Comparative analysis of two mixtures of biomaterials for maxillary sinus augmentation: clinical and histological study.

Tamer Ahmed Nasr [1] , Ayman Gouda [1] , Eman Helal [2] , Rehab Ahmed Soliman [3]

associate professor, Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Misr International University, Cairo, Egypt [1] , associate professor, Fixed and removable Prosthodontics Department, National research Centre, Cairo, Egypt. [2] , lecturer, Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Misr International University, Cairo, Egypt.[3]

Original Article

ABSTRACT

Aim: the aim of this study to assess and compare changes in gained bone height following sinus augmentation by two different biomaterials, Hyaluronic acid versus simvastatin as osteoconductive materials.

Material and Methods: a randomly allocated twenty patients with edentulous posterior maxilla into 2 groups. All sinuses were augmented by open lateral window using one of the combinations of simvastatin and β-TCP as group A or hyaluronic acid mixed with xenograft as group B. The amount of newly formed bone was evaluated by radiographic analysis. This assessment was occurred at period intervals one week and six months postoperatively. The histological evaluation was done to the bone collected by trans-crestal bone biopsies taken after six months during the second-stage surgery for implant placement. All collected data were tabulated as mean and standard deviation (SD) values. The comparisons between the groups was done by Fisher's Exact test. The significance level was set at $P \leq 0.05$.

Results: radiographic and descriptive histological analysis showed superior results in favor of sinus augmented with TCP-Simvastatin complex in terms of amount of bone gain and histological bone maturation.

Conclusion: it was clinically valuable to use the hyaluronic acid and Simvastatin as safe bone grafting materials in cases of antral augmentation with the superiority in bone gain and maturation in favor of TCP- Simvastatin complex.

Key Words: Sinus, augmentation, grafting material, biomaterial, simvastatin, Hyaluronic acid, dental implant.

Received: 4 March 2024, **Accepted:** 10 March 2024.

Corresponding Author: Tamer Ahmed Nasr ,Associate Professor at Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Misr International University, Cairo, Egypt , **Mobile:** 01111979442 , **E-mail:** tamer.nasr@miuegypt.edu.eg

ISSN: 2090-097X, April 2024, Vol. 15, No. 2

INTRODUCTION:

Restoring function with longevity of service while planning prosthetic restoration in the posterior maxilla is considered one of the major challenging areas in oral implantology. Several anatomic limitations could be faced during rehabilitation of posterior maxilla such as deficient alveolar bone height, the shape of the palate and pneumatized maxillary sinus. In addition, the quality and quantity of remaining maxillary bone in the posterior area is deficient by nature. Furthermore, the thinner cortices of compact bone with minimal strength also affect the implant placement at this region. [1]

Pneumatization of these sinuses add an additional confront by decreasing the vertical and horizontal bony components compromising the implant positioning. Therefore, several techniques were introduced to overcome the lack of alveolar bone height. Among these procedures is sinus lifting either via lateral or crestal approaches, which gives answers to those limitations and helps in restoring the masticatory function. [2]

Applying grafting material to augment sinus lifting necessitate certain properties that ideally needed to achieve the needed results such as osteogenicity, osteoinductivity, osteoconductivity, biocompatiblity and volumetrically stable to provide an enough healthy bone to insert implant subsequently. [3]

Variety of materials have been used to solve this problem. Autogenous bone graft is considered the gold standard because of its high biocompatibility, osteogenic property osteoinductive, osteoconductive and good clinical outcomes. [4] But, the harvesting of autogenous bone carries more risks of morbidity and discomfort. [5] Deproteinized bovine bone was frequently used for sinus lifting. This type of grafts has physical properties very similar to those of the human bone. This aids in inducing physiological bone remodeling with significant bone gain. [6] The increase in biocompatibility of this material is because of its preparation, which eliminate the organic components and preserving the inorganic followed by sterilization by heat and irradiation. [7] As a patient centered outcome

Personal non-commercial use only. OMX copyright © 2021. All rights reserved *DOI:10.21608/OMX.2024.274423.1229*

by reducing the time needed the process of bone healing that can be achieved by rapid degradation of the bone substitute. [8]

