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ORIGINAL ARTICLE

Microcomputed tomographic analysis of bone microarchitecture after sinus augmentation with hyaluronic matrix: a case–control study

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Abstract

Background The aim of this study was to analyze trabecular microarchitecture of augmented sinuses with hyaluronic matrix and xenograft by microcomputed tomography, and to investigate whether hyaluronic matrix has an effect on the newly formed bone quality.

Materials and methods Thirteen patients undergoing maxillary sinus augmentation were included in this split-mouth study. Right and left sinus sites were randomly assigned to test and control group. In test group, the sinus was grafted with hyaluronic matrix and xenograft; in control group, only with xenograft. Four months after augmentation, bone samples were harvested during implant placement and analyzed for the following trabecular microarchitecture parameters using microcomputed tomography: bone volume (BV), total volume (TV), bone volume fraction (BV/TV), bone surface (BS), specific bone surface (BS/BV), bone surface density (BS/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), trabecular pattern factor (Tb.Pf), and fractal dimension (FD).

Results There was statistically significant difference only for BS/TV parameter between two groups. BS/TV was higher in hyaluronic matrix group compared with control group.

Conclusions Addition of hyaluronic matrix to xenograft may enhance bone quality in terms of bone surface density. However, more research investigating the microstructural variation of augmented sinuses is needed with a greater sample.

Keywords Sinus augmentation · Hyaluronic acid · Microcomputed tomography · Trabecular microarchitecture

Background

Maxillary sinus augmentation by lateral window approach allows implant placement in the resorbed posterior maxilla. It is a predictable procedure with high success rates [1]. Various graft materials have been applied for this procedure. Although autogenous graft is accepted as possessing ideal properties [2], it has been substituted by other graft materials because of its disadvantages such as postsurgical morbidity, increased surgical time, and higher resorption rates [3]. Allografts, xenografts, and alloplastic materials are frequently used for this purpose. Xenografts including anorganic bovine bone and collagenated heterologous bone graft (CHBG) have osteoconductive effects and can be used in combination with other biomaterials to promote osteoinductive efficacy [4, 5].

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan and used in various medical fields including ophthalmology, orthopedic surgery, and dermatology owing to its biochemical and biophysical properties [6]. Interactions

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of HA with extracellular matrix macromolecules and cell surface contribute to morphogenesis, tissue remodeling, and inflammation [7]. It participates in several biological procedures such as mediation of cellular signaling; regulation of cell adhesion, proliferation, and differentiation [6]. Sasaki and Watanabe [8] stated that high-molecular HA is capable of accelerating new bone formation through mesenchymal cell differentiation in bone wounds.

HA-based materials were applied with bone grafts in sinus augmentation studies [9, 10]. These studies supported that it has positive effects on bone formation by providing enough space between graft particles and allowing vascular, cellular invasion to the grafted area.

The success of sinus augmentation is based on the quality of newly formed bone. There are many factors that affect bone quality [11]. It depends not only on the bone mass but also on its distribution in three-dimensional (3D) space (i.e., microarchitecture) [12]. Bouxsein [12] described trabecular microarchitecture as the shape and orientation of basic structural elements. It is evaluated with the number of trabeculae, their average thickness, the average distance between adjacent trabeculae, and trabecular connectivity. Several methods are used for trabecular microarchitecture assessment [13]. Histomorphometric analysis is considered the gold standard for assessing bone, because only it gives the opportunity for direct analysis of cellular components [14]. However, different techniques allow more than one measurement in a nondestructive way compared with histomorphometric analysis. Microcomputed tomography (microCT), one of these techniques, was first introduced by Feldkamp et al. [15] and considered a promising method for 3D evaluation of maxillary sinuses after augmentation [16].

The aim of this study was to analyze trabecular microarchitecture of augmented sinuses with hyaluronic acid-based matrix and CHBG by microCT, and to investigate whether hyaluronic matrix has an effect on the newly formed bone quality in terms of microarchitecture.

