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RESEARCH ARTICLE

Histomorphometric Comparison of Resorbable Collagen Sponges with Xenogen Grafts in Terms of New Bone Formation in Sinus Floor Elevations: An Experimental Study in the Rabbits

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ABSTRACT

Due to a number of complicated factors, implanting the edentulous posterior maxilla is often a difficult procedure. It is stated that maxillary sinus floor elevation is a predictable treatment option to obtain sufficient bone height and volume for implant placement. In this study, it was aimed to compare the resorbable collagen sponges which are thought to be used in maxillary sinus floor elevation with xenogen graft particles, histopathologically and histomorphometrically in terms of new bone formation. For this purpose; In 16 New Zealand white rabbits, bilateral sinus floor elevation was performed, the cavities formed under the sinus membrane were augmented by placing a collagen sponge on the right side and an equal volume of xenogen grafts on the left side. In the postoperative period, the rabbits were sacrificed at the end of the 4th and 8th weeks, 8 each time. The obtained samples were divided into 4 groups and evaluated histopathologically and histomorphometrically. Results: Histopathological evaluation revealed that the two materials were biocompatible materials and formed a suitable environment for the transfer of osteogenic cells. Histomorphometric evaluations showed that there was no difference between the materials in terms of percentage of new bone formation. ($p \leq 0.05$) However, the newly formed bone area and osteoid area were found to be much larger in the areas where xenogen grafts were used ($p \leq 0.05$). Collagen sponge was unable to maintain its volume during the test period and resorbed. Minimal resorption was observed in xenogen graft particles.

Keywords: Sinus floor elevation, resorbable collagen sponge, xenograft, histomorphometry

INTRODUCTION

Today, implant-supported prostheses have revolutionized dentistry by offering a predictable and functional fixed treatment option for missing teeth. The posterior maxilla has been shown to be one of the most challenging areas for implant survival.[1, 2]

Several treatment options have been proposed for fixed prosthetic rehabilitation of the edentulous posterior maxilla. Sinus floor elevation is applied using graft materials to direct bone augmentation and create new bone tissue for the future implant placement site.[3-10]

If the cavity created under the sinus membrane is preserved for a sufficient period of time without inserting autogenous bone or graft materials, new bone is expected to form in this space. Histomorphometic evaluation is the gold standard for evaluating bone healing in augmented sinuses.

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MATERIALS AND METHODS

A total of sixteen adult New Zealand white rabbits (eight females and eight males) weighing between 3–4 kg was used in the study.

In the study, control groups used xenogenic graft material, Bio-Oss® (Geistlich Pharma AG, Wolhusen, Switzerland), while test groups used CollaPlug® (Zimmer Dental, Carlsbad, California, America), a sponge wound dressing material containing resorbable collagen. Bio-Gide® (Geistlich Pharma AG, Wolhusen, Switzerland) collagen membrane was used to cover the bone windows opened to reach the maxillary sinus.

S1 Group: Samples that were taken in the fourth week and using resorbable sponges for augmentation.

G1 Group: Samples that were taken in the fourth week and using xenogenic graft particles for augmentation.

S2 Group: Samples that were taken in the eighth week and using resorbable sponges for augmentation.

G2 Group: Samples that were taken in the eighth week and where xenogenic graft particles were used for augmentation.

1. Surgical Method

Under veterinary control, general anesthesia was given to the sixteen rabbits included in the study by the intramuscular administration of 50 mg/kg Ketamine HCl (Ketasol 10%, Richter Pharma, Austria) and 7 mg/kg Xylazine HCL (Rompun 2%, Bayer, Istanbul).