Based on this concept, the addition of different biological materials, to speed up the healing process was utilized. [9] The main purpose is to ensure adequate protein concentrations at the defect site helping osteocytes to migrate, proliferate and differentiate. [10] Through this idea, composite biosynthetic grafts consisting of an osteoconductive carrier combining with osteogenic cells and/or growth factors became a target in choosing a better bone substitute. [11] Composite synthetic grafts offer an alternative for the shortcomings found with autografts and can hypothetically gain the three essential principals of bone-regeneration which can lead to more effective combination. [11]

Simvastatin is a synthetically derived substance after fermentation of Aspergillus terreus. It is the main component of lipid-lowering medication which used orally in patients suffering from hypercholesterolemia and hyperlipidemia. it has numerous benefits. One of them is its anabolic effect on bone and prevention of bone resorption. Furthermore, it has anti-inflammatory effects and can promote osteoblastic differentiation by increasing the expression of vascular endothelial growth factor (VEGF) in the osteoblasts. [12] Numerous studies approved its promising outcome on rats and dogs in inducing new bone formation in regenerative procedures. [13- 17]

On the other hand, hyaluronic acid, which is a non-sulfated, linear polysaccharide composed of repeating disaccharide units of glucuronic Acid-N-acetyl D-glucosamine, showed the same results. It is the main components of the extra cellular tissue and fluid. This natural polymer has excellent biological properties. [18] Hyaluronic acid considered as a one of the major glycosaminoglycans that plays an important role in increasing the differentiation and migration of the mesenchymal cells into osteoblasts which enhance the bone formation. [19]

Dogan et al in 2017, [20] confirmed the premise of sinus augmentation by adding hyaluronic acid to collagenated heterologous bone graft. They proved the enhancement of bone formation when comparing this mixture with the same type of graft alone in the initial healing phase. They worked on a thirteen healthy patients who required a bilateral two-staged maxillary sinus lifting. On comparing the test and control groups, there was a significant higher percentage of newly formed bone in the study group after a healing period of four months. [20] Furthermore, Histological analysis was considered a gold standard to confirm the results of bone formation in most of published human sinus augmentation studies. [38] The purpose of Histologic evaluation is to understand the interactions that occur between the bone and the graft. Utilizing the Cone beam computerized tomography and the clinical evaluation in comparing the success of bone grafting following sinus evaluation proved successful in recent studies. [39,40]

So, this study was designed to assess and com¬pare the clinical, histological and radiographical variations of bone graft mixed with hyaluronic versus Simvastatin when combined with beta trical¬cium phosphate as osteoconductive and osteoinductive mate¬rials in maxillary sinus augmentation.

MATERIALS AND METHODS

Twenty patients with a free end saddle posterior maxilla or partially edentulous condition participated in a randomized control trial. Two groups of patients were randomly assigned to each other. Both groups had the maxillary sinus open lifting operation and augmentation with either combination of simvastatin1 and β-TCP2 (group A or hyaluronic acid gel3 mixed with xenograft4 (group B). Throughout the study, the study was double blinded which is means the participants and outcome assessors were kept blind. ***All patients were selected using the following criteria:*** All cases had insufficient alveolar bone height in the edentulous posterior maxilla (available bone ≤ 5mm) which were seeking implant placement. All patients must be free from any antral pathosis and/or systemic diseases that may interfere with the normal bone healing which could affect the prognosis.

All patients were clinically examined and enrolled in the study according to the inclusion criteria. Preoperative ***Cone beam computer tomography (CBCT)*** was performed for all selected patients to measure the amount of the residual bone height available in the edentulous posterior maxilla from the crest of the ridge to the floor of the sinus. Each patient in both groups received a fabricated study model and radiographic stent. During the second stage of surgery, the radiographic stent was converted into a surgical stent for implant insertion.

