



## ORIGINAL ARTICLE

# The vertical course of bone regeneration in maxillary sinus floor augmentations: A histomorphometric analysis of human biopsies

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## Abstract

**Background:** Maxillary sinus floor augmentation (MSFA) is a well-established and predictable augmentation method in severely resorbed maxillae. However, data on the vertical course of bone graft consolidation within the maxillary sinus are rare. The aim of the present study was to quantify the vertical distribution of new bone formation (nBF) in MSFA and to characterize the vertical gradient of bone graft consolidation.

**Methods:** Eighty-five human sinus biopsies were harvested  $6 \pm 1$  months after MSFA. Histological thin-ground sections were prepared and histomorphometrically analyzed. The volume of newly formed bone (nBV/TV) was measured in serial zones of 100  $\mu$ m proceeding from the bottom of the sinus floor (SF) up to the apical top of the biopsy. The gradient of nBV/TV within the augmentation area was determined by the vertical distribution of nBV/TV along these zones.

**Results:** In the premolar region, nBV/TV slightly declined from 20.4% in the zone adjacent to the SF to 17.7% at a distance of 8 mm. The gradient was steeper in the molar region: nBV/TV decreased from 18.7% to 12.8%. This decline was even more distinct when the volume fraction and the height of the residual bone of the SF were low.

**Conclusions:** nBF follows a gradient from native bone of the SF towards the apical part of the augmentation area. The distance to primordial bone thus plays a critical role for bone regeneration in MSFA, particularly in the molar region.

## KEYWORDS

bone regeneration, bone substitutes, histological analysis, maxillary sinus floor elevation

## 1 | INTRODUCTION

The maxillary sinus floor augmentation (MSFA) is an effective and predictable therapy to increase bone supply

in the edentulous maxillary region.<sup>1,2</sup> Besides a successful surgical procedure, the decisive factor for augmentation success is the consolidation of the grafted material into bone.

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**TABLE 1** Number of biopsies with deproteinized bovine bone mineral and adjuncts

Bone graft materials	n	%
DBBM	7	8.2
DBBM + aB	44	51.8
DBBM + aBcells	15	17.7
DBBM + aB + PC	14	16.4
DBBM + MSC	5	5.9
<b>Total</b>	<b>85</b>	<b>100</b>

aB, autologous bone; aBcells, autologous bone cells; DBBM, deproteinized bovine bone mineral; MSC, mesenchymal stem cells; PC, platelet concentrates.

Controversy exists in the literature regarding the tissue from which bone regeneration originates in MSFA. Both, the residual bone of the sinus floor (SF) and the Schneiderian membrane (SM) are discussed in this context:<sup>3-6</sup>

Palma et al.<sup>7</sup> performed MSFA in capuchin primates and found *de novo* bone formation in contact with SM, indicating an osteogenic potential of SM. This observation is in accordance with Srouji et al.<sup>8</sup> and Rong et al.<sup>9</sup> who studied the role of the SM in an ectopic tissue transplant model in nude mice and in a sinus lifting model in canines. Both reported that the SM appears to have osteogenic and osteoinductive properties and thus might contribute to bone formation in MSFA.

Jungner et al.<sup>4</sup> by contrast could not detect any bone formation originating from the SM in capuchin primates. In fact, the authors found new bone formation (nBF) sprouting from the bottom of the SF, extending into the elevated area surrounding the implant. This is in line with Busenlechner et al.<sup>10</sup> and Fuerst et al.<sup>11</sup> who reported that in mini-pigs, graft consolidation after MSFA largely depends on the osteoinductive potential of the surrounding bone. A graft consolidation gradient was identified showing more new bone in zones adjacent to the SF and less new bone in the more distant zones.

At present, clinical recommendations for MSFA mainly address the choice of surgical approach, single- versus two-stage procedure based on minimum requirements for the width and the height of the residual alveolar ridge.<sup>12,13</sup> However, recommendations on the lifting height of the SM and subsequently the augmentation height itself are rare and usually only consider the possible installation of an implant length of 12 to 13 mm.<sup>13-16</sup> The question whether a larger augmentation height actually results in a larger graft consolidation height or whether excessive bone grafting might even be detrimental to successful graft consolidation remains open.

Based on this background, the aim of the present study was to quantify the vertical distribution of nBF in human sinus biopsies 6 months after MSFA by means of modern histomorphometry. We hypothesized that nBF in the

augmented area follows a gradient from the native bone of the SF towards the apical part of the augmented area and the elevated SM. Unlike previous studies<sup>10,11,17,18</sup> that investigated nBF in a few pre-defined discrete zones, we herewith introduced a new method that allows describing the vertical distribution and extension of new bone continuously over the whole length of the biopsy.