Following the midline of the nasal bone, a 5 cm long incision was made, including skin and subcutaneous tissues. The full-thickness flap was elevated and the nasal bone, and nasoincisal suture were exposed. In order for the windows on both sides of the nasoincisal suture to be of equal size, a 6 mm diameter marking was first made with a trephine bur. Then, the osteotomy was completed with steel and diamond burs, and the maxillary sinus membrane was reached. The sinus membrane was elevated in all directions with the help of special elevators to create the necessary space for graft placement (Figure 1.A)

CollaPlug® collagen sponge and Bio-Oss® xenogenic graft particles are prepared with a volume of 0.5 ccs.

CollaPlug® was placed in the space created in the right maxillary sinuses of all the rabbits, while Bio-Oss® xenogenic graft particles were placed in the space created in the left maxillary sinuses (Figure 1.A, 1.B). The bone windows were covered with Bio-Gide® resorbable membrane (Figure 1.B). Flaps were sutured in the original position with 3.0 vicryl (Coated Vicryl, Doğsan, Istanbul, Turkey).

As planned in the study, eight of the subjects were euthanized by administering 150 mg/kg ketamine intramuscularly following general anesthesia on the fourth week. The remaining eight subjects were euthanized on the eighth week.

After removing the surrounding soft tissues, the maxilla of the subjects was excised under the orbital floor with appropriate discs and burs. The samples obtained were fixed in 10%

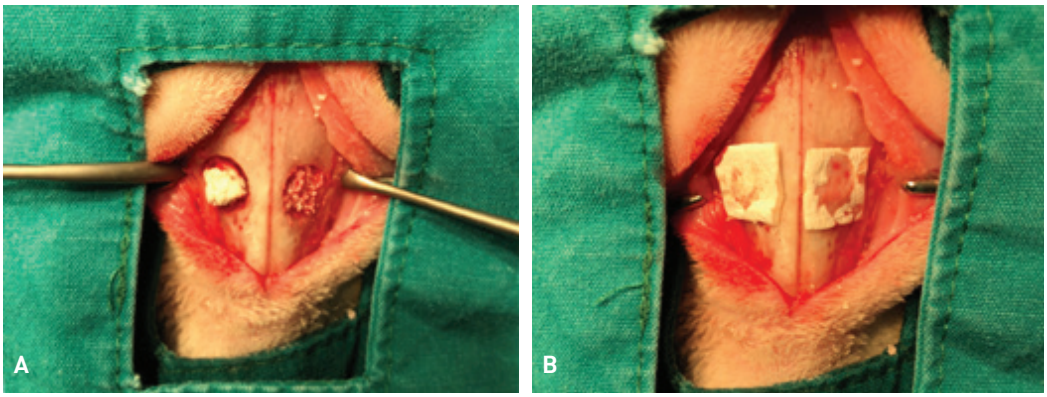

Figure 1. A. CollaPlug® was placed in the space created in the right maxillary sinuses of all the rabbits, while Bio-Oss® xenogenic graft particles were placed in the space created in the left maxillary sinuses, B. The bone windows were covered with Bio-Gide® resorbable membrane.

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formaldehyde solution for histopathological examination and labeled by group name.

2. Histological Examination

Histopathological and histomorphometric evaluations were performed in Başkent University Faculty of Medicine, Department of Pathology.