Open sinus lifting procedure (for both groups)

Un¬der ***local anaesthesia*** [5], the surgical procedures were performed using infraorbital and posterior superior alveolar nerve block with palatal infiltration. Full thickness mucoperiosteal flap was elevated to expose the lateral wall of the maxillary sinus. The entrance to the maxil-lary sinus was through the lateral window technique. A bone window was outlined using a no. 8 diamond bur mounted on straight hand piece with copious irrigation (sterile saline solution) with cautious taken to not penetrate the sinus membrane. The process of bone removal was done through the cortical bone to reach the membrane without perforation. Complete osteotomy along the boundary of the osseous window until the Schneiderian mem¬brane. The Schneiderian membrane was carefully elevated till the desired height. Fig(1)

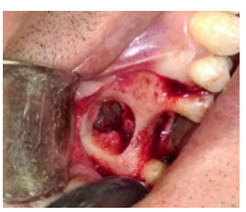

Figure (1): clinical image during open sinus lateral window

Preparation of β.TCP- Simvastatin complex: (group A)
• Simvastatin[1] powder was liquefied in 97% ethanol. Then the solution was added to the β-TCP [2] powder using a dropper. Each gram of β-TCP[2] received a total of 7.21 mg of Simvastatin[1]. The entire procedure was carried out in a completely sterile condition using a laminar flow hood. The Simvastatin[1]- β-TCP[2] complex was used to obturate all the new available volume after being hydrated with saline. Then the window was covered using a resorbable collagen membrane. Finally, the flap was re-position and sutured using 4/0 resorbable vicryl suture.

hyaluronic acid gel mixed with xenograft (group B):
Xenograft [4] was mixed with hyaluronic acid [3] followed by the protocol of graft packed and compacted inside the antrum until the new available volume created was filled. The lateral window was filled with the hyaluronic acid gel as a barrier before flap closure. Fig (2)

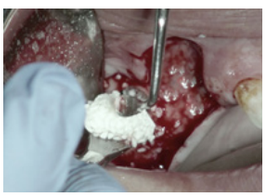

Figure (2): apllication of the HA xenograft mixture in side the lifted sinus.

Postoperative care:
suture removal and wound inspection were performed 7 days following the surgery. Postoperative instructions and medication including Hibiotic 1g 6 (2 tablets per day for 7 days), Brufen 600mg [7] (2 tablets per day- 7 days) and Otrivin nasal drop [8] (2–3 drops every 12 h for 7 days) were prescribed for the patients. All Patients were exam¬ined clinically every week for the first month, then at 3, 6 months.
Radiographic evaluation postoperatively: fig (4,5)
Postoperative CBCT radiographs were used to evaluate each patient 1 week and 6 months to assess the bone graft and prior to the second stage surgery. all radiographs were done using the same machine and same exposure parameters. Image reconstruction was performed using special software [9]. Radiographic evaluation was used to assess the bone quantity gained after augmentation. All measures were recorded in 1 week and 6 months postoperatively. Those measures were performed at the highest point of new sinus floor level using a millimeter scale present in the software.

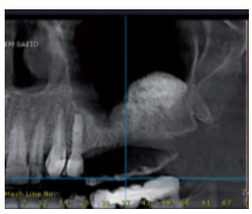

Figure (4): panaromic view after 6 months (group A)

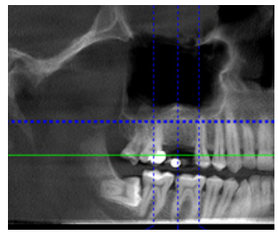

Figure (5): panaromic view after 6 months (group B)

Second stage surgery:
After 6-months of surgery, the preparation for implant placement was planned. first local analgesia was administered followed by crestal incision and a full thickness mucoperiosteal flap elevation. At second-stage surgery, core biopsies were collected fig (3), guided by the transparent acrylic stent which was used in the first stage surgery before implant installment. By 3mm diameter trephine bur, the collection of the samples was done through transcortical bone from the previous grafted sinuses. The drilling depth was calculated first from the CBCT to guarantee the involvement of both newly formed bone and native bone inside the core biopsy.

