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New bone formation after transcrestal sinus floor elevation was influenced by sinus cavity dimensions: A prospective histologic and histomorphometric study

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Abstract

Objective: The aim of this multicenter prospective study was to analyze clinically and histologically the influence of sinus cavity dimensions on new bone formation after transcrestal sinus floor elevation (tSFE).

Material and Methods: Patients needing maxillary sinus augmentation (residual crest height <5 mm) were treated with tSFE using xenogeneic granules. Six months later, bone-core biopsies were retrieved for histological analysis in implant insertion sites. Bucco-palatal sinus width (SW) and contact between graft and bone walls (WGC) were evaluated on cone beam computed tomography, and correlations between histomorphometric and anatomical parameters were quantified by means of forward multiple linear regression analysis.

Results: Fifty consecutive patients were enrolled and underwent tSFE procedures, and forty-four were included in the final analysis. Mean percentage of newly formed bone (NFB) at 6 months was 21.2 ± 16.9%. Multivariate analysis showed a strong negative correlation between SW and NFB (R^2 = .793) and a strong positive correlation between WGC and NFB (R^2 = .781). Furthermore, when SW was stratified into three groups (<12 mm, 12 to 15 mm, and >15 mm), NFB percentages (36%, 13% and 3%, respectively) resulted significantly different.

Conclusions: This study represented the first confirmation based on histomorphometric data that NFB after tSFE was strongly influenced by sinus width and occurred consistently only in narrow sinus cavities (SW <12 mm, measured between buccal and palatal walls at 10-mm level, comprising the residual alveolar crest).

KEYWORDS

histomorphometry, osteotomes, sinus floor elevation, sinus width, transcrestal

1 | INTRODUCTION

Sinus floor elevation is today the most widespread treatment option for maxillary posterior ridges with insufficient bone height to allow implant-supported rehabilitations. Sinus augmentation with lateral approach, proposed in 1976 by Tatum and first published by Boyne and James (1980), has been extensively studied afterwards, representing now an effective and predictable treatment (Aghaloo & Moy, 2007; Pjetursson, Tan, Zwahlen, & Lang, 2008).

Transcrestal sinus floor elevation (tSFE), which was first proposed by Tatum (1986), has been introduced as a more conservative and minimally invasive alternative to the lateral approach. In this procedure, an osteotomy is performed through the residual crest and the sinus floor using various devices, such as osteotomes, specially

designed burs, ultrasonic instruments, or combinations of the above (Cosci & Luccioli, 2000; Kim et al., 2012; Lee, Kang-Lee, Park, & Han, 2009; Summers, 1994; Troedhan, Kurrek, Wainwright, & Jank, 2010; Trombelli et al., 2014). After obtaining the fracture of the sinus floor, Schneiderian membrane is indirectly elevated by progressive increments of biomaterial, or by hydrodynamic pressure or by the implant itself, according to the different techniques.

Despite the use of different approaches, both lateral and transcrestal procedures are performed with the aim to create a space between sinus floor and Schneiderian membrane and fill it with bone grafting materials or blood clot in order to regenerate new osseous tissue and enhance vertical bone volume.

A variety of different biomaterials have been tested for lateral sinus augmentation: Even if autogenous bone has been regarded for a long time as the gold standard, nowadays bone substitutes (allografts, xenografts and synthetic materials) can be considered as reliable alternatives (Dursun et al., 2016; Mangano et al., 2015; Monje et al., 2017; Portelli et al., 2017; Stacchi, Lombardi, Oreglia, Alberghini Maltoni, & Traini, 2017), showing also high dimensional stability over time (Favato et al., 2015). Nature and quality of the newly formed tissue were analyzed in-depth: a recent systematic review examined more than 250 publications reporting histomorphometric data of biopsies collected at various time points from sinuses grafted by lateral approach (Danesh-Sani, Engebretson, & Janal, 2017). Unfortunately, to our knowledge, similar data are not available in the literature for the regenerative outcomes of tSFE. Only two case reports (Bernardello, Massaron, Spinato, & Zaffe, 2014; Trombelli, Franceschetti, Trisi, & Farina, 2015) and two case series (Esfahanizadeh et al., 2012; Wainwright et al., 2016) presented histomorphometric data for a total of 19 biopsies retrieved after 6 months of healing, using different biomaterials. Furthermore, new bone formation reported in these studies varied considerably (range 7.6%–75.1%), indicating that healing process after tSFE was not homogeneous or predictable, but no hypotheses were expressed to explain this variability.

The role of three-dimensional anatomical sinus characteristics in conditioning healing and mineralization process after regenerative procedures is not well defined yet. The influence of the buccopalatal width of the sinus on the amount of new bone formation and on graft stability over time has been speculated both for lateral and transcrestal sinus augmentation. Previous studies demonstrated with histologic data a negative correlation between sinus width and new bone formation after performing lateral augmentation (Avila et al., 2010; Kolerman, Tal, & Moses, 2008; Soardi, Spinato, Zaffe, & Wang, 2011). Radiographic studies by Spinato, Bernardello, Galindo-Moreno, and Zaffe (2015), Zheng et al. (2016) and Cheng et al. (2017) showed a positive correlation between graft resorption and sinus width after tSFE. The hypothesis that sinus dimensions and shape could influence new bone formation after tSFE has been expressed by a recent pilot study with histologic and histomorphometric analyses on a small number of patients (Lombardi et al., 2017): This factor could possibly explain the great variability of results found in the above-mentioned studies (Esfahanizadeh et al., 2012; Wainwright et al., 2016).