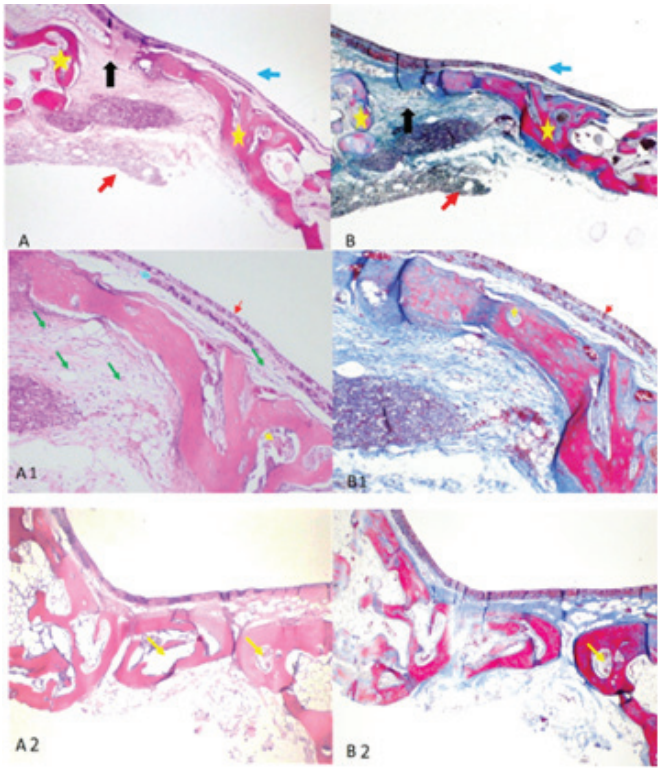

Figure 2. A, 2.B. Week four collagen sponge group (S1). H&Ex40 (2.A), MTKx40 (2.B). New bone formations formed between the maxillary wall and the Schneiderian membrane. No bone formation (black arrow). (Blue arrow: sinus mucosa, yellow star: newly formed bone trabeculae, red arrow: maxillary sinus wall osteotomy area.), 2.A.1, 2.B.1. Red arrow: surface lined with ciliated single-layer columnar epithelium, green arrow: vessel sections in the stroma, yellow arrow: bone marrow distance in newly formed bone, 2.A.2, 2.B.2. Week eight collagen sponge group (S2). Loose connective tissue without inflammation under the surface epithelium and new bone formation, including bone marrow space. (Yellow arrows: bone marrow areas.)

3. Histomorphometric Evaluation

Histomorphometric evaluations were done with OsteoidHisto (Insitute of Ageing and Chronic Diseases, University of Liverpool, Liverpool, UK), which is an Open-Source Software program. For this purpose, microscopic photographs were taken at x20 magnification in MTK stained sections with ROI via microscope imaging program (Olympus, U-TV1XC, Tokyo, Japan) and loaded into OsteoidHisto for measurements to be taken semi-automatically.

4. Statistical Method

The Mann Whitney U test was used to determine the mean of the first and second measurements of each group and whether the differences between these averages were significant. The Wilcoxon Sign Test was conducted to determine whether the difference between the first and second measurement average and the difference between the average was significant for the CollaPlug® and Bio-Oss® groups. Analyses were made with SPSS 20.0 software at a 95% confidence level.

RESULTS

1. S1 Group

After week four, the sponge group was observed to have loose connective tissue, minor salivary glands and vascular structures and bone trabeculae surrounded by an osteoblastic rim under the sinus mucosa epithelium lined with a single row of ciliated cubic-columnar epithelium. While full-thickness bone formation was not observed in some areas, fibrous connective tissue, including vascular structures, was observed, and osteoid formation was seen in the local bone adjacent to central areas. No residual material was found in this group. Rare inflammatory cells and vascular proliferation were observed, especially in the osteotomy area of the maxillary wall. (Figure 2.A, 2.B, 2.A.1, 2.B.1)

2. G1 Group

Osteoid formation surrounding the residual graft material was observed in all subjects in the xenogenic graft group at week four. While the newly formed osteoid was mostly observed in areas from the adjacent local bone to the center, there were osteoblastic cell lines around it, but osteoclasts were detected very rarely. There were osteocyte lacunae in the osteoid. The newly formed bone volume was measured as 23 ± 6.5%, and the newly formed bone area as 577287 ± 193011 μm². The osteoid