Materials and methods

Thirteen individuals in good general health (five men and eight women, mean age 50 years, ranging from 33 to 69 years) participated in this case–control study. All patients were informed about the procedure, and written informed consent was obtained from the patients. The study protocol was prepared according to the Declaration of Helsinki [17, 18]. Approval was obtained from Clinical Researches Ethics Board of Hacettepe University. Patients with bilateral posterior maxillary edentulism (≤ 4 mm residual crest height) and requiring sinus augmentation before implant treatment were included in the study. Individuals taking medications known to affect bone metabolism (e.g., steroids, bisphosphonates), those with significant systemic disease, pregnant, nursing women, and smokers were excluded from the study.

Bilateral maxillary sinus augmentation was performed with lateral window approach as described by Tatum [19]. In this split-mouth study, right and left sinus sites were randomly assigned to test and control group. The sinus was grafted with hyaluronic matrix (Hyaloss^{TM} matrix, ANIKA Therapeutics, Italy) and CHBG (Apatos mix, OsteoBiol®, Italy) in test group and only with CHBG in control group. Hyaluronic matrix, in the form of fibers, consists of esterified bacterial origin HA. It immediately takes gel form in contact with sterile saline (Fig. 1).

Four months after augmentation, during implant placement, 26 bone samples were taken from the grafted sinus areas with a 2-mm-diameter trephine bur. After removal, these samples were placed in 10% neutral buffered formalin solution.

MicroCT analysis

Bone samples were fixed to the scanner compartment of the microCT device (Skyscan 1174, Skyscan, Kontich, Belgium) via patafix. After the area setting of 800 µA, 50 kV, and 40.89 µm pixel size was arranged and saved, each sample was scanned with the same setting. The rotation step of microCT was set at 0.7° and the sample was determined to perform 180° rotation scan with 2300 ms exposure. Raw data were obtained during scanning and subsequent reconstructions of these data were carried out with the software NRecon (NRecon version 1.6.9.4, Skyscan, Kontich, Belgium), provided by the manufacturer. During reconstruction beam hardening, ring artifact reduction, smoothing, and frame averaging were individually adjusted to the optimum value for each sample. As a result of the reconstruction of the raw data, 8-bit gray value images were obtained. Reconstructed images were transferred to CTAn (version 1.13.5.1)

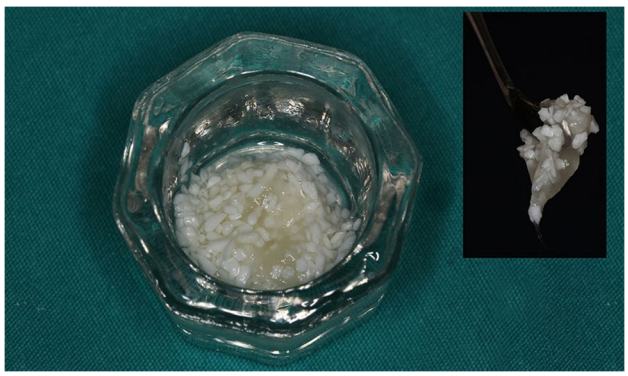

Fig. 1 Figure showing hyaluronic matrix and xenograft mixture. Hyaluronic matrix immediately takes gel form in contact with sterile saline

software. Using CTAn scan, region of interest (ROI) was drawn within the sample to analyze the 3D microarchitecture of each sample.