## 2 | MATERIALS AND METHODS

Seven Medical Universities (Departments of Oral Surgery, Department of Prosthodontics and Departments of Oral and Maxillofacial Surgery) from Austria (n = 2) and Germany (n = 5) provided biopsies of MSFA for a multicenter study of Reich et al.<sup>19</sup> The present study investigates the histologic material under a new scientific perspective which has not been studied to date. This study was approved by the human subjects ethics board of Austria and Germany [Austria: 102/2004, 22/2007, 18-053 ex 06/07; Germany: 837.274.04 (4432)] and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

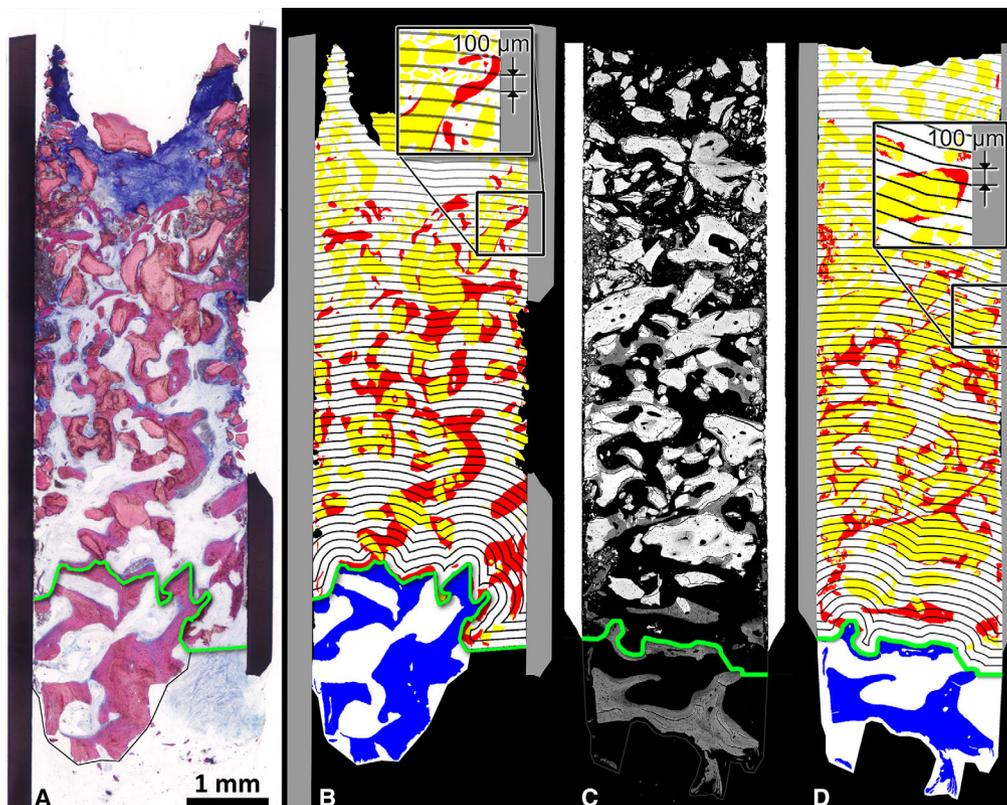
### 2.1 | Eligibility criteria for recruitment

Patients destined for a two-stage approach of MSFA with a residual alveolar bone height (oldB.Ht) of the posterior maxilla of <5 mm, requiring at least one dental implant (premolar or molar region) and aged >18 years were enrolled. Exclusion criteria were recent tooth extraction at the site of implant installation (within the last 3 to 18 months), periodontal disease, pathological conditions of the maxillary sinus, metabolic or degenerative diseases of the bone (e.g., osteoporosis, diabetes mellitus, hyperparathyroidism), long-term medication with corticosteroids or NSAIDs, smoking (>5 cigarettes/day), and alcoholism. All patients provided written informed consent.

### 2.2 | MSFA and sample processing

MSFA procedures were performed following a lateral approach<sup>20,21</sup> under local or general anaesthesia. After window preparation and careful elevation of SM, the grafting material was placed into the created void space. Patients with obvious signs of inflammation, large SM perforations or other complications were excluded from this study.