Figure (3): clinical image showing specimen collection by triphine

Specimen processing:
The specimens were immediately fixed in 10% buffered formalin for 1 week, then decalcified and processed according to a standardized protocol in 10% diluted formic acid then subsequently dehydrated in a series of increasing alcohol concentrations followed by xylol. Then all samples were embedded longitudinally into paraffin blocks and oriented in a standardized way for labelling. Sections of 4µm thicknesses were cut in a longitudinal plane using microtomes (leica, watzlar, Germany). Sections were stained using Masson Trichrome stain for histological analysis. Fig (6,7)

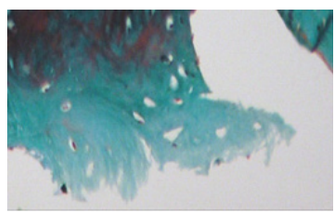

Figure (6): histomorphometric image after specimen collection from group B

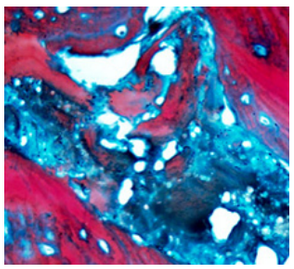

Figure (7); histomorphometric analyssi of a specimen collected from group

The implant was tightened using torque wrench. So the intra-osseous portion of implant was completely inserted sub-bony level. Finally, the flap was re-approximated into position and sutured using 3/0 vicryl suture. Fig (8)

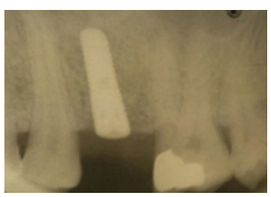

Figure (8): preapical x-ray after 3 months after implant installment.

Post-operative care

After three months of osseo-integration, the abutments were attached to the fixture and prosthetic rehabilitation of the teeth was performed.

Statistical Analysis

Numerical data was analyzed for normality by inspecting the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). All data showed normal (parametric) distribution. Data were presented as mean and standard deviation (SD) values. Student's t-test was used to compare between the two groups. Repeated measures ANOVA test was used to compare bone height measurements in the two groups as well as to study the changes by time within each group. Bonferroni's post-hoc test was used for pair-wise comparisons when ANOVA test is significant. Qualitative data were offered as frequencies and percentages. Fisher's Exact test was used for comparisons between the groups. The significance level was set at $P \leq 0.05$. Statistical analysis was accomplished with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Twenty patients were enrolled in the current study, ten patients per each group. Clinical results revealed complete healing in all cases without any complications of the surgical site with rapid resolution of postoperative inflammation.

Demographic data:

There was no statistically significant difference between mean age values in the two groups. There was also no statistically significant difference between gender distributions in the two groups.

Table 1 : Mean, standard deviation (SD), frequencies (n), percentages and results of Student's t-test and Fisher's Exact tests for comparisons of demographic data in the two groups .

	Group I (n = 10)	Group II (n = 10)	P-value
Age (Years)			
Mean (SD)	40.3 (5.7)	41.9 (5.3)	0.525
Gender [n (%)]			
Male	5 (50)	7 (70)	0.650
Female	5 (50)	3 (30)	

*: Significant at $P \leq 0.05$

Percentage of mature bone:

Group I showed statistically significantly higher mean percentage of mature bond than Group II (P-value = 0.001, Effect size = 1.77).

Table 2 : Mean, standard deviation (SD) values and results of Student's t-test for comparison between percentage of mature bone in the two groups

Group I (n = 10)		Group II (n = 10)		P-value	Effect size (d)
Mean	**SD**	**Mean**	**SD**		
37.4	4.2	28.8	5.5	0.001*	1.77

*: Significant at $P \leq 0.05$

Bone height measurement (mm)

There was no statistically significant difference between mean bone height measurements in the two groups preoperatively (P-value = 0.407, Effect size = 0.039).

Post-operatively; Group I exhibited statistically significantly higher mean bone height measurement than Group II (P-value <0.001, Effect size = 0.631). According to the changes by time within each group, there was a statistically significant increase in mean bone height after 6 months in both groups (P-value <0.001, Effect size = 0.939) and (P-value <0.001, Effect size = 0.852), respectively.

Comparison between amounts of bone gain in the two groups revealed that Group I showed statistically significantly higher mean amount of bone gain than Group II (P-value <0.001, Effect size = 2.054).