From each ROI, the following trabecular microarchitecture parameters were analyzed according to the previously described variables in the literature [20, 21]: (1) bone volume (BV) (mm^3), volume of the region segmented as bone; (2) total volume (TV) (mm^3), volume of the entire ROI; (3) bone volume fraction (BV/TV) (%), ratio of the bone volume to the total volume of the ROI; (4) bone surface (BS) (mm^2), surface of the region segmented as bone; (5) specific bone surface (BS/BV) (mm^2/mm^3), ratio of the segmented bone surface to the segmented bone volume; (6) bone surface density (BS/TV) (mm^2/mm^3), ratio of the segmented bone surface to the total volume of the ROI; (7) trabecular thickness (Tb.Th) (mm), mean thickness of the trabeculae in the ROI; (8) trabecular separation (Tb.Sp) (mm), mean distance between trabeculae; (9) trabecular pattern factor (Tb.Pf) (1/mm), which is an inverse connectivity index: the higher it is the trabeculae are less connected; (10) fractal dimension (FD), which indicates the complexity of the specimen surface.

Statistical analysis

The study sample was determined according to the previous study conducted by the same research group [9].

Statistical analysis was performed by the software IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). All of the microCT parameters were summarized as median values and interquartile ranges [25th percentile (Q1)-75th percentile (Q3)]. The parameters between control and test group were compared with Wilcoxon's rank-sum test. The correlations among the parameters for each group were calculated using Spearman's rank correlation coefficient. Statistical significance was set at $P < 0.05$ and $P < 0.01$.

Results

Table 1 lists the median values of all measured parameters for test and control group. There was statistically significant difference only for BS/TV parameter between two groups. BS/TV was higher in hyaluronic matrix group compared with control group.

Spearman correlation analysis among microCT parameters revealed correlations at the 0.05 and 0.01 levels. Significant correlations were found in control group (Table 2). Tb.Sp was negatively correlated with BV/TV ($r = -0.758$, $P = 0.011$), and BS/TV ($r = -0.661$, $P = 0.038$). As an index showing inverse connectivity, Tb.Pf showed a positive correlation with BS/BV ($r = 0.685$, $P = 0.029$) in control group.

Table 1 Descriptive data of trabecular microarchitecture parameters

	Test	Control	
	Median (min–max)	Median (min–max)	*P* value
TV	91.57 (30.11–144.94)	100.84 (42.51–328.00)	0.203
BV	20.42 (6.76–37.98)	19.07 (12.78–41.07)	0.445
BV/TV	20.30 (12.11–36.21)	23.78 (12.52–33.48)	0.878
BS	147.07 (58.46–311.70)	149.59 (77.62–333.10)	0.799
BS/BV	7.53 (6.64–17.19)	7.10 (5.70 –11.02)	0.059
BS/TV	1.85 (1.30–2.49)	1.79 (0.80–2.16)	**0.009**
Tb.Pf	−3.93 (−6.86–−0.05)	−4.27 (−7.26–−1.62)	0.241
Tb.Th	0.45 (0.22–0.60)	0.51 (0.37–0.78)	0.114
Tb.Sp	0.73 (0.45–1.18)	0.84 (0.64–1.63)	0.203
FD	2.69 (2.38–2.73)	2.67 (2.62–2.75)	0.959

TV total volume, *BV* bone volume, *BV/TV* bone volume fraction, *BS* bone surface, *BS/BV* specific bone surface, *BS/TV* bone surface density, *Tb.Pf* trabecular pattern factor, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, and *FD* fractal dimension

*Significant correlation ($P < 0.05$)

In hyaluronic matrix group, Tb.Sp was positively correlated with BS/BV ($r = 0.721$, $P = 0.019$) (Table 3). FD revealed strong positive correlation with Tb.Th both in the test ($r = 0.673$, $P = 0.033$) and control group ($r = 0.806$, $P = 0.005$).

Discussion

Dental implants are exposed to functional loading after prosthetic treatment. Therefore, it is important to learn the quality of newly formed bone, particularly in the posterior maxilla with a high rate of type 4 bone [22]. There are many factors that affect bone quality [11]. Microarchitecture is expressed as one of the determinants of bone quality. Orientation of trabeculae in 3D plane gives information about biomechanical properties of trabecular bone. Hence, as the implant is surrounded by trabecular bone, it is recommended to evaluate trabecular microarchitecture as part of bone assessment before implant surgery [23].

