in the periphery of the tissues and stimulate bone healing and remodeling are useful in this respect. It is well known that a close spatial and temporal relationship exists between osteogenesis and angiogenesis and that growth factors can be used to augment both neovascularization and osteogenesis across bone defects [12-14].

The consensus of the sixth European Workshop on Periodontology [15] emphasized the research need to answer comparative questions to establish the clinical benefit of bone augmentation with respect to alternative treatments [7]. This review aims to determine whether there are advantages in using growth and other osteoinductive factors with bone substitutes for sinus floor augmentation.

2. METHODS AND MATERIALS

A systematic search strategy was used. In the initial phase of the review, a computerized literature search was performed in Medline and Embase databases. Keywords were “sinus augmentation” OR “sinus floor augmentation” OR “sinus floor elevation” OR “sinus grafting” OR “sinus lift” AND “growth factors” OR “osteinductive factors”. There was no language restriction. Additional publications were identified from the reference lists of the retrieved articles. A search with the utilization of MeSH terms (“Sinus Floor Augmentation” AND “Vascular Endothelial Growth Factors”, “Hematopoietic Cell Growth Factors”, “Endothelial Growth Factors”, “Transforming Growth Factors”, Fibroblast Growth Factors”, ”Growth Differentiation Factors”) did not provide additional publications.

2.1 Inclusion Criteria

Studies examining the effects of synthetic materials in combination with growth factors.

2.1.1 Exclusion criteria

- Reports with a sample size of less than 5 patients or 5 animals, in case of experimental studies.
- Redundant publications.
- Letters, reviews and comments.
- PRP studies (since there are a number of systematic reviews and meta-analyses indicating that PRP treatment does not seem to improve the clinical outcome of sinus lift procedures [16,17] or may lead to inferior outcomes with regard to the osseointegration of dental implants and the
height of new bone as compared with the use of pure growth factors [18].

Titles, abstracts or articles derived from this broad search were independently screened by two authors (CCN and AMV) based on the inclusion criteria. [Newcastle-Ottawa Quality Assessment Scale Case Control Studies” was utilized for the evaluation of human studies [19].

3. RESULTS

By the electronic literature search, a total of 114 titles were identified. One more study was added after the manual screen of the references lists. Twelve original articles fulfilled the inclusion criteria (1 human and 11 animal studies) as shown in supplementary Fig. 1 [Link: www.sciencedomain.org/download.php?f=Supplementary7122014BJMMR15613.pdf&aid=8863&type=a] and Table 1.

A variety of animal models were utilized for experiments with rabbits being the most common.

Synthetic materials tested were hydroxyapatite (HA), b-Tricalcium phosphate (β-TCP), calcium phosphate cement (CPC), poly-d, l-lactic-co-glycolic acid gelatine (PLPG) sponge, silk gel and others.

Osteoinductive factors that were most studied were Bone Morphogenetic Protein (BMP) and Growth and Differentiation Factor-5 (GDF-5).

Osseointegration of dental implants, implant success rate, bone-to-implant contact, histologic or radiological evaluation of new bone formation were the most common outcomes.

Only one human study was identified of relatively good quality based on NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE for case control studies (Table 1). Due to the great heterogeneity of the studies regarding design, materials and outcomes, a meta-analysis was not performed.

As it can be seen in Table 1, synthetic materials combined with growth factors lead to superior results than alloplasts alone in the majority of studies. In more details, animal studies examined this combination have shown superior results in regard to osseointegration of dental implants, implant success rate, bone-to-implant contact, histologic and radiological evaluation of new bone formation. Moreover, both human and animal studies have induced comparable histologic, histometric and radiological evidence of bone formation with autologous bone.

As shown in animal studies, bone tissue engineering is a promising method, especially with the use of bone marrow mesenchymal stem cells (bmMSC) that have been genetically modified to express growth factors (Table 1).