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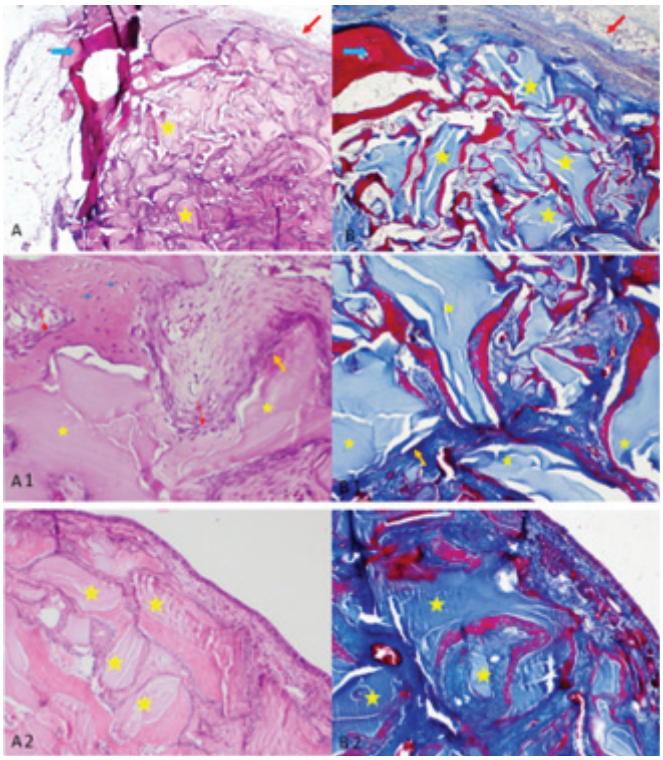
area was measured as 256953 ± 102380 µm². In areas where osteoid was not formed, fibrous connective tissue, including vascular structures, was seen in between (Figure 3.A, 3.B, 3.A.1, 3.B.1) The connective tissue percentage was determined to be 42.23 ± 13.60% on average. In this group, the mean residual graft volume was measured as 34.79 ± 11.80%. Rare chronic inflammatory cells were detected in the osteotomy site of the maxilla wall. The total ROI area was measured as an average of 3664094.4 ± 731074.5 µm².



Figures 3. A, 3.B. Week four xenogenic graft group (G1). H&Ex20 (3.A), MTKx40 (3.B). Residual graft material filling the augmented area and surrounding osteoid, fibrous connective tissue. (Yellow star: residual graft material, red arrow: maxillary wall osteotomy area, blue arrow: local bone tissue.) 3.A.1, 3.B.1. New bone formations surrounded by osteoblastic cells formed around residual graft material. In some areas, fibrous connective tissue is observed around and between the graft material. (Yellow star: graft material, orange arrow: non-osteoid transitional areas around the graft, blue arrows: osteocytes, red arrow: osteoblastic rim.) 3.A.2, 3.B.2. Week eight xenogenic graft group (G2). Mucosal epithelium lined by ciliated single-layer epithelium and bone tissue surrounded by an osteoblastic rim underlying denser connective tissue and residual graft materials. In the MTC stained section, the newly formed bone is red, the connective tissue is blue, and the residual graft is pale blue. (Yellow star: graft material.)

3. S2 Group

After week eight, new bone formations were seen in all subjects in the collagen sponge group. The percentage of newly formed bone volume was measured as 39.5 ± 9.5%, and the newly formed bone area was measured as 280446 ± 146950 µm². While full-thickness bone was usually formed in the augmented area, there was occasional connective tissue interruption. The connective tissue percentage was found to be 60.52 ± 9.55% on average. Similar to week four, no residual material was found in this group. Inflammatory cells were not seen in this group. The total ROI was measured as 967726.6 ± 387179.4 µm². (Figure 2.A.2, 2.B.2)

4. G2 Group

After week eight, residual graft material and new bone formations were detected around graft particles, which was slightly more than after week four. This newly formed bone was in the spaces between and in close contact with the graft particles. The newly formed bone volume was measured as 41.4 ± 9.5% and the newly formed bone area as 791391 ± 257161 µm². Sparse osteoclasts were observed around the bones lined with osteoblastic cells. The connective tissue observed in between was denser than in the other groups (Figure 3.A.2, 3.B.2). The connective tissue percentage was determined as 28.42 ± 15.67% on average. In this group, the residual graft volume decreased slightly compared to the fourth week and was measured as 30.19 ± 8.46% on average. Inflammatory cells were not seen in this group. The total ROI was determined as 3073085.2 ± 637331.1 µm².