MicroCT allows us to evaluate bone samples in 3D plane and to learn about trabecular microarchitecture of the samples. It is a non-destructive method and gives high-resolution images of bone structure [15]. There are a limited number of studies examining augmented sinus region by microCT in terms of trabecular microarchitecture [16, 24–33]. In these sinus augmentation studies, heterogeneity exists with respect to the grafting material, healing time, and measured outcomes. Moreover, a detailed discussion of microarchitecture parameters is unavailable. This may be attributed to the evaluation of trabecular microarchitecture being a relatively new area of research for implant surgery. However, the majority of these studies agreed that microCT is

Table 2 Correlation chart for control group

	TV	BV	BV/TV	BS	BS/BV	BS/TV	Tb.Pf	Tb.Th	Tb.Sp	FD
TV										
Correlation coefficient	1.000	.855**	−.903**	.879**	.406	−.685*	.430	−.115	.770**	.248
Significance		.002	.000	.001	.244	.029	.214	.751	.009	.489
N	10	10	10	10	10	10	10	10	10	10
BV										
Correlation coefficient	.855**	1.000	−.612	.976**	.309	−.394	.515	−.115	.673*	.079
Significance	.002		.060	.000	.385	.260	.128	.751	.033	.829
N	10	10	10	10	10	10	10	10	10	10
BV/TV										
Correlation coefficient	--.903**	−.612	1.000	−.648*	−.345	.867**	−.297	.055	−.758*	−.297
Significance	.000	.060		.043	.328	.001	.405	.881	.011	.405
N	10	10	10	10	10	10	10	10	10	10
BS										
Correlation coefficient	.879**	.976**	−.648*	1.000	.479	−.358	.564	−.297	.709*	−.018
Significance	.001	.000	.043		.162	.310	.090	.405	.022	.960
N	10	10	10	10	10	10	10	10	10	10
BS/BV										
Correlation coefficient	.406	.309	-.345	.479	1.000	.127	.685*	−.612	.212	−.176
Significance	.244	.385	.328	.162		.726	.029	.060	.556	.627
N	10	10	10	10	10	10	10	10	10	10
BS/TV										
Correlation coefficient	−.685*	−.394	.867**	−.358	.127	1.000	.067	−.273	−.661*	−.467
Significance	.029	.260	.001	.310	.726		.855	.446	.038	.174
N	10	10	10	10	10	10	10	10	10	10
Tb.Pf										
Correlation coefficient	.430	.515	−.297	.564	.685*	.067	1.000	−.200	.370	−.018
Significance	.214	.128	.405	.090	.029	.855		.580	.293	.960
N	10	10	10	10	10	10	10	10	10	10
Tb.Th										
Correlation coefficient	−.115	−.115	.055	−.297	−.612	−.273	−.200	1.000	−.212	.806**
Significance	.751	.751	.881	.405	.060	.446	.580		.556	.005
N	10	10	10	10	10	10	10	10	10	10
Tb.Sp										
Correlation coefficient	.770**	.673*	−.758*	.709*	.212	−.661*	.370	−.212	1.000	.018
Significance	.009	.033	.011	.022	.556	.038	.293	.556		.960
N	10	10	10	10	10	10	10	10	10	10
FD										
Correlation coefficient	.248	.079	−.297	−.018	−.176	−.467	−.018	.806**	.018	1.000
Significance	.489	.829	.405	.960	.627	.174	.960	.005	.960	
N	10	10	10	10	10	10	10	10	10	10

Correlation between variables: *TV* total volume, *BV* bone volume, *BV/TV* bone volume fraction, *BS* bone surface, *BS/BV* specific bone surface, *BS/TV* bone surface density, *Tb.Pf* trabecular pattern factor, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, and *FD* fractal dimension