Therefore, the aim of this multicenter prospective study was to analyze clinically and histologically the influence of sinus cavity dimensions on new bone formation after tSFE. The null hypothesis of this study is that there was no difference in new bone formation (detected by histologic and histomorphometric parameters) when tSFE was performed in sinuses of different bucco-palatal width.

2 | MATERIAL AND METHODS

2.1 | Study protocol

The present multicenter prospective single-cohort study was reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org). STROBE checklist may be found online in the supporting information tab for this article. All procedures were performed in strict accordance with the recommendations of the Declaration of Helsinki as revised in Fortaleza (2013) for investigations with human subjects. The study protocol was approved by the Unified Ethical Regional Committee (C.E.R.U.) of Friuli Venezia Giulia, Italy (approval n. 60/2015/OS) and was registered in the database of the National Institutes of Health for Clinical Trials (NCT03209284). All patients signed an informed consent form to document that they understood the aims of the study (including procedures, follow-up evaluations, and any potential risk involved) and authorized the use of their data for research purposes. Patients were allowed to ask questions pertaining to this study and were thoroughly informed of possible alternative treatments.

2.2 | Selection criteria

Any patient requiring unilateral sinus floor elevation for single implant placement, based on accurate diagnosis and treatment planning, was eligible for entering this study. All subjects underwent a preliminary visit including evaluation of their medical and dental history and thorough clinical examination.

Patients were consecutively enrolled in this study, provided that they complied with the following inclusion criteria:

- the presence of a residual bone crest with a height <5 mm on the maxillary sinus floor in the site where implant placement was programmed;
- healed bone crest (at least 6 months elapsed after tooth loss);
- age >18 years;
- patient willing and fully capable to comply with the study protocol;
- written informed consent given.

Patients were excluded from this study if presenting one of the following general exclusion criteria:

- absolute contraindications to implant therapy (Hwang & Wang, 2006)
- irradiated in the head and neck area

- uncontrolled diabetes (HBA1c > 7.5%)
- pregnant or breastfeeding
- heavy smokers (>20 cigarettes/day)
- participating in other studies, if the present protocol could not be properly followed.

Local exclusion criteria consisted of the following:

- maxillary sinus pathologies contraindicating sinus augmentation
- acute oral infections
- poor oral hygiene and motivation (full mouth plaque score >30)
- untreated periodontal disease
- Schneiderian membrane perforation during surgery.

Patients were recruited and treated in Trieste University hospital and two private practices (Cassano allo Ionio and Genova, Italy) by three experienced operators (CS, TL, RO). The same operators performed all follow-up visits and recorded eventual complications and adverse events.

2.3 | Presurgical phase

Patients included in the study were carefully examined assessing periodontal conditions (probing and periapical radiographs), residual bone volume/maxillary sinus anatomy (CBCT scan), and occlusal relationships (diagnostic wax-up). A surgical guide in transparent acrylic resin was manufactured by duplicating the diagnostic wax-up.

Patients underwent deplaquing 1 week prior to surgery and were prescribed with chlorhexidine digluconate 0.2% mouthwash twice a day starting 3 days before surgery and then daily for 10 days.

2.4 | Surgical procedure

Patients were premedicated with 2 g of amoxicillin/clavulanate potassium one hour prior to the surgery. Perioral skin was disinfected using iodopovidone 10%, and subjects were asked to rinse with chlorhexidine mouthwash 0.2% for 30 s. Under local anesthesia (articaine 4% with epinephrine 1:100,000 – Artin, Omnia S.p.A., Fidenza, Italy), a minimally invasive full-thickness flap was raised and, with the assistance of the surgical guide, a transcrestal access to the sinus was performed using calibrated drills with stops (Mica, MegaGen Implant Co. Ltd, Gyeongbuk, South Korea). After checking the integrity of the Schneiderian membrane with Valsalva maneuver, sinus was grafted by condensing gradual increments of xenogeneic granules (Smartbone, IBI SA, Mezzovico-Vira, Switzerland), until a minimum height of 10 mm was obtained (comprising the residual bone crest).

The crestal access to the sinus was finally protected with hemostatic collagen sponges (Hemocollagene, Septodont SAS, Saint-Maur-des-Fossés, France), and flaps were closed with Sentineri sutures (Sentineri, Lombardi, Berton, & Stacchi, 2016) and single stitches using synthetic monofilament (PTFE, Omnia S.p.A., Fidenza, Italy).

Patients were prescribed with antibiotics for 6 days (amoxicillin 1 g twice a day or, in allergic patients, clarithromycin 250 mg twice a day) and NSAID (ibuprofen 600 mg), when needed.

Sutures were removed, and a control CBCT scan was performed after 10 days. Postsurgical visits were scheduled at 30-day intervals to check the course of healing.

After 6 months, a CBCT scan was performed to evaluate the volumetric outcome of the regenerative procedure and to plan implant insertion. With the assistance of the surgical template, a bone-core biopsy was harvested in each grafted area by using 3-mm-diameter trephine drills (2982.Y0.30, DenTag S.r.l., Maniago, Italy), and a dental implant was inserted in the site (AnyOne, MegaGen Implant Co. Ltd, Gyeongbuk, South Korea). Implants were left submerged for an additional 4-month healing period and then were restored with screwed ceramic crowns.