5. Statistical Results

When the variation between the first and second measurements of each group's new bone formation volume was examined, no significant difference was found between the groups at four weeks and eight weeks (Table 1).

When the variation between the first and second measurements of each group's new bone area (B. Ar) is examined, the measurements differ significantly between the collagen sponge and xenogenic graft groups. In both measurements, the average of the xenogenic graft group was significantly higher than the average of the collagen sponge group (Table 1).

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When the variation between the first and second measurements of each group's osteoid area (Os. Ar) was examined, the measurements showed a significant difference between the collagen sponge and xenogenic graft groups. In both measurements, the average of the xenogenic graft group(G1-G2) was significantly higher than the average of the collagen sponge group (S1-S2) (Table 1).

When the collagen sponge group (S1-S2) was examined for the parameters of new bone volume (BV/TV), new bone area (Os. Ar), and soft tissue volume (STV/TV), a significant difference was observed between the first and second measurements (p←0.05). While a significant decrease was observed in the second measurement of the soft tissue volume (STV/TV) compared to the first measurement, a significant increase was observed from the first measurement to the second measurement for new bone volume (BV/TV) and new bone area (Os. Ar) (Table 2).

Table 1: The variation between the first and second measurements of each group's for the parameters of new bone volume (BV/TV), new bone area (B. Ar), and osteoid area (Os. Ar)

		N	Average	Standard Deviation	t	p
New Bone Volume (%) BV/TV	S1	8	27,0	9,9	0,968	0,350
	G1	8	23,0	6,5		
	S2	8	39,5	9,5	-0,401	0,695
	G2	8	41,4	9,5		
New Bone Area (µm2) B. Ar	S1	8	284496	94817	-6,199	0,002*
	G1	8	577287	193011		
	S2	8	146950	146950	-9,543	0,000*
	G2	8	257161	257161		
Osteoid Area (µm2) Os. Ar	S1	8	61956	24615		0,000*
	G1	8	256953	102380		
	S2	8	114458	58861		0,000*
	G2	8	524009	286233		

Table 2: The collagen sponge group examination for the parameters of new bone volume (BV/TV), new bone area (B. Ar), and soft tissue volume (STV/TV)

Collagen Sponge Group		N	Average	Standard Deviation	p
Vascular Proliferation	1.	8	14,75	5,26	0,004*
	2.	8	6,88	1,81	
New Bone	B. Ar (1)	8	284496	94817	0,091
	B. Ar (2)	8	280446	146950	
	Os. Ar (1)	8	61956,3	24614,8	0,020*
	Os. Ar (2)	8	114458,2	58861,1	
	BV/TV (1)	8	27,03	9,93	0,015*
	BV/TV (2)	8	39,48	9,55	
Soft Tissue Volume	STV/TV (1)	8	72,97	9,93	0,015*
	STV/TV (2)	8	60,52	9,55	

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When the variation between the first and second measurements in the xenogenic graft group(G1-G2) was examined for the parameters of new bone area (B. Ar), osteoid area (Os. Ar), new bone volume (BV/TV), and soft tissue volume (STV/TV), there was a significant difference between the first and second measurements. (Table 3)

A significant increase from the first measurement to the second measurement was observed in new bone area (B. Ar), osteoid area (Os. Ar), and new bone volume (BV/TV). A significant decrease in soft tissue volume (STV/TV) was observed.