Table: Descriptive statistics and results of repeated measures ANOVA test for comparison between bone height measurements (mm) in the two groups, the changes by time within each group and Student's t-test for comparison between amounts of bone gain in the two groups

Time	Group I (n = 10)		Group II (n = 10)		P-value	Effect size (Partial Eta Squared)
	Mean	SD	Mean	SD		
Pre-operative	3.83	0.59	4.11	0.86	0.407	0.039
6 months	12.95	1.55	9.68	1.04	<0.001*	0.631
Amount of bone gain	9.13	1.81	5.57	1.65	<0.001*	2.054
P-value	<0.001*		<0.001*			
Effect size (Partial Eta Squared)	0.939		0.852			

*: Significant at $P \leq 0.05$

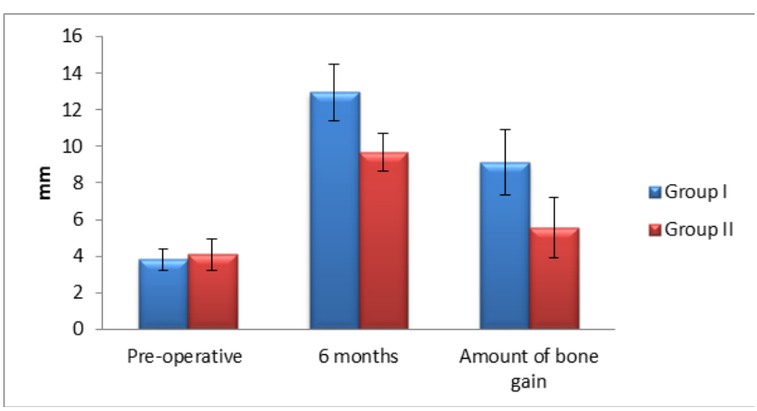

Figure: Bar chart representing mean and standard deviation values for bone height measurements and amounts of bone gain in the two groups.

By histological analysis of the collected sections, the mature bone tissue and osteoid tissue were evaluated in relation to the total surface area. Masson Trichrome stained sections showed, after a healing period of 6 months, an irregular newly formed bone trabeculae showing mineralized areas stained red, while the unmineralized areas are stained blue. (MT x 200 magnification, scale bar:100 mm)

DISCUSSION:

Insufficient residual alveolar bone height is a common limitation for placement of dental implants in posterior maxilla. However, this problem is exaggerated when a coincidence of both resorbed alveolar ridge and maxillary sinus pneumatization occurs. Therefore, Maxillary sinus lifting and augmentation utilizing various grafting materials is considered one of the effective solutions that allow restoring the lost bony structure in the posterior maxilla that ensure a long-term success at implant sites. [21-24]

In the current study, the open sinus procedure was per¬formed during sinus elevation augmentation sur¬gery. We utilized the lateral window technique, which was proved in previous studies, to be the suitable technique in cases of massive loss of alveolar bone in posterior maxilla. [25,26] This technique allows the placement of a sufficient amount of the graft material into the sinus with direct access to the sinus floor while preserving the residual alveolar ridge. The aim of this study was to evaluate the quality of bone formation after augmentation of the maxillary sinus with two different mixtures of biomaterials compared to each other's before implant installment question through the assessment of their effect clinically and radiographically on remodeling and transformation into new bone.

Hyaluronic acid has been reported to play critical roles in a wide variety of biological events such as wound healing, chondrogenesis, osteogenesis and immune response. Sasaki & Watanabe in 1995, [13] showed that Hyaluronic acid can accelerate new bone formation through mesenchymal cell differentiation, in a bone marrow ablation model in rat femurs. This result proved that Hyaluronic acid possesses biochemical and physical properties suitable to play an important role in the early events of osteogenesis. [33]

Another important study that done by Schwartz et al 2007 which was performed on the effect of Hyaluronic acid clinically in maxillary sinus augmentation. [34] They studied thirty-two sinus lift procedures in 26 patients. Ridge heights were visualized by computed tomography (CT) and measured by morphometric analysis at 8 months post-surgery. When implants were placed, the amount of new bone formed within the bone cores was different depending on the graft material used. They proved that Hyaluronic acid, alone or in combination with other materials, can be used successfully for sinus floor elevation. [34]

Mundy et al [35] in 1999 was the first one who discovered the direct effect of statins on bone formation. According to this study, the use of statins either locally or systemically, can stimulate bone formation and regeneration. The idea of using Simvastatin with β-TCP in this study was first used by Rojbani et al [36] who suggested that combining an osteoconductive bone graft as α-TCP, β-TCP and hydroxyapatite with simvastatin may activates bone regeneration, affects the degradability of the graft material and improves bone formation in calvarial defects of rats. Another supportive study was done by Gouda et al [37] who found that in the simvastatin - β-TCP complex group, the amount of bone was significantly higher compared to the β-TCP group , this study also proved the safety of using Simvastatin in sinus lifting in humans.