2.5 | Radiographic measurements

Measurements were taken from the three CBCT cross-sectional slices (step 1 mm; width 1 mm) corresponding to the position where the biopsy was retrieved. Two independent calibrated examiners (CS and FB) measured (i) residual bone height (RBH) between the alveolar ridge and the sinus floor; (ii) sinus width (SW) (distance between buccal and palatal walls at 10-mm level, comprising the residual alveolar crest, as described by Avila et al. (2010) and Soardi et al. (2011)); (iii) number of sinus bone walls in contact with the graft (WGC) (2: graft in contact with both lateral and medial walls; 1: graft in contact with lateral or medial wall; 0; graft not in contact with both lateral and medial bone walls); (iv) maximum graft height (GH) from the sinus floor (at 10 days and at 6 months after surgery); (v) total crestal height (CH) at 6 months (RBH+GH). Distances were measured using the specific tool of an imaging software (OsiriX MD, Pixmeo SARL, Bernex, Switzerland). RBH, SW, GH, and CH were expressed in millimeters. Intra-examiner and inter-examiner repeatability were assessed though the intra-class correlation coefficients on 10 pairs of recordings randomly selected (Shrout & Fleiss, 1979). All the coefficients for the intra- and inter-examiner repeatability for RBH, SW, GH, and CH were at least 0.98.

2.6 | Sample processing for histological analysis

Blinded histologic and histomorphometric assessment of all specimens was performed by one of the authors (TT). The biopsies, left inside the trephine burs to maintain the orientation of the bone cores, were carefully rinsed with cold 5% glucose solution to remove blood residuals maintaining the correct osmolarity (278 mOsm/L).

Specimens were subsequently fixed for 5 days in a 10% buffered formalin solution at pH 7.2, washed in sodium phosphate-buffered solution, and then dehydrated in an ascending series of alcohol rinses. After preinfiltration treatment for 10 days in a 50% resin/alcohol solution (LR White, London Resin Co. Ltd., Aldermaston, United Kingdom), bone cores were easily removed from trephine burs with a custom-made plunger. Complete infiltration with 100% embedding resin solution (two changes) was obtained using a vacuum chamber until specimens have become transparent (approximately 10 days).

After thermal prepolimerization at 61°C for eight hours, specimens were further included in a photo-activated resin (Technovit 7200 VLC, Kulzer, Germany) to facilitate their orientation for the cutting procedures. After final polymerization, undecalcified sections were cut at 50 μm using a high-precision cutting system with a circular diamond disc and then ground down to about 30 ± 10 μm under running water with a series of polishing discs from 400 to 1,200 grit, followed by final polishing with 0.1 μm alumina particles in a microgrinding system (TT System, TMA2, Grottammare, Italy).

Histological slides were then multistained with Ladewig fibrin stain, toluidine blue/Azure II counterstained with acid fuchsine or double stained with toluidine blue/pironine G at 1% and Azure II.

2.7 | Histomorphometry

The following variables were measured: (i) total area of the biopsy (in mm^2), (ii) percentage of newly formed bone (NFB), (iii) percentage of connective tissue/marrow spaces (MS), and (iv) percentage of residual graft particles (RG). The analysis was performed using transmitted brightfield light microscopes (BX 51, Olympus America Inc., Melville, NY, USA or Axiolab, Carl Zeiss AG, Oberkochen, Germany), connected to high resolution digital camera (FinePix S2 Pro; Fujifilm Holding Corp., Tokyo, Japan). A software with image capturing capabilities (Image-Pro Plus 6.0; Media Cybernetics Inc., Bethesda, MD, USA) was used to collect and analyze images. Software was calibrated for each experimental image by means of the "Calibration Wizard" feature, which reports the number of pixels between two selected points (cover slip with a square grid of 1 mm). Linear remapping of the pixel numbers was used to calibrate the distance in μm or in mm in function of the degree of magnification.

2.8 | Predictor and outcome variables

This prospective study tested the null hypothesis of no differences in new bone formation among sinuses of different width against the alternative hypothesis of a difference.

The primary predictor variables were sinus width (SW) and the number of sinus walls in contact with the graft (WGC). Other variables, possibly correlated with the predictor and outcome variables, were also included as follows: (i) patient related variables, including age, gender and smoking status (ii) anatomical variables, including residual bone height (RBH).

Primary outcome measure:

- new bone formation (NFB) after 6 months of healing

Secondary outcome measures:

- radiographic findings: graft resorption (GR: difference between GH at 10 days and GH at 6 months)
- implant failure: implant mobility or implant removal suggested by progressive marginal bone loss. Implant stability was tested by tightening abutment screws (35 N/cm) at prosthesis delivery
- any complications or adverse events

2.9 | Statistical analysis

SPSS software, version 13.0 (SPSS® Inc., Chicago, Illinois, USA), was used to perform statistical analyses. Data normality was tested with Kolmogorov–Smirnov test and Q-Q normality plots of the residuals and equality of variance among the datasets using a Levene test. All datasets met the required assumptions for using parametric methods, with few exceptions (NFB and GR) where root-square transformations were required to produce a normal distribution. Descriptive statistics included mean, standard deviation, and median.