Table 3: The xenogenic graft group examination for the parameters of new bone volume (BV/TV), new bone area (B. Ar), and soft tissue volume (STV/TV)

Xenogenic Graft Group		N	Average	Standard Deviation	p
Vascular Proliferation	1.	8	13,38	2,56	0,000*
	2.	8	6,50	1,60	
New Bone	B. Ar (1)	8	577287	193011	0,027*
	B. Ar (2)	8	791391	257161	
	Os. Ar (1)	8	256953	102380	0,009*
	Os. Ar (2)	8	524009	286233	
	BV/TV (1)	8	22,98	6,50	0,002*
	BV/TV (2)	8	41,38	9,47	
Residual Graft	GV/TV (1)	8	34,79	11,80	0,246
	GV/TV (2)	8	30,19	8,46	
Soft Tissue Volume	STV/TV (1)	8	42,23	13,60	0,019*
	STV/TV (2)	8	28,42	15,67	

DISCUSSION

Sinus floor elevation is performed with the use of graft materials to guide bone augmentation and create new bone tissue at the site of future implant placement.[3-10]

In our study, while high volumetric stability was observed in the regions where we used xenogenic grafts, serious volume loss was observed in the regions where we used collagen sponge.

Yıldırım et al. performed a total of fifteen sinus floor elevations in eleven patients and used xenogenic graft particles (Bio-Oss®) as augmentation material. As a result of histomorphometric measurements, an average of 14.7% of new bone formation and 29.7% of residual grafts were observed.[11] In our study, when the results from week eight were taken into account, the presence of residual grafts was found at a rate of 30.19%, similar to their study. However, when evaluated in terms of new bone formation, in our study, unlike their study, new bone formation was observed at a rate of 41.38%. The reason for this difference could be the use of different living materials in the studies and different surgical techniques.

Data from animal experiments and reports from clinical studies in humans have clearly demonstrated that new bone formation occurs under the elevated Schneiderian membrane (SM) without the use of graft material.[12-15] Elevation of the Schneiderian membrane creates a cavity that is immediately filled with a blood clot. If the formed clot can be preserved for a sufficient time without resorption, it will be replaced by newly formed bone. However, if there is no structure protecting the formed space, the blood clot will be rapidly absorbed, the elevated sinus membrane will collapse, and new bone formation will not occur.[16]

Berberi et al. used resorbed sponge containing type 1 collagen as sinus augmentation material in their prospective clinical study. In their study, in which they showed histologically new bone formation with the biopsies they obtained after a six-month recovery period, they also stated that they provided an average of 8 mm bone gain in all regions in the radiological examination.[17]

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Smith et al. performed sinus floor elevations in sheep in their study and used Bio-Oss® particles as augmentation material. They found no signs of inflammation in any of the biopsies they took at four, six, and twelve weeks.[18] In our study, unlike Smith et al.'s study, mild inflammation was observed in the osteotomy area at the fourth week, while no signs of inflammation were found at the eighth week, similar to their study.

This suggests that both xenogenic graft particles (Bio-oss®) and collagen sponges (Collaplug®) are biocompatible materials and do not cause any foreign body reaction.[19] In the groups measured at four weeks (S1 and G1), the mild inflammation observed in the osteotomy area was thought to be due to the degradation of the barrier membrane placed in this area.

In sinus floor elevation applications, implants and/or various biomaterials are placed in the space created after the elevation of the Schneiderian membrane, thus protecting this space and forming new bone in this area. Histological and histomorphometric examinations can be performed on biopsies obtained after the required waiting time. The BV/TV values of the new bone formed after the histomorphometric examinations show the percentage of the new bone formation volume in the total tissue in the area of interest.[20] This value can also be considered as the ability of the placed material to form new bone. In order to compare the new bone formation abilities of the graft materials used in our study, histomorphometric examination was performed on the biopsies obtained at four and eight weeks, and the BV/TV values of the newly formed bone were compared.

Statistical analyses based on the data we obtained showed that there was no significant difference between the BV/TV values of the two materials compared at four and eight weeks. This suggests that the new bone formation abilities of the two materials are similar. When the results of both materials at four and eight weeks were compared, new bone formation increased significantly. This increase suggests that bone remodeling continues throughout the study and, considering that the eight-week period in rabbits corresponds to six to eight months in humans, a six-month waiting period is required to place implants in the augmented sinus areas.