After a healing period of 6 ± 1 months, sinus biopsies from the premolar and/or the molar region were



**FIGURE 1** Histomorphometric measurement of the vertical distribution of nBV/TV over the length of the augmentation area (illustrated by a histological thin-ground section and a SEM image and their corresponding color-coded classification images). **A)** stained histological thin-ground section, **B)** color-coded classification image of A; **C)** SEM image, **D)** color-coded classification image of C; blue: bone of the sinus floor, red: newly formed bone, yellow: bone substitute particles, white: marrow area/soft tissue; green: border between the SF and the augmentation area). In parallel to the green line, contour lines were set at an interval of 100  $\mu\text{m}$  to measure nBV/TV within each of the resulting serial zones. The gradient over the full length of the augmentation height was calculated for all biopsies

harvested using a trephine burr before implant placement. Implants were inserted along the long axis of the drill hole.

### 2.3 | Eligibility of MSFA biopsy samples

Biopsies originating from previous clinical studies<sup>22–24</sup> have already been used for a multicenter study published by Reich et al.<sup>19</sup> analyzing the impact of the maxillary region and patients' age and sex on bone regeneration after MSFA.

This current study re-analyzed parts of the original samples based on the following criteria:

Biopsies were included if:

1. both the native bone of the SF and the augmented area were present
2. deproteinized bovine bone mineral (DBBM; BioOss, Geistlich Pharma, Wolhusen, Switzerland) was used as bone substitute alone or in combination with adjuncts:

autologous bone (aB) harvested intraorally, culture-expanded aB cells (aBcells) isolated from the anterior iliac crest, aB with platelet concentrate, and aB with mesenchymal stem cells aspirated from the tibia (Table 1, see Supplementary Material S1 in online *Journal of Periodontology*).

### 2.4 | Histology

Biopsy specimens (n = 85) were fixed in phosphate-buffered formalin, dehydrated in ascending grades of alcohol, and embedded in a light-curing resin (Technovit 7200 VLC + BPO; Kulzer, Wehrheim, Germany). Undecalcified thin-ground sections were produced (EXAKT Apparatebau, Norderstedt, Germany) along the long axis of the biopsies as described by Donath.<sup>25</sup> Forty-three (50.6%) of the sections were stained using Levai–Laczko dye<sup>26</sup> and digitized with a camera mounted on a microscope (Nikon DXM 1200/Microphot-FXA, Tokyo, Japan). Multiple single images per specimen were merged to obtain high resolu-



tion overview images (2.212  $\mu\text{m}$  per pixel) (Lucia G 4.71, LIM., Praha, Czech Republic).

SEM images were generated of the remaining 42 sections (49.4%) using back-scattered electrons at 15/20 kV (JSM-6310, Jeol, Tokyo, Japan) with a resolution of 2.695  $\mu\text{m}$  per pixel. The comparability of the results the SEM and the histological image sources, was previously checked using an intraclass correlation coefficient within 10 biopsy specimens (0.92 or >0.92)<sup>19</sup>.

## 2.5 | Histomorphometric analysis

Digital images were semi-automatically segmented and classified into different tissue types using Definiens Developer XD (Definiens, Munich, Germany): pre-existing bone of the SF as well as newly formed bone, bone substitute material, and soft tissue/marrow area within the augmentation area. If areas were inaccurately classified, correction was performed manually under visual control.

### 2.5.1 | Gradient of new bone volume fraction (nBV/TV) in serial zones

The “old” bone of the SF was separated from the actual augmentation area with a manually drawn line (Adobe Photoshop, Adobe, San Jose, CA). In parallel to this borderline, contour lines at an interval of 100  $\mu\text{m}$  were set over the whole length of the augmentation area. nBV/TV was measured within each of these created serial 100- $\mu\text{m}$  zones, beginning from the zone adjacent to the SF up to the apical top of the augmentation area (Fig. 1). The gradient was calculated based on these values.

## 2.6 | Statistical analysis

### 2.6.1 | Generalized mixed model predicting the vertical distribution of nBV/TV

Bone volume per tissue volume was modeled as a generalized mixed model with Gaussian error term and log link,<sup>27</sup> adding *biopsy ID*, *patient ID*, *augmentation material*, and *centre ID* as nested random effects. To correct for potential confounding of the effect of various biomaterials, the augmentation materials were incorporated into the mixed effects multiple regression model as a single fixed factor as described by Katz.<sup>28</sup> This allows to take into account possible influences of the confounding factors on the correlation of the interesting variables.<sup>29</sup> The

distance of the respective zone to the SF was included as a main covariate of interest. Region (premolar/molar), sex, bone volume fraction and bone height of the pre-existing bone of the SF, referred to as oldBV/TV and oldB.Ht, were included as potential confounders. Further, interaction terms with the distance of the respective zone to the SF were considered to allow for different slopes for all the above.