Differences in NFB and in GR among cases grouped according to either SW (as <12 mm, 12–15 mm and >15 mm) or WGC (as 0-wall, 1-wall and 2-wall) were evaluated by means of one-way analysis of variance (ANOVA), followed by Bonferroni's corrected independent sample *t* test.

Finally, forward multiple linear regressions were performed to identify the variables affecting either NFB or GR (both entered after root square transformation). In particular, age, gender, smoking habits, RBH, SW, and WGC were entered as independent variables. RBH and SW were entered as continuous variables, while WGC was entered as a dummy variable with the 0-wall group as a reference category. Moreover, GR and NFB were also entered for NFB and GR models, respectively. To avoid collinearity among the explanatory variables, by means of variance inflaction factor and tolerance, SW and WGC were entered separately in two different models. Correlation between SW and WGC was also evaluated by means of Spearman's correlation coefficient (−.814, $p < .001$). The cutoff levels of significance were .05 and .10 for entry and removal, respectively. A p-value < .05 was considered as being statistically significant.

3 | RESULTS

3.1 | Study population and clinical results

Fifty consecutive patients (25 males and 25 females, age range between 31 and 84, mean 58.3 ± 9.8, 13 smokers, 37 no smokers) were included in this study and underwent transcrestal floor elevation. Surgeries were performed between July 2014 and September 2015 by three experienced operators (CS $n = 25$; TL $n = 16$; RO $n = 9$). Three patients dropped out from the study due to Schneiderian membrane perforation during surgery (3/50–6%): in two of these cases surgical procedure continued by opening a window on the lateral sinus wall, followed by perforation sealing with autologous platelet-rich fibrin membranes and graft insertion, in the third case procedure was aborted. One patient dropped out from the study for infective complications: She presented 3 weeks after surgery with swelling, pain, and exudate from the wound. Graft was immediately removed after opening a lateral bone window, and patient was prescribed with antibiotics for 10 days. Two more patients were excluded from the analysis because presented a late dissemination of the grafting material, without associated symptoms: Graft was present in the CBCT scan performed 10 days after surgery but disappeared completely after 6 months. In total,

six patients out of 50 (12%) presented some intra or postoperative complications.

Healing was uneventful in 44 patients, which were included in the final analysis: 44 bone-core biopsies were harvested, and 43 implants were inserted in the grafted sinuses. It was impossible to insert one implant due to lack of primary stability. Forty implants were osseointegrated after 4 months of healing (93.0%), and all of them resulted satisfactorily in function after 1 year of prosthetic loading.

Table 1 presents main demographic characteristics and clinical outcomes of the patients included in the final analysis.

3.2 | Histologic and histomorphometric analyses

The total biopsy area (BA), measured on longitudinal sections of retrieved bone cores, was 851.6 mm^2. After 6 months of healing, the cumulative percentage of NFB was 21.2 ± 16.9%, MS was 61.3 ± 12.6%, and RG was 17.5 ± 8.8%. Histological analysis showed remarkable differences among samples with special reference to the characteristics of density, presence, and amount of newly formed bone (Figure 1). NFB values according to SW and WGC score are summarized in Tables 2 and 3.

In particular, when SW was stratified into three different categories (<12, 12 to 15, and >15 mm), it was observed that as SW increases, NFB percentage decreases. When SW was <12 mm, after 6 months of healing mean NFB was 36%, MS was 52%, and RG 12% (Figure 2). In the group with SW comprised between 12 mm and 15 mm, NFB was 13%, MS was 65%, and RG 22%, while in the wider sinuses (>15 mm), NFB was 3%, MS was 74%, and RG 23% (Figure 3). Differences among groups resulted statistically significant. Moreover, at the pairwise comparisons, 12–15 mm and >15 mm groups yielded NFB percentage values significantly greater as compared to those of the <12 mm group. Similarly, NFB percentage recorded in >15 mm group was significantly lower as compared to that of 12–15 mm group.

WGC groups (0, 1, and 2 bone walls in contact with the graft) also showed a direct correlation with NFB percentage after 6 months of healing. When graft was in contact with both lateral and medial sinus walls (WGC 2), mean NFB was 34%, MS was 54%, and RG 12%. Microscopically, the histological appearance of samples of this group showed intense osteoblastic activity, the presence of new blood vessels, and some multinucleated giant cells (Figure 4).

In the group where graft was in contact with one sinus wall (WGC 1), NFB was 9%, MS was 67%, and RG 24%, and when graft had no bone contact (WGC 0), being surrounded only by the sinus membrane, NFB was 3%, MS was 74%, and RG was 23%. The microscopic appearance of samples of these groups showed particles of biomaterial encapsulated by fibrous tissue with many fibroblasts and few areas of newly formed bone (Figure 5). Differences among groups were statistically significant. Moreover, at the pairwise comparisons, WGC 2 and WGC 1 groups yielded NFB percentage values significantly greater as compared to those of WGC 0 group. Similarly, NFB percentage recorded for WGC 2 group was significantly lower as compared to that of WGC 1 group.

3.3 | Radiographic measurements

Patients included in this study (n = 44) presented RBH ranging from 1.1 to 4.9 mm (mean 3.4 ± 1.1 mm), as measured on the respective CBCT cross-sectional slices. CH after 6 months ranged from 6.1 to 18.8 mm (mean 12.0 ± 2.6 mm), with a mean CH increase of 8.6 ± 2.7 mm. Evaluated sinuses (n = 44) had a mean SW of 12.8 ± 3.3 mm and a median of 12.2 mm.