4. DISCUSSION

Although, hydroxyapatite, β-TCP, bioactive glass and xenografts have demonstrated almost equal efficacy for use in sinus lift procedures the question on how to achieve the most favorable bone-healing capacity, from a biological prospective, remains [32,33]. Most research studies on the bone biomaterials for sinus-lift tried therefore to improve the quality of the regenerated bone volume and to accelerate its healing for early implant placement [13,17]. Noteworthy research activity (both experimental and clinical) was identified in the area of growth factors-induced bone augmentation [15] with promising results.

4.1 Special Considerations

Although, sinus lift is one of the best in vivo human model for the testing of bone biomaterials in the maxillofacial area [13] and the combination of bone grafts and osteoinductive factors is currently being discussed as a suitable method for enhancing de novo bone formation, there are several considerations regarding favorable outcomes of this method.

First of all, implant survival may be confounded by factors other than the graft material used for sinus floor augmentation, like patients’ age or smoking habits [8]. Moreover, osseointegration of implants placed in the augmented area is a poor parameter for comparing different biomaterials, because integration is always present, regardless of the materials used [9]. Finally, one should also keep in mind that implant success as presented in animal research cannot be extrapolated as such to the clinical situation [9].
Table 1. Human and animal studies combining growth factors or PRF with various types of bone substitutes NOS: NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE

| Studies                  | Humans/Animals | Test group (TG)                                                                 | Control group (CG)     | Results                                                                 | Conclusion-commends                                                                 |
|--------------------------|----------------|--------------------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Stavropoulos A, et al.   | humans         | two groups: rhGDF-5/β-TCP with at 3-month or 4-month healing period             | autologous bone/β-TCP | 91.5 success rate in EG, 28-31.4% new bone formation in TG vs 31.8% in CG | combination of alloplast with a growth factor resulted in comparable amounts of new bone and of similar quality as those obtained with an autologous bone/β-TCP composite graft, NOS******* |
| Allegrini S Jr, et al.   | rabbits        | bovine bone powder/HA/collagen/BMP                                             | bovine bone powder/HA/collagen | BMP stimulated bone formation during the early period of healing and resulted in more newly formed bone          |
| Gruber RM, et al.        | pigs           | two groups: 400μg rhGDF-5/TCP, 800μg rhGDF-5/TCP                               | TCP                    | more volume density and bone-to-implant contact rates in the experimental groups                                     |
| Gruber RM, et al.        | pigs           | rhGDF-5/β-TCP                                                                  | autogenous/β-TCP       | more volume density and bone-to-implant contact rates in the experimental group                                     |
| Jiang XQ, et al.         | rabbits        | three groups: bmMSC/TCP, AdEGFP-bmMSC/TCP, AdBMP-2-bmMSC/TCP                  | TCP                    | more bone formation in the AdBMP-2-bmMSC/TCP group                                                                   |
| Sun XJ, et al.           | rabbits        | two groups: AdBMP-2-bmMSC/ ceramic material                                     | AdEGFP-bmMSC/ceramic material | more bone formation in AdBMP-2-bmMSC/ceramic material                                                                |

Commend: this study as well Sun's and Xia's utilize gene modified growth factor producing MSC rather than pure growth factors