This model predicts the volume of newly formed bone for a given distance to the SF as illustrated by a marginal model plot (Figs. 2 through 4). The prediction line in this plot represents a fictional “median patient” that is generated from the data of the sample. To determine if the region has an influence on the vertical distribution of nBV/TV over the length of the biopsy, premolar, and molar biopsies were analyzed separately.

Normality and homoscedasticity was checked graphically using residual plots.

### 2.6.2 | Influence of oldB.Ht and oldBV/TV of the pre-existing residual bone of the sinus floor on the prediction of nBV/TV

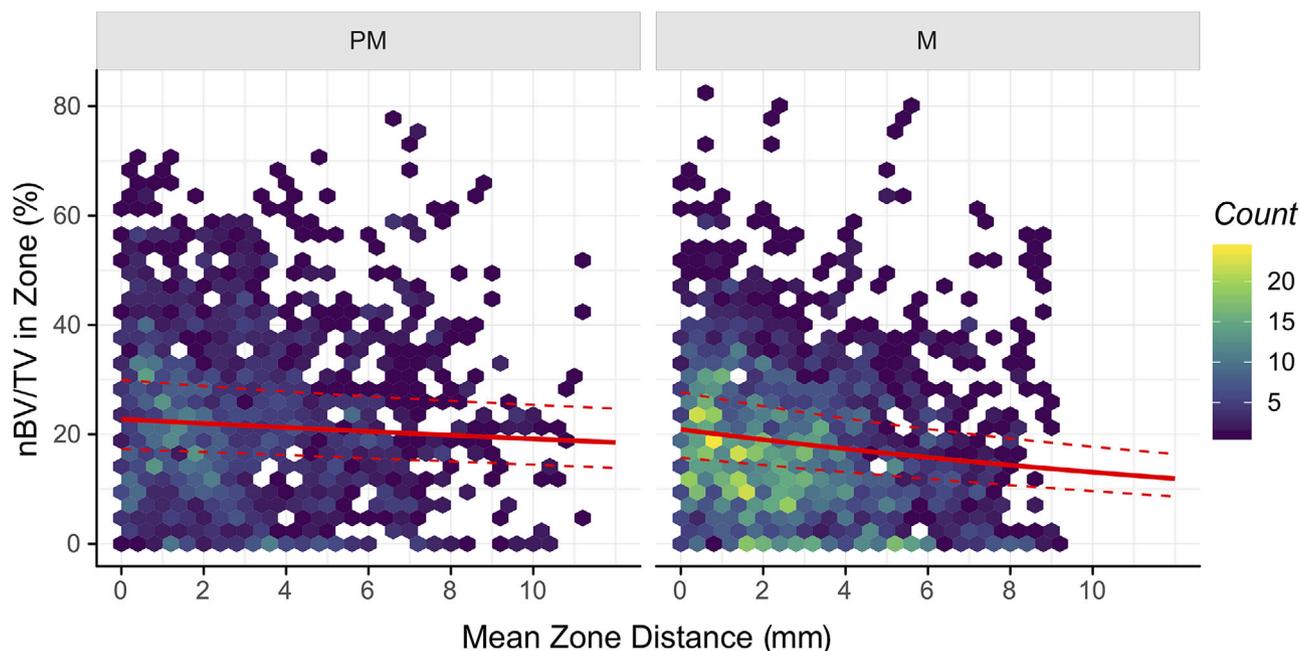
To analyze to what extent the status of the residual bone of the SF had an influence on the prediction of the course of nBV/TV, we show the results of the above model for the three quartiles of the parameters oldB.Ht and oldBV/TV. This allows a model prediction for a fictional patient with “low oldBV/TV” (Q1, 26.6%), “medium oldBV/TV” (Q2, 38.4%), and “high oldBV/TV” (Q3, 48.8%) and “low oldB.Ht” (Q1, 0.7 mm), “medium oldB.Ht” (Q2, 1.2 mm), and “high oldB.Ht” (Q3, 1.6 mm), respectively.

Tests on the significance of changes in these predictions were calculated. Regression lines including a 95% confidence interval are shown in a marginal model plot for typical (mode, median, or quantile) values of the confounders. All computations were done using R (version 3.5.1),<sup>30</sup> and graphics were created using ggplot2.<sup>31</sup>

## 3 | RESULTS

### 3.1 | Sample characteristics

The final study sample consisted of 85 biopsies augmented with DBBM alone or in combination with adjuncts (Table 1), providing a total of 3,925 measurements. The potential confounding effect of different adjuncts was considered in the generalized mixed model and corrected in the statistical evaluation using multivariable regressions.<sup>28,29</sup>