WGC score was 2 in 24 patients (54.5%—mean SW of the group 10.6 ± 1.8 mm), in 10 cases WGC was 1 (22.7%—mean SW of the group 13.6 ± 2.0 mm), in the last ten cases (22.7%—mean SW of the group 17.3 ± 2.2 mm), the graft had no contact with both lateral and medial bone walls, being completely surrounded by the Schneiderian membrane (WGC = 0).

GH measured 10 days after surgery ranged between 6.8 and 17.2 mm (mean vertical gain 10.3 ± 2.2 mm); after 6 months of healing, GH ranged between 2.9 and 16.7 mm (mean vertical gain 8.6 ± 2.7 mm). Mean GR after 6 months was 1.7 ± 1.5 mm (range 0.1–7.7 mm), and its values according to SW and WGC score are summarized in Tables 2 and 3. GR was lower in SW <12 mm and in WGC 2 groups, while was higher in SW >15 mm and WGC 0 groups. Differences among groups were statistically significant. Moreover, at the pairwise comparisons, only WGC 2 and SW <12 mm groups yielded GR values significantly lower as compared to WGC 0 and SW >15 mm groups, respectively.

Mean SW and WGC of patients with the three failed implants were 18.5 ± 2.0 mm and 0, respectively. Mean RBH of patients with failed implants was 2.9 ± 0.9 mm (range 2.1–4.1 mm), and it was not significantly different from mean RBH of the entire population.

Multiple forward linear regression models with NFB after 6 months of healing as dependent variable showed a significant positive association with WGC (R^2 = .781, beta coefficients, .927 and 4.115 for the one-wall and two-wall groups, respectively), and a significant negative association with SW (R^2 = .793, beta coefficient, −.927). Multiple forward linear regression models with GR after six months of healing as dependent variable showed a significant negative association with WGC (R^2 = .192, beta coefficient, −.468 for the two-wall group), and a significant, although weak, negative association with NFB (R^2 = .140, beta coefficient, −.093). Complete results are summarized in Table 4.

4 | DISCUSSION

The present study was the first to demonstrate with histomorphometric data that new bone formation after tSFE is negatively correlated with bucco-palatal sinus width and positively correlated with the number of sinus walls in contact with the grafting material. As a general rule, bone regeneration is more effective in defects which are completely surrounded by vital bone, because neoangiogenesis and migration of mesenchymal osteoprogenitors cells are the most important factors in promoting osseous healing (Carano & Filvaroff, 2003; Retzepi & Donos, 2010). A close contact between grafting

TABLE 1 Demographic characteristics and clinical outcomes of the patients included in the final analysis

ID	Gender	Age	Smoke	RBH (mm)	6 months CH (mm)	CH Increase (mm)
1001	F	72	NS	3.2	13.2	10.0
1002	F	56	NS	2.7	10.6	7.9
1003	M	60	S	4.5	12.6	8.1
1004	M	61	NS	2.1	18.8	16.7
1005	M	50	S	2.8	12.6	9.8
1006	M	69	S	2.1	13.2	11.1
1007	F	66	NS	2.9	14.8	11.9
1008	F	76	NS	3.8	14.1	10.3
1009	F	59	S	4.7	14.8	10.1
1010	M	63	NS	4.8	14.7	9.9
1011	M	58	NS	4.7	11.5	6.8
1012	F	61	NS	4.1	10.4	6.3
1013	F	62	NS	2.7	11.9	9.2
1014	M	84	NS	2.8	14.7	11.9
1015	M	51	NS	2.1	14.8	12.7
1016	F	75	NS	4.9	10.6	5.7
1017	M	42	NS	1.9	7.5	5.6
1018	F	61	S	1.7	11.5	9.8
1019	M	57	NS	2.6	8.2	5.6
1020	F	53	NS	4.8	15.0	10.2
1021	F	48	NS	4.7	12.3	7.6
2001	M	48	NS	4.5	12.1	7.6
2002	M	31	S	4.9	15.4	10.5
2003	F	54	NS	4.8	14.7	9.9
2004	M	54	NS	3.6	14.3	10.7
2005	F	53	NS	1.7	10.6	8.9
2006	M	39	NS	3.9	8.4	4.5
2007	M	39	NS	4.8	10.8	6.0
2008	F	63	NS	2.4	13.3	10.9
2009	M	69	NS	3.8	11.3	7.5
2010	M	69	NS	4.2	8.4	4.2
2011	F	56	S	4.8	16.1	11.3
2012	F	53	NS	3.2	6.1	2.9
2013	F	59	NS	2.5	12.9	10.4
2014	F	64	NS	4.7	11.2	6.5
3001	M	55	NS	1.8	11.7	9.9
3002	M	55	NS	2.1	11.1	9.0
3003	F	57	S	4.1	12.8	8.7
3004	M	65	NS	4.3	10.4	6.1
3005	M	61	S	3.5	8.1	4.6
3006	F	58	NS	1.9	9.9	8.0
3007	F	58	NS	3.1	7.2	4.1
3008	F	56	S	1.1	11.8	10.7
3009	M	60	S	2.7	12.4	9.7
Overall	22 F/22 M	58.2 ± 9.9	11 S/33 NS	3.4 ± 1.1	12.0 ± 2.6	8.6 ± 2.7

CH, crestal height; F, female; ID, patient identification code; M, male; NS, no smoker; RBH, residual bone height; S, smoker.
Overall refers to the entire sample.
Data are presented as mean ± standard deviation.