In the current study, sinus lifting was grafted primarily then implant placement was performed 6 months later. This study was designed to evaluate the bone height by using CBCT scans. All sinuses enrolled in this study was augmented by either Simvastatin combined with β-TCP as group A or hyaluronic acid gel mixed with xenograft as group B. By evaluation of both groups after six months, there was a statistically significant increase in mean bone height when compared to pre-operative measurements. On the other hand, by comparing the radiographic results of the amounts of bone gain between the two groups after 6 months, there was a statistically significantly higher mean in Group A than Group B.

The Messon's Trichrome stain was used to histological evaluation. This type of stain is specific for showing the osteoid tissue (immature) and mature bone tissue. By histological evaluation of sections stained by MT, we found a significant increase in the percentage of matured bone tissue in group A more than group B.Even though large variety of grafting materials have been tested for maxillary sinus floor augmentation in both clinical and experimental studies [27-32], this current study was the first that compare Hyaluronic acid versus Simvastatin as a grafting material for maxillary sinus floor augmentation. So, we cannot link our finding with other studies. Our results recommended that Simvastatin is clinically beneficial and safe alternatives bone grafting materials in cases of maxillary sinus augmentation. Further clinical studies are needed to evaluate the histological and radiological outcomes of Hyaluronic acid and simvastatin, determine the optimal therapeutic doses or delivery forms for sinus augmentation and the effectiveness for humans for bone regeneration.

CONFLICT OF INTEREST

This clinical study was self-funded by the authors, with no conflict of interest.

REFERENCES

1. Steigmann M, Garg AK: A Comparative Study of Bilateral Sinus Lifts Performed with Platelet-Rich Plasma Alone Versus Alloplastic Graft Material Reconstituted with Blood. Implant Dent. 2005 Sep; 14(3): 261-6.

2. Mazor Z, Horowitz RA, Del Corso M, Prasad HS, Rohrer MD, Dohan Ehrenfest DM: Sinus Floor Augmentation with Simultaneous Implant Placement Using Choukroun's Platelet-Rich Fibrin as the Sole Grafting Material: A Radiologic and Histologic Study at 6 Months. J Periodontol. 2009; 80:2056-64.

3. Pjetursson BE, Tan WC, Zwahlen M, Lang NP: A systematic review of the success of sinus floor elevation and survival of implants inserted in combination with sinus floor elevation. Part I: Lateral approach. J Clin Periodontol. 2008; 35 (Suppl. 8): 216-240.

4. Tadjoedin ES, de Lange GL, Lyaruu DM, Kuiper L, Burger EH: High concentration of bioactive glass material (BioGran) vs. autogenous bone for sinus floor elevation. Clin Oral Implants Res. 2002 Aug; 13(4):428-36.

5. Kalk WWI, Raghoebar GM, Jansma J, Boering G: Morbidity from iliac crest bone harvesting. J Oral Maxillofac Surg. 1996 Dec; 54(12):1424-9.

6. Degidi M, Artese L, Rubini C. Microvessel density in sinus augmentation procedure using anorganic bovine bone and autologous bone: 3 months results. Implant Dent. 2007;16:317-325.

7. Tatum H Jr: Maxillary and sinus implant reconstructions. Dent Clin North Am. 1986; 30(2):207-29.

8. Sanchez AR, Sheridan PJ, Kupp LI: Is platelet-rich plasma the perfect enhancement factor? A current review. Int J Oral Maxillofac Implants. 2003 Jan-Feb; 18(1):93-103.

9. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, McAllister BS,Murphy KS, McClain PK, Nevins ML, Paquette DW, Han TJ, Reddy MS, Lavin PT, Genco RJ, Lynch SE: Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. J Periodontol. 2005; 76:2205–2215.