**FIGURE 2** Vertical distribution of nBV/TV over the length of the augmentation area. Marginal model plot, based on a generalized mixed model; PM (pre-molar)/M (molar). Each color-coded hexagon of the scatter plot indicates the number of zones subjected to nBV/TV measurement of one biopsy sample. The regression line represents a fictional “median patient” that is generated from the data of the sample. This model predicts the volume of newly formed bone for a given distance to SF. The mean nBV/TV declined in both the PM and M region with increasing distance to SF. This negative gradient was steeper in the M region compared with the PM region. At a distance of 8 mm from SF, nBV/TV is limited to 17.7% in the pre-molar region and 12.8% in the molar region

The 85 biopsies are derived from 55 patients, thereof 54 biopsies from 32 females and 31 biopsies from 23 males. Mean age of patients was 51.82 years (SD: 9.93) (female mean age: 52.47 years, SD: 8.93; male mean age: 50.9 years, SD: 11.33). Thirty-three biopsies were harvested from the pre-molar and 52 from the molar region.

The biopsies had a mean augmentation height of 4.58 mm (SD: 2.5). The minimum augmentation height was 0.45 mm and the maximum 11.35 mm. The frequency distribution among all biopsies is depicted in Figure 5. Biopsies with an augmentation height of 3 to 4 mm were the most numerous class in this sample ( $n = 17$ ) followed by biopsies with an augmentation height of 2 to 3 mm ( $n = 15$ ) and 7 to 8 mm ( $n = 11$ ). Augmentation heights of  $>8$  mm were observed in nine biopsies. No significant difference in the mean augmentation height was found between biopsies of the pre-molar and the molar region ( $P = 0.968$ ).

### 3.2 | nBV/TV in the pre-molar and the molar region

The vertical distribution of nBV/TV over the length of the augmentation area is depicted in Figure 2, demonstrating a mild negative gradient of nBV/TV along the augmentation area in the pre-molar region. The mean nBV/TV slightly

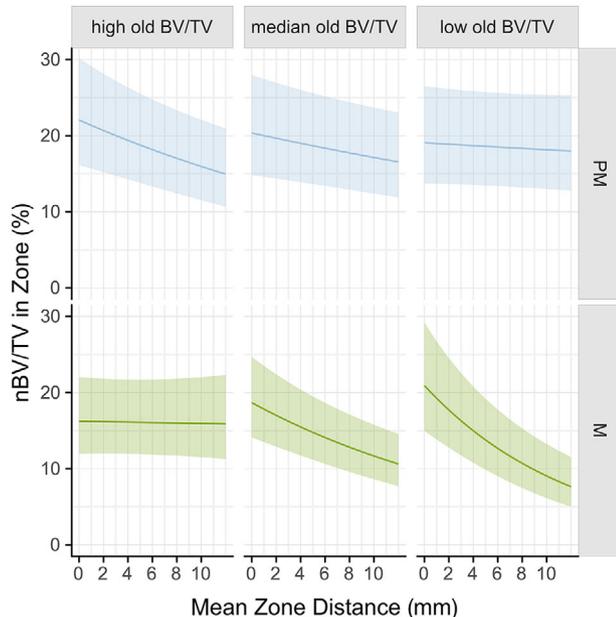
declined from 20.4% in the first 100- $\mu$ m zone adjacent to SF to 17.7% at a distance of 8 mm. In the molar region, the gradient was more pronounced within the same distance: nBV/TV decreased from 18.7% to 12.8%.

The distance of a zone to the SF was highly associated with nBV/TV within the respective zone ( $P \leq 0.001$ ).

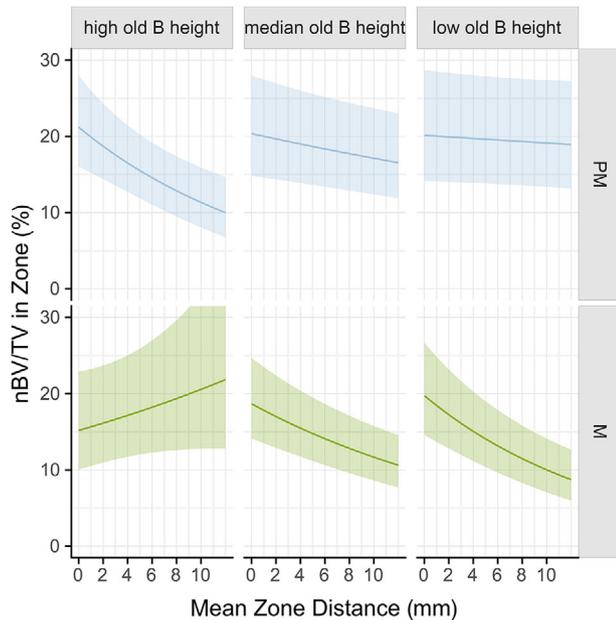
### 3.3 | Influence of oldBV/TV and oldB.Ht on the prediction of nBV/TV