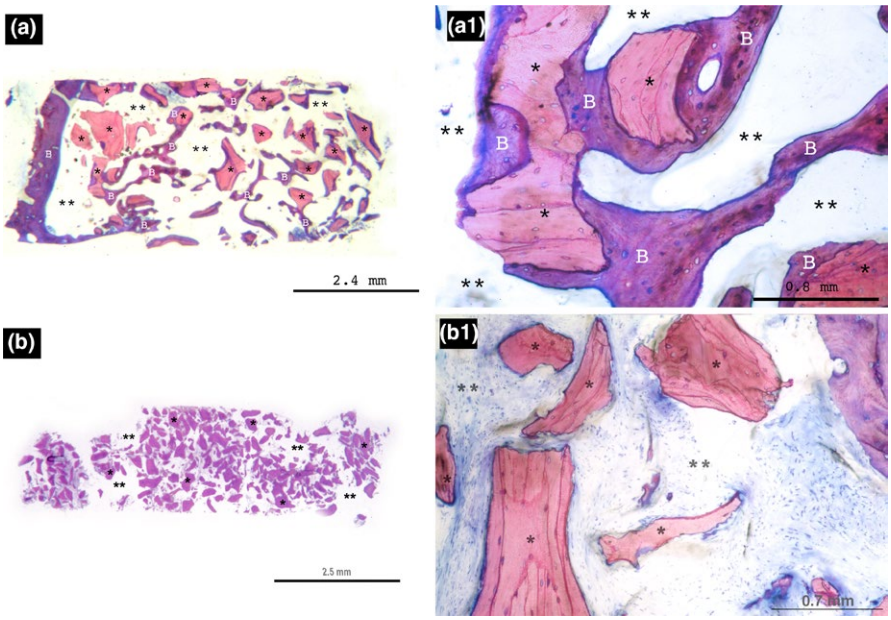

FIGURE 1 In (a), bone biopsy from a narrow maxillary sinus with lateral and medial sinus walls in contact with the grafting material. Original magnification 12×. Toluidine blue and pironine G stain. (*) residual biomaterial particles; (**) bone marrow spaces; (B) newly formed bone. In (a1), magnification 200× of (a), residual biomaterial particles (*) appeared surrounded and joined together by newly formed bone trabeculae (B). (**) bone marrow spaces. Toluidine blue and pironine G stain. In (b), bone biopsy from a wide maxillary sinus with no contact between lateral and medial sinus walls and the grafting material. Original magnification 12×. Toluidine blue stain. (*) residual biomaterial particles; (**) connective tissue. In (b1), magnification 200× of (b), residual biomaterial particles (*) appeared to be surrounded by soft tissue (**). Azure II and fuchsine acid stain

TABLE 2 NFB and GR at 6 months according to SW (n = 44)

	Groups			
Parameter	<12 mm	12–15 mm	>15 mm	Significance
n	21	11	12	–
NFB (%)	35.6 ± 11.2	13.1 ± 8.9 a	3.3 ± 3.1 a,b	<0.001; S
GR (mm)	1.2 ± 1.7	1.9 ± 1.2	2.3 ± 1.1 a	0.024; S

Data are presented as mean ± standard deviation. NFB, newly formed bone; GR, graft resorption; SW, sinus width. Results at the multiple pairwise comparisons: a, significantly different than the <12 mm group; b, significantly different than the 12–15 mm group. S, significant.

TABLE 3 NFB and GR at 6 months according to WGC (n = 44)

	Groups			
Parameter	0-wall	1-wall	2-wall	Significance
n	10	10	24	–
NFB (%)	2.6 ± 2.8	9.2 ± 6.1 a	33.9 ± 11.7 a,b	<0.001;S
GR (mm)	2.5 ± 1.1	2.0 ± 1.3	1.2 ± 1.6 a	0.012; S

Data are presented as mean ± standard deviation. NFB, newly formed bone; GR, graft resorption; WGC, sinus walls in contact with graft. Results at the multiple pairwise comparisons: a, significantly different than the 0-wall group; b, significantly different than the one-wall group. S, significant.

material and bone walls is also crucial for a fast and effective delivery in the regeneration area of nutrients, oxygen supply, and osteogenesis mediators (e.g., bone morphogenetic proteins, alkaline phosphatase, osteopontin, osteonectin, osteocalcin) at the early stages of healing (De Santis et al., 2017; Scala et al., 2010).

Sinus walls, sinus floor, and Schneiderian membrane represent the potentially osteogenic surfaces which may be in contact with the grafting material after sinus floor elevation procedures. The lateral wall, despite its anatomical composition which is mainly cortical bone, has been reported to have high osteogenic potential