growth factors-gene enhanced bone tissue engineering is a promising method
| Authors                 | Species | Treatment | Outcomes                                                                 |
|------------------------|---------|-----------|--------------------------------------------------------------------------|
| Ho SK, et al. [26], 2010 | rabbits | three groups: DBM, DBM/BMP, poloxamer gel/BMP | autogenous bone DBM/BMP resulted in more bone formation in 2 week and in equal amount of new bone with control group in 8 weeks BMP-containing bioimplants demonstrated promise as alternatives to autogenous bone grafts for sinus-augmentation procedures. These bioimplants had more rapid initial bone production than all other materials |
| Gutwald R, et al. [27], 2010 | sheeps | rhBMP-2/PLPG sponge | autograft bone-to-implant contact (BIC) and bone density (BD) were significantly higher in the test group if the implants were placed at the time of the sinus lift growth factors may be proved useful in early implant placement |
| Kim BJ, et al. [28], 2011 | rabbits | two groups: rhBMP-2/TCP, PRF/TCP | TCP more bone formation in TGs and especially in PRF/TCP group |
| Xia L, et al. [29], 2011 | rabbits | four groups: BMP-2/CPC, bmMSC/CPC, bmMSC/BMP-2/CPC | CPC more bone formation in experimental groups especially those with bmMSC rhBMP-2/CPC possessed excellent osteoinductive ability, while combining with bMSCs could further promote new bone formation and maturation in maxillary sinus elevation |
| Zhang W, et al. [30], 2011 | rabbits | three groups: silk gel/BMP-2, silk gel/VEGF, silk gel/VEGF/BMP-2 | silk gel more bone formation in silk gel/VEGF/BMP-2 group |
| Xia L, et al. [31], 2011 | rabbits | four groups: BMP-2 and Nell-1 modified bmMSC and TCP, BMP-2 modified bmMSC and TCP, Nell-1 modified bmMSC and TCP, EGFP modified bmMSC and TCP | Nell-1 and BMP-2 gene-transduced autologous bMSCs/β-TCP complex had the largest bone area and most mature bone structure among the groups nell+1 and BMP-2 have a synergistic effect |
Probably, one of the most noticeable facts in this review’s Table is the great heterogeneity in methods and outcomes of the studies. Various defects, surgical procedures, synthetic materials, growth factors and their concentration, as well as animal species were used. One or two stage techniques and lateral or crestal approaches have different indications [34]. The various ceramics or other synthetic materials have distinct absorption rates and histomorphometric results.

Moreover, different growth factors elicit diverse molecular signaling pathways in cells that participate in bone regeneration and animal models are not necessarily identical regarding bone trauma responses. In addition, bone formation, volume density, implant survival, and bone-to-implant contact are the most common outcomes reported in the various studies and these are not necessarily inter-related significantly. Despite this great diversity of the studies regarding their methods and outcomes, valuable conclusions can still be elicited.

4.2 Osteoinductive Factors

BMP-2 and GDF-5 were the two most common osteoinductive factors studied, showing a significant effect on new bone formation [23,29]. Both belong to the TGF-β superfamily of proteins acting as potent regulators during embryogenesis and bone and cartilage formation and repair in adults. Growth differentiation factor 5 is a member of the bone morphogenetic protein (BMP) family. BMPs have attracted a lot of publicity lately, especially in the developing field of regenerative medicine since BMP-functionalised coatings have proven to be a simple and effective strategy for osteoinductive functionalisation of orthopaedic implants [35]. These glycoproteins act as a disulfide-linked homo- or heterodimers, being potent regulators of bone and cartilage formation and repair, cell proliferation during and bone homeostasis [36].

4.3 Future Directions

Sinus augmentation is considered to be a very secure procedure, and the consensus is that most bone materials can give good results in terms of bone healing and implant survival [13]. Furthermore, surgical intervention itself can liberate growth factors and autogenous bone morphogenetic proteins responsible for wound healing and bone regeneration [37-39]. However, there are clinical and experimental indications that the incorporation of additional growth factors into the sinus graft may reduce the healing time and enhance bone formation within the subantral environment.

Finally, tissue engineering with the incorporation of mesenchymal stem cells may be the most promising technology [40]. In this new cell-based tissue engineering approach, stem cells are combined with an osteoconductive scaffold and growth factors and applied immediately to the patient [41,42]. As it can be seen in Table 1, even more advanced techniques have been developed lately concerning stem cells’ genetic transformation in order to produce increased concentrations of growth factors and experimental data have yielded positive results.

5. CONCLUSION

The overarching aim of this review was to determine whether there are advantages in using growth and other osteoinductive factors with bone substitutes for sinus floor augmentation. Despite the great heterogeneity of the related studies in design, materials and outcomes, incorporation of growth factors into the synthetic scaffold appears to have positive results regarding healing time, bone formation and avoidance of autologous grafts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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