10. Haidar Z, Hamdy R, Tabrizian M. Delivery of recombinant bone morphogenetic proteins for bone regeneration and repair. Part A: Current challenges in BMP delivery. Biotechnology Letters 2009; 31:1817–24.

11. Handschel J, Naujoks C, Langenbach F. Comparison of ectopic bone formation of embryonic stem cells and cord blood stem cells in vivo. Tissue Eng Part A. 2010;

12. Maeda T, Kawane T, Horiuchi N. Statins augment vascu¬lar endothelial growth factor expression in osteoblastic cells via inhibition of protein prenylation. Endocrinology. 2003;144: 681-92.

13. Nyan M, Sato D, Kihara H, Machida T, Ohya K, Kasugai S. Effects of the combination with alpha-tricalcium phos¬phate and simvastatin on bone regeneration. Clin Oral Im¬plants Res. 2009; 20: 280-287.

14.Maciel-Oliveira N, Bradaschia-Correa V, Arana-Chavez VE. Early alveolar bone regeneration in rats after topical administration of simvastatin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011; 112:170-179.

15.Rutledge J, Schieber MD, Chamberlain JM, Byarlay M, Killeen AC, Giannini PJ, et al. Simvastatin application to augment facial jaw bone in a dog model: pilot study. J Periodontol 2011;82:597

16. Pradeep AR, Rao NS, Bajaj P, Kumari M. Efficacy of subgingivally delivered simvastatin in the treatment of patients with type 2 diabetes and chronic periodontitis: a randomized double-masked controlled clinical trial. J Peri¬odontol. 2013; 84:24-31.

17. Yaghobee S, Panjnoush M, Chokami Rafiei S, Amini Shakib P, Mahmoodi S, Rasouli-Ghahroudi AAR, Pour¬safar F. Effect of Simvastatin on Bone Regeneration: A Histologic and Histomorphometric Analysis. J Oral Max¬illofac Surg. 2020;78:927-934.

18. Manferdini C, Guarino V, Zini N, Raucci MG, Ferrari A, Grassi F, Gabusi E, Squarzoni S, Facchini A, Ambrosio L, Lisignoli G: Mineralization behavior with mesenchymal stromal cells in a biomimetic hyaluronic acid-based scaffold. Biomaterials. 2010; 31:3986–3996.

19. Price RD, Berry MG, Navsaria HA: Hyaluronic acid: the scientific and clinical evidence. J Plast Reconstr Aesth Surg 2007; 60: 1110-1119.

20. Dogan E, Dursun E., Tosun E., Bilgic E., Akman A. C., Orhan K., Celik H. H., Korkusuz P., Caglayan F.: Evaluation of hyaluronic matrix efficacy in sinus augmentation: a randomized-controlled histomorphometric and micro–computed tomography analysis. Int. J. Oral Maxillofac. Surg. 2017; 931-937.

21. Lundgren S, Cricchio G, Hallman M, Jungner M, Rasmus¬son L, Sennerby L. Sinus floor elevation procedures to en¬able implant placement and integration: techniques, bio¬logical aspects and clinical outcomes. Periodontol 2000. 2017; 73:103-120.

22. Fermergård R, Astrand P. Osteotome sinus floor elevation and simultaneous placement of implants--a 1-year ret¬rospective study with Astra Tech implants. Clin Implant Dent Relat Res. 2008; 10: 62-69.

23. Nedir R, Nurdin N, Khoury P, et al. Osteotome sinus floor elevation with and without grafting material in the severely atrophic maxilla. A 1-year prospective random¬ized controlled study. Clin Oral Implants Res. 2013; 24: 1257-1264.

24. Al-Moraissi EA, Altairi NH, Abotaleb B, Al-Iryani G, Halboub E, Alakhali MS. What Is the Most Effective Re¬habilitation Method for Posterior Maxillas With 4 to 8 mm of Residual Alveolar Bone Height Below the Maxillary Sinus With Implant-Supported Prostheses? A Frequentist Network Meta-Analysis. J Oral Maxillofac Surg. 2019;77: 70.e1-70.e33.

25. Juzikis E, Gaubys A, Rusilas H. Uses of maxillary sinus lateral wall bony window in an open window sinus lift pro¬cedure: literature review. Stomatologija.
2018; 20:14-21.