*Significant correlation ($P < 0.05$)

**Significant correlation ($P < 0.01$)

effective for evaluating 3D bone structure. Huang et al. [27] evaluated bone microarchitecture by microCT after sinus augmentation with autogenous bone graft and stated that it is important to understand the trabecular remodeling of autogenous bone graft and hereby to determine the implant prognosis in grafted maxillary sinus region. Kühl et al. [16] performed sinus augmentation using different graft materials and evaluated whether microCT is suitable for examining the

Table 3 Correlation chart for hyaluronic matrix group

	TV	BV	BV/TV	BS	BS/BV	BS/TV	Tb.Pf	Tb.Th	Tb.Sp	FD
TV										
Correlation coefficient	1.000	.879**	.236	.879**	.236	.055	− .297	.224	.127	.576
Significance		.001	.511	.001	.511	.881	.405	.533	.726	.082
N	10	10	10	10	10	10	10	10	10	10
BV										
Correlation coefficient	.879**	1.000	.612	.891**	− .091	.224	− .539	.455	− .055	.600
Significance	.001		.060	.001	.803	.533	.108	.187	.881	.067
N	10	10	10	10	10	10	10	10	10	10
BV/TV										
Correlation coefficient	- .236	.612	1.000	.442	− .552	.503	− .515	.588	− .176	.309
Significance	.511	.060		.200	.098	.138	.128	.074	.627	.385
N	10	10	10	10	10	10	10	10	10	10
BS										
Correlation coefficient	.879**	.891**	.442	1.000	.285	.382	− .309	.345	.345	.576
Significance	.001	.001	.200		.425	.276	.385	.328	.328	.082
N	10	10	10	10	10	10	10	10	10	10
BS/BV										
Correlation coefficient	.236	− .091	− .552	.285	1.000	.224	.564	− .430	.721*	− .261
Significance	.511	.803	.098	.425		.533	.090	.214	.019	.467
N	10	10	10	10	10	10	10	10	10	10
BS/TV										
Correlation coefficient	.055	.224	.503	.382	.224	1.000	− .030	− .055	.382	− .297
Significance	.881	.533	.138	.276	.533		.934	.881	.276	.405
N	10	10	10	10	10	10	10	10	10	10
Tb.Pf										
Correlation coefficient	− .297	− .539	− .515	− .309	.564	− .030	1.000	− .224	.442	− .455
Significance	.405	.108	.128	.385	.090	.934		.533	.200	.187
N	10	10	10	10	10	10	10	10	10	10
Tb.Th										
Correlation coefficient	.224	.455	.588	.345	− .430	− .055	− .224	1.000	-.321	.673*
Significance	.533	.187	.074	.328	.214	.881	.533		.365	.033
N	10	10	10	10	10	10	10	10	10	10
Tb.Sp										
Correlation coefficient	.127	− .055	− .176	.345	.721*	.382	.442	− .321	1.000	− .079
Significance	.726	.881	.627	.328	.019	.276	.200	.365		.829
N	10	10	10	10	10	10	10	10	10	10
FD										
Correlation coefficient	.576	.600	.309	.576	− .261	− .297	− .455	.673*	− .079	1.000
Significance	.082	.067	.385	.082	.467	.405	.187	.033	.829	
N	10	10	10	10	10	10	10	10	10	10

Correlation between variables: *TV* total volume, *BV* bone volume, *BV/TV* bone volume fraction, *BS* bone surface, *BS/BV* specific bone surface, *BS/TV* bone surface density, *Tb.Pf* trabecular pattern factor, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, and *FD* fractal dimension

*Significant correlation ($P < 0.05$)

**Significant correlation ($P < 0.01$)

morphometric structure of healing grafts. Consequently, it was stated that this method is promising.

Although microCT is a successful method in this regard, there is a need for a clinically applicable method as microCT can only be applied to ex vivo bone samples. Apart from histomorphometry and microCT, there are some microarchitecture evaluation methods such as high-resolution magnetic resonance imaging (HR-MRI) and

high-resolution peripheral quantitative computed tomography (HR-pQCT). HR-MRI and HR-pQCT are capable of 3D imaging, but they cannot be applied in vivo in the craniofacial region either.

To the authors' knowledge, this is the first study that microCT technique has been used to perform a microarchitecture evaluation of bone samples, retrieved from hyaluronic matrix applied maxillary sinuses. Microstructural properties displayed statistically significant difference only for BS/TV parameter between two groups. As a parameter showing bone surface density, BS/TV was higher in hyaluronic matrix group compared with control group. This is a notable result that addition of hyaluronic matrix to xenograft may be an alternative treatment for implant placement in poor bone density areas such as type 4 bone. This result should be confirmed by implant stability and torque analyses at the time of implant placement.

HA (also termed hyaluronan) has several biological properties. The cellular effects of HA are mostly explained by its unique hydrodynamic properties and its interactions with structural hyaluronan-binding proteins of extracellular matrices. It acts as a template for assembly of a multicomponent pericellular matrix [7]. In this matrix, interactions with cell surface hyaluronan receptors (e.g., CD44, RHAMM) and direct transmembrane attachment to hyaluronan synthase affect cell behavior in terms of cell proliferation, motility, and invasion. Although it is not clear whether HA has direct or indirect effect on osteogenic cells, it was shown to increase bone formation in vitro by mesenchymal cell migration and differentiation [34]. Huang et al. [35] concluded that HA increases the proliferation and differentiation of osteoprogenitor cells to osteoblasts in the rat calvarial-derived cell culture and also found increased alkaline phosphatase activity and osteocalcin gene expression with HA administration. As a result, it was suggested that HA may enhance osteogenic and osteoinductive properties of bone grafts due to its stimulatory effects on osteoblasts. Stiller et al. [36] reported higher osteogenic marker expression with HA containing graft application in a sinus augmentation study. Another possible explanation of increased bone formation is that low molecular weight degradation products of HA promotes neovascularization by increasing endothelial cell proliferation and blood vessel invasion [8, 37]. This possibility has been noted in sinus augmentation studies using HA containing grafts and finding abundant vascular spaces [9, 10].

Some microstructure parameters (BV, Tb.Pf, Tb.Sp) were more favorable in hyaluronic matrix group; however, there was no statistically significant difference (Table 1). Moreover, BV/TV, BS, and Tb.Th were statistically insignificant higher in the control group. Given the biological properties of HA, these discrepancies may be attributed to the small sample of this study. In addition, a longer healing period may be required to show a statistically significant difference for all these parameters.

Conclusions

Considering the relationship between bone quality and implant success [38], it is important to evaluate the quality of the newly formed bone after augmentation. While HA was determined to have favorable effect on bone quality in terms of bone surface density, further studies are required with a greater sample and implant survival results. In addition, more microarchitecture analyses of augmented sinuses are essential to be able to compare microarchitecture parameters between studies.

Abbreviations CHBG: Collagenated heterologous bone graft; HA: Hyaluronic acid; 3D: Three dimensional; MicroCT: Microcomputed tomography; ROI: Region of interest; BV: Bone volume; TV: Total volume; BV/TV: Bone volume fraction; BS: Bone surface; BS/BV: Specific bone surface; BS/TV: Bone surface density; Tb.Th: Trabecular thickness; Tb.Sp: Trabecular separation; Tb.Pf: Trabecular pattern factor; FD: Fractal dimension; HR-MRI: High-resolution magnetic resonance imaging; HR-pQCT: High-resolution peripheral quantitative computed tomography

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Declarations

Ethical approval Approval was obtained from Clinical Researches Ethics Board of Hacettepe University (2014/08—16 (KA-14030)). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Conflict of interest The authors declare no competing interests.

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