In an experimental animal study, Choi et al. stated that the structural strength of collagen sponges is insufficient to protect the augmented volume in the sinus.[21]

When the osteoid area values obtained in our study were compared statistically, it was found that the regions where xenogenic graft was used were significantly higher than the regions where collagen was used. This situation makes us think that the prepared samples contain less osteoid area due to the rapid resorptions and volume losses of collagen sponges.

The exact origin of osteogenic cells in bone repair of the maxilla is unknown. They can migrate to the area by blood or reproduce from existing stem cells in the area, or both can occur at the same time. The Schneiderian membrane (SM) may also contain osteoprogenitor cells. In a series of in vitro and in vivo studies in human subjects, Srouji et al. successfully demonstrated osteoprogenitor cells in sinus membrane samples. These cells formed histologically prominent bone in ectopic regions following transplantation into mice.[22] However, it is unclear whether osteoprogenitor cells originating from the sinus membrane play an important role in new bone formation after sinus floor elevation.

Scala et al., in another study, applied sinus floor elevation and simultaneous implantation with the lateral window method without using graft material and determined that new bone formation occurs from the maxillary sinus walls and septum.[23]

In our study, new bone formations were mostly seen from the maxillary sinus walls toward the central regions. Although the contribution of the Schneiderian membrane to new bone formation in the later stages of healing or when more stable conditions are provided, this contribution could not be demonstrated in the early results of our study.

Choi et al., in their study examining the structural strength of collagen sponges impregnated with bone morphogenic protein, determined that the collagen sponges were completely resorbed in the histological examination of the biopsies taken from the rabbits after eight weeks.[24]

In our study, complete resorption was observed in the areas where collagen sponge was used in the samples taken at both four and eight weeks, similar to the other studies using this material, and no residual structure was encountered.[24]

In a study conducted by Lambert et al., they examined the impact of different materials on sinus floor elevation. They created spaces in the maxillary sinuses of rabbits and filled them with either clot, autogenous bone, or xenogenic graft. After six months, they found that 77.6% of subjects with blood

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clots, 81.3% with autogenous bone, and 49.2% with xenogenic grafts exhibited a soft tissue component.[25]

In our study, we investigated the rate of soft tissue formation in areas treated with a collagen sponge. At week four, the measurement showed a rate of 72.9±9.9%, which decreased to 60.52±9.55% at week eight. This decline between the two time points was attributed to ongoing new bone formation during the regeneration process.

In this study, the effects of sponges containing type 1 atecollagen (CollaPlug®) and xenogen grafts (Bio-Oss®) on new bone formation in sinus floor elevation applications were examined histologically and histomorphometrically. No significant inflammation and foreign body reaction were observed in the areas where both materials were used. Both materials provided new bone formation in the areas where they were used. No histomorphometric difference was found between the two materials when evaluated in terms of their ability to form new bone.

CONCLUSION

Both materials provided a similar amount of vascular proliferation in the areas where they were used, creating a suitable environment for the transfer of osteogenic cells. The collagen sponge could not maintain its initial volume throughout the experiment and the augmented area collapsed to a large extent. The xenogen graft showed superior volumetric stability and maintained its volume throughout the study, acting as a framework for the newly formed bone. While the collagen sponge was completely resorbed during the experiment, a very low tendency to resorption was observed in the xenogen graft particles. When the newly formed bone and osteoid areas were evaluated, it was seen that the xenogen graft created much more new bone and osteoid areas than the atecollagen sponge. While the new bone formed in the areas where atecollagen sponge was used showed lower density, the bone-graft complex was observed in a denser structure in the areas where xenogen graft was used. A denser trabecular bone network was formed in the areas where atecollagen sponge was used compared to the xenogen graft.

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DATA SHARING STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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