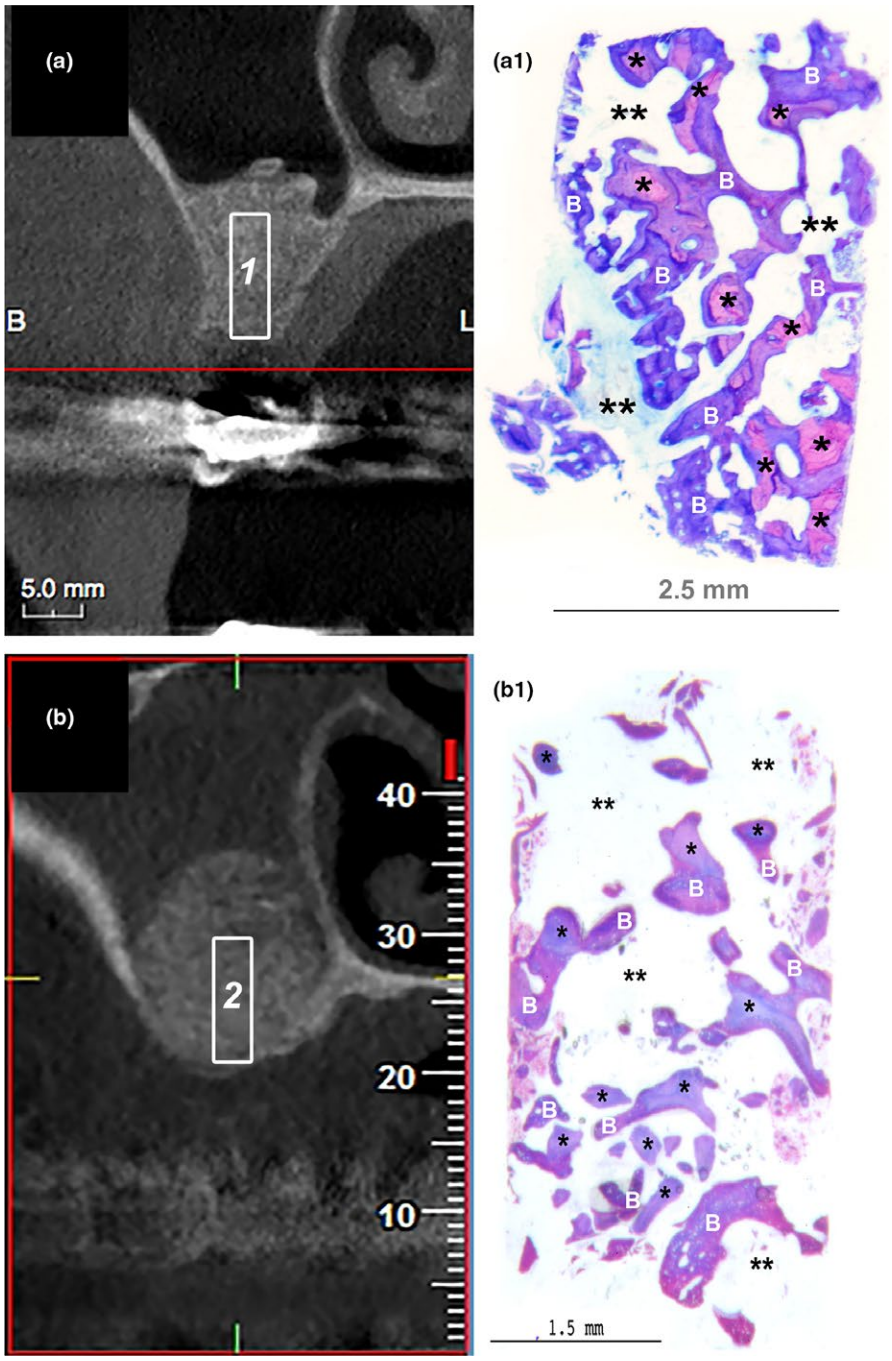

FIGURE 2 Two illustrative CBCT cross-sectional slices taken from two patients after the surgical procedure were represented in (a) and (b). Both lateral and medial sinus walls appeared in contact with the grafting biomaterial: in (a) sinus width was narrower than in (b). The rectangles 1 and 2 approximately indicated the area of bone biopsies retrieved after 6 months of healing. In (a1), the histological analysis showed several trabeculae of newly formed bone (B) with some biomaterial particles (*) completely surrounded by bone. Several marrow spaces (**) were also present. Toluidine blue and pironine G stain (25× magnification). In (b1), bony trabeculae were less represented than in (a1). Biomaterial particles (*) were surrounded by newly formed bone (B) and marrow spaces (**) appeared well represented. Toluidine blue and pironine G stain (25× magnification)

(Johansson, Isaksson, Lindh, Becktor, & Sennerby, 2010) and to present a significant quote of vital osteocytes (Zaffe & D'Avenia, 2007): hence, excessive dimensions of the bony window during lateral sinus augmentation seem to have a negative influence on maturation and consolidation of the newly formed tissue (Avila-Ortiz et al., 2012). The medial sinus wall represents another important source for cells and vascularization: An adequate Schneiderian membrane detachment permits to expose a larger bone surface, favoring graft vascularization, cells colonization, and new bone formation (Margolin et al., 1998; Wallace, 2006). Moreover, the mineralization of a grafted area in the maxillary sinus starts near the floor of the sinus and along lateral and medial walls, advancing in centripetal direction (Busenlechner et al., 2009). This progression is anticipated by vascular ingrowth and distribution of osteoprogenitor cells following the same pattern (Margolin et al., 1998).