To analyze the impact of the status of the residual bone of the SF on the prediction of nBV/TV, regression lines were calculated at low (Q1, 26.6%/0.7 mm), median (Q2, 38.4%/1.2 mm), and high (Q3, 48.8%/1.6 mm) values of oldBV/TV (%) and oldB.Ht (mm), respectively (Figs. 3 and 4):

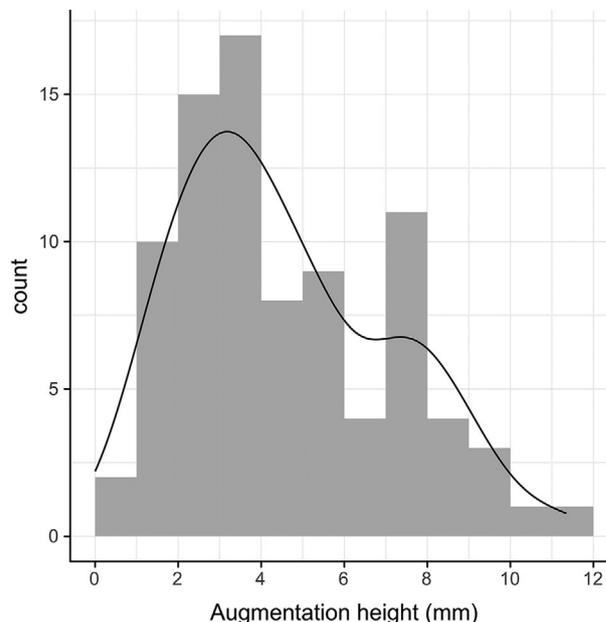
oldBV/TV (median: 42.0%) significantly influenced the prediction of nBV/TV in both regions ( $P < 0.001$ ). In the pre-molar region, the regression of nBV/TV for high oldBV/TV showed an exponential decline with increasing distance to the SF which most probably is a distortion due to the low number of long biopsies in this quartile. As indicated by the confidence band (Fig. 3, light blue) variation of new bone values within the respective zones is high, specifically in the pre-molar region.



**FIGURE 3** Different regression lines of the gradient of nBV/TV considering the volume fraction of the pre-existing residual bone of the sinus floor (oldBV/TV). The lines present slightly different predictions of nBV/TV, referring to low (Q1, 26.6%), median (Q2, 38.4%), and high (Q3, 48.8%) values of oldBV/TV (%). PM, premolar region; M, molar region



**FIGURE 4** Different regression lines of the gradient of nBV/TV considering the height of the pre-existing residual alveolar bone (oldB.Ht). The lines present slightly different predictions of nBV/TV, referring to low (Q1, 0.7 mm), median (Q2, 1.2 mm) and high (Q3, 1.6 mm) values of oldB.Ht (mm). PM, premolar region; M, molar region



**FIGURE 5** Distribution of augmentation heights (Histogram overlaid with kernel density estimate). The majority of biopsies had an augmentation height of 3 to 4 mm, followed by 2 to 3 mm and 7 to 8 mm. Biopsies with an augmentation height of >8 mm were less common

In the molar region, the decline of nBV/TV was significantly more distinct when oldBV/TV was low. While for high oldBV/TV, nBV/TV is limited to be 16.0% at a 8 mm distance, it is only 10.7% for low oldBV/TV.

oldB.Ht (median: 1.4 mm) also had a significant effect on the prediction of nBV/TV ( $P < 0.001$ ). In the premolar region, predictions followed the same trend as observed for oldBV/TV. By contrast, in the molar region, nBV/TV inclined from 15.2% to 19.4% when oldB.Ht was high, which again may be distorted by the low number of biopsies and indicated by the wide confidence band (Fig. 4, light green). The decline of nBV/TV was significantly more distinct when oldB.Ht was low/median, namely decreasing from 19.8% to 11.5% and 18.7% to 12.8%, respectively.

This implies that a low quantity of the pre-existing residual bone of the SF is expected to result in less nBF in the apical parts of the augmentation area in the molar region. Medium and high oldBV/TV and oldB.Ht on the other side alleviate this negative gradient observed for low oldBV/TV and low oldB.Ht.

## 4 | DISCUSSION

The elevation height of SM is generally determined by the oral surgeon based on the height of the residual bone of the SF, the desired implant length, the choice of bone graft and on preferences and experience. Clinical

recommendations on the elevation height of SM are rare and hardly have scientific basis. Whether a higher MSFA actually results in a larger graft consolidation remains open to date.