26. Tawil G, Tawil P, Khairallah A. Sinus Floor Elevation Us¬ing the Lateral Approach and Bone Window Reposition¬ingI: Clinical and Radiographic Results in 102 Consecu¬tively Treated Patients Followed from 1 to 5 Years. Int J Oral Maxillofac Implants. 2016; 31: 827-834.

27.Raghoebar GM, Onclin P, Boven GC, Vissink A, Meijer HJA. Long-term effectiveness of maxillary sinus floor augmentation: A systematic review and meta-analysis. J Clin Periodontol. 2019 Jun;46 Suppl 21:307-318

28.Aghaloo TL, Misch C, Lin GH, Iacono VJ, Wang HL. Bone Augmentation of the Edentulous Maxilla for Implant Placement: A Systematic Review. Int J Oral Maxillofac Implants. 2016; 31:19-30.

29.Starch-Jensen T, Aludden H, Hallman M, Dahlin C, Chris¬tensen AE, Mordenfeld A. A systematic review and meta-analysis of long-term studies (five or more years) assess¬ing maxillary sinus floor augmentation. Int J Oral Maxil¬lofac Surg. 2018; 47: 103-116.

30. Ting M, Rice JG, Braid SM, Lee CYS, Suzuki JB. Max¬illary Sinus Augmentation for Dental Implant Rehabilita¬tion of the Edentulous Ridge: A Comprehensive Overview of Systematic Reviews. Implant Dent. 2017; 26:438-64.

31. Netto HD, Miranda Chaves MD, Aatrstrup B, Guerra R, Olate S. Bone Formation in Maxillary Sinus Lift Using Autogenous Bone Graft at 2 and 6 Months. Int J Morphol. 2016;34: 1069-1075.

32.Ocak H, Kutuk N, Demetoglu U, Balcıoglu E, Ozdamar S, Alkan A. Comparison of Bovine Bone-Autogenic Bone Mixture Versus Platelet-Rich Fibrin for Maxillary Sinus Grafting: Histologic and Histomorphologic Study. J Oral Implantol. 2017; 43:194-201.

33. Sasaki T, Watanabe C: Stimulation of osteoinduction in bone wound healing by high-molecular hyaluronic acid. Bone. 1995; vol 16: 9–15.

34. Schwartz Z, Goldstein M, Raviv E, Hirsch A, Ranly DM, Boyan BD: Clinical evaluation of demineralized bone allograft in a hyaluronic acid carrier for sinus lift augmentation in humans: a computed tomography and histomorphometric study. Clin. Oral Impl. Res. 2007; 18:204–211.

35. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G. Stimulation of bone formation in vitro and in rodents by statins. Science1999; 286:1946–1949..

36.Rojbani H, Nyan M, Ohya K, Kasugai S. Evaluation of the osteoconductivity of α-tricalcium phosphate, β-tricalcium phosphate, and hydroxyapatite combined with or without simvastatin in rat calvarial defect. J Biomed Mater Res A. 2011; 98: 488-498.

37. Gouda A, Helal E, Ali S, Bakry S, Yassin S. Maxillary si¬nus lift using osteoinductive simvastatin combined with β-TCP versus β-TCP- a comparative pilot study to evalu¬ate simvastatin enhanced and accelerated bone formation. Acta Odontol Scand. 2018; 76: 39-47.

38. Noumbissi SS, Lazada JL, Boyne PJ: Clinical, Histologic, And Histomorphometric evaluation of mineralized solvent-de-hydrated bone allograft (Puros) in human maxillary sinus grafts. J Oral Implantol 2005; 31:171-178.

39. Guarnieri R, Belleggia F, Ippoliti S, DeVilliers P, Stefanelli LV, Di Carlo S, Pompa G: Clinical, Radiographic, and Histologic Evaluation of Maxillary Sinus Lift Procedure Using a Highly Purified Xenogenic Graft (Laddec®).J Oral Maxillofac Res. 2016;7(1):e3.

40. Gholami GA, Najafi B, Mashhadiabbas F, Goetz W, Najafi S: 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. 2012; 23, 1198–1204.