Role of Schneiderian membrane in intra-sinusal bone regeneration has been widely discussed. *In vitro* experiments demonstrated the presence in the membrane of mesenchymal progenitor cells and cells committed to the osteogenic lineage (Gruber, Kandler, Fuerst, Fischer, & Watzek, 2004; Srouji et al., 2009), but recent studies questioned the real clinical contribution coming from this source. Scala et al. (2010, 2012) and Jungner et al. (2015), in histologic studies on monkeys, demonstrated that bone formation after sinus floor elevation started from the residual crest and from bony walls, without a

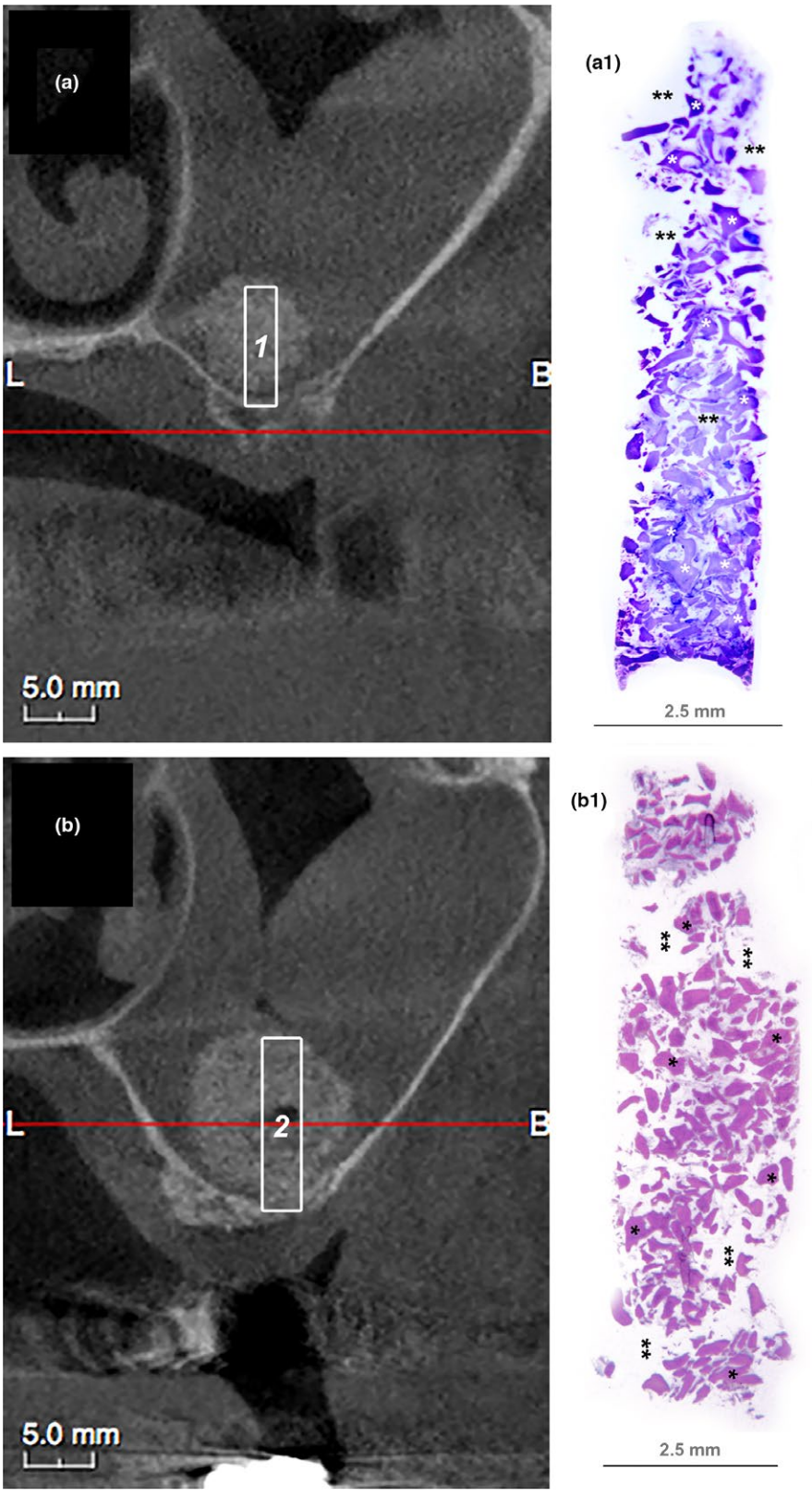

FIGURE 3 Two illustrative CBCT cross-sectional slices taken from two patients after the surgical procedure were represented in (a) and (b). Sinus width was >15 mm, and grafting biomaterial was in contact only with medial sinus wall (a) or had no contact with sinus walls (b). The rectangles 1 and 2 approximately indicated the area of bone biopsies. In (a1), histological analysis showed the absence of bony trabeculae, with biomaterial particles (*) completely filling the biopsy area. Marrow spaces (**) were poorly represented due to the high compaction of biomaterial particles. Toluidine blue stain (25× magnification). In (b1), histological appearance is comparable to (a1). Toluidine blue and pironine G stain (25× magnification)

direct participation of the membrane in the process. Rong, Li, Chen, Zhu and Huang (2015), in a canine model, evaluated the regenerative contribution of the single components by physically separating bone walls or Schneiderian membrane from the graft by ultrathin titanium sheets. This study confirmed that membrane presents some osteogenic potential but its effective role in sinus floor elevation is much weaker than that of the surrounding bone walls. Furthermore, a recent animal study investigating the influence of a resorbable barrier membrane placed subjacent to a pristine sinus mucosa on the healing outcome of a sinus floor elevation procedure showed that