Thus, the aim of the present study was to quantify the vertical distribution of nBF in human sinus biopsies 6 months after MSFA. Assuming that the regeneration potential of bone is (predominantly) vested in the residual bone of the SF,<sup>4,10,11,18</sup> we hypothesized that the graft consolidation follows a gradient from native bone of the SF towards the apical part of the augmentation.

In fact, our results demonstrated that nBF declined with increasing distance to the residual bone of the SF which suggests the critical role of primordial bone for bone regeneration in MSFA.

The observed negative gradient is in line with others who reported a decrease of nBF in the more apical parts of the augmented area in animal and clinical studies.<sup>10,11,17,18,24,32,33</sup> Other studies could not detect a gradient, but a rather uniform distribution of new bone.<sup>5,34</sup>

The reason for these conflicting findings might be attributed to different (animal) models, evaluation methods (qualitative description of histological images, definition of analyzed zones) and healing periods. The latter must be regarded as a very important factor, since nBF and graft consolidation are dynamic processes that proceed and change the bone volume over time.<sup>35-37</sup> Comparing different models with different healing properties at different time points thus might result in the comparison of different levels of bone regeneration. A recent study of Kolerman et al.<sup>18</sup> reported notably higher nBV/TV measured within 2 mm zones after 9 months ( $\approx 30\%$  adjacent to the residual bone and  $23\%-27\%$  at a distance of 2 to 4 mm) which is difficult to compare with our results.

Interestingly, the predicted decline of nBV/TV was steeper in the molar than in the premolar region after 6 months. While nBV/TV adjacent to the SF was relatively similar in the premolar (20.4%) and the molar region (18.7%), the vertical distribution was very different: nBV/TV only slightly declined to 17.7% at a distance of 8 mm from the SF in the premolar region but dropped to 12.8% in the molar region. This suggests that nBF underachieves in the molar region even when the augmentation height is  $\geq 8$  mm. In other words, a large augmentation height in the molar region might not contribute to nBF in the more apical areas 6 months after MSFA.

While some studies found new bone sprouting also from the SM,<sup>8,9,38,39</sup> our results could not provide indications that SM plays a major role in this context. Our model was not designed to measure the influence of the SM since biopsy cores seldom extend exactly to the SM. However, the histological analysis of the biopsies revealed

that in the most apical part of many biopsies, graft particles close to the SM were frequently not integrated into new bone but tended to be surrounded by or encapsulated in poorly vascularized, fibrous connective tissue. This might be interpreted as an indirect hint that the osteogenic/osteoinductive role of the SM is at least only minor compared with that of SF.<sup>9</sup>

Fibrous tissue in the apical region of the augmentation area was also described by others<sup>40-42</sup> using various bone grafts for MSFA: Similarly to our histological observation, these fibrous areas were rich in fibroblasts and poor in blood vessels resembling scar tissue. Both, the sinus mucosa and the trap door/window of the lateral approach in MSFA were considered as a source of soft tissue invasion.<sup>33,41,43</sup> Based on the histological observations that fibrous tissue formation predominantly occurs in the apical portion of the augmentation area,<sup>41</sup> it seems reasonable to assume that nBF from the SF and soft tissue ingrowth from the apical side (SM or lateral window) stand in competition with each other.<sup>43</sup> From this point of view, an excessive augmentation height not necessarily results in a larger graft consolidation height but conceivably might be considered as a space holder critical to counteract fibrous tissue invasion from the SM or the lateral bone window.<sup>33</sup>

The second focus of the present study was laid on the role of the status of the SF on the vertical gradient of newly formed bone within the augmentation area. As demonstrated in a previous study,<sup>19</sup> the height and the volume fraction of the SF had a significant impact on the overall volume of newly formed bone within the total augmentation area. The worse the status of the residual alveolar bone, the less total nBV/TV was present in the augmentation area. As shown in this current study, oldB.Ht and oldBV/TV also had a significant impact on the vertical course of nBV/TV over the length of the augmentation: In the molar region, the gradient of nBV/TV was notably steeper when the status of the residual bone was poor: nBV/TV is limited to 10.7% at a distance of 8 mm from the SF when oldBV/TV is low. If, however, the bone volume fraction of the SF is high, nBF amounts to 16%. Unfortunately, long biopsies (augmentation height  $> 8$  mm) from the premolar region with high and dense residual bone are relatively rare which might have distorted the predictions for these subgroups (Figs. 3 and 4).

Given that the osteogenic potential in MSFA originates from the residual bone, it is plausible that a better overall state results in an augmented, accelerated healing capacity also in the apical parts of the augmentation. In practical terms, a timely augmentation as long as residual bone is not subjected to atrophy seems particularly reasonable in the molar region. Avila-Ortiz et al.<sup>44</sup> and Price et al.<sup>5</sup> could not demonstrate a relationship between the dimensions of



the residual crest and graft consolidation. However, they used circular histological cross-sections of human biopsies whereas our study used longitudinal sections through the long axis of biopsies, which allowed the continuous measurement of nBF over the whole length of the augmentation.

To obtain a more holistic picture of the influencing factors of nBF also the dimensions of the maxillary sinus should be considered. As reported by Klijn et al.<sup>45</sup> the width of the residual alveolar crest is significantly lower in the premolar than in the molar region. The same is true for the width of the maxillary sinus,<sup>46,47</sup> the distance between the medial/palatal and the lateral/buccal sinus wall is shorter and therefore narrower in the premolar region than in the molar region. Avila et al.<sup>33</sup> determined the impact of the buccal and palatal sinus walls on the amount of nBF 6 months after MSFA. The larger the buccopalatal distance, that is, the wider the sinus (as expected in the molar region), the less new bone was formed. By contrast, Pignaton et al.<sup>48</sup> could neither detect an influence of the sinus width (narrow/average/wide) nor the residual bone height ( $\leq 2$  mm and  $> 2$  mm) on the outcome of MSFA after 8 months. The situation in the augmented sinus is comparable with a three-wall defect as in periodontal bony defects or experimental monocortical drillhole defects in the animal calvaria. Unfortunately, we could only assess the influence of one wall, that is, the SF. The impact of the spatial relationship of the sinus walls and nBV/TV remains issue of future studies.

The same applies for the spatial relationship of nBV/TV and SM. Particularly in long biopsies, apical graft particles were often not integrated and tended to be encapsulated by fibrous tissue only. These rather loose graft particles often fragmented when the biopsy cores were harvested. In some cases it could not be entirely avoided that the most apical non-consolidated graft particles became lost during biopsy processing. However, completely fragmented biopsies were not included in the study to avoid bias. The low number of long biopsies is indeed a limitation of this study. In future studies, emphasis should be directed on the cautious extraction of biopsies and on imaging methods (such as computed tomography or MRI) before biopsy extraction. Computed tomography scans would provide valuable information about the exact position and extension of the biopsy, the sinus dimensions, and the vicinity of the biopsy to the sinus walls – another osteogenic source for bone regeneration within the maxillary sinus.

In this context, it needs to be mentioned that the height of the residual bone (“oldB.Ht”) in the present study was calculated by dividing the area of the pre-existing bone region by the diameter (width) of the biopsy. This method was applied to obtain a robust, consistent mea-

surement also of the few “geometric outliers” in which pre-existing bone was slightly angled or oblique due to natural anatomic variations of the SF.

The most significant limitation of this study is the heterogeneity of DBBM used as a biomaterial alone or in combination with different adjuncts. Most of the biopsy samples (59 of 85) were a combination of DBBM and aB/cells. In fact, statistical methods were used to compensate for the influence of DBBM and its combinations. Further studies using a more homogeneous sample are needed to verify the observed gradient.

## 5 | CONCLUSIONS

The results of the present study demonstrate that nBF declines with increasing distance to the residual bone of the SF. This gradient was more pronounced in the molar than in the premolar region. A poor overall condition of the residual bone of the SF is expected to result in less nBF in the apical parts of the augmentation area, particularly in the molar region. After a healing period of 6 months post-MSFA, graft particles in the apical portion of the augmentation areas tend to be loose and encapsulated by fibrous tissue. This most apical part of the MSFA ( $> 8$  mm distance to SF) appears to make only a minor contribution to the treatment outcome since nBF at this distance was relatively low. This might have clinical implications on the planning of the lifting height of SM in MSFA and thus on the choice of the implant length thereby providing the basis for the establishment of MSFA height recommendations in the future.

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## AUTHOR CONTRIBUTIONS

Dr. Beck contributed to concept/design, data collection, and drafting article and approval of the article. Dr. Reich contributed to concept/design, data collection, and drafting and approval of the article. Lettner contributed to concept/design, data collection, and approval of the article. Heibel contributed to concept/design, data collection, and drafting and approval of the article. Dr. Tangl contributed to data collection and drafting and approval of the article.

Prof. Dr. Redl contributed to data collection and drafting and approval of the article. Prof. DDR. Ulm contributed to concept/design and drafting and approval of the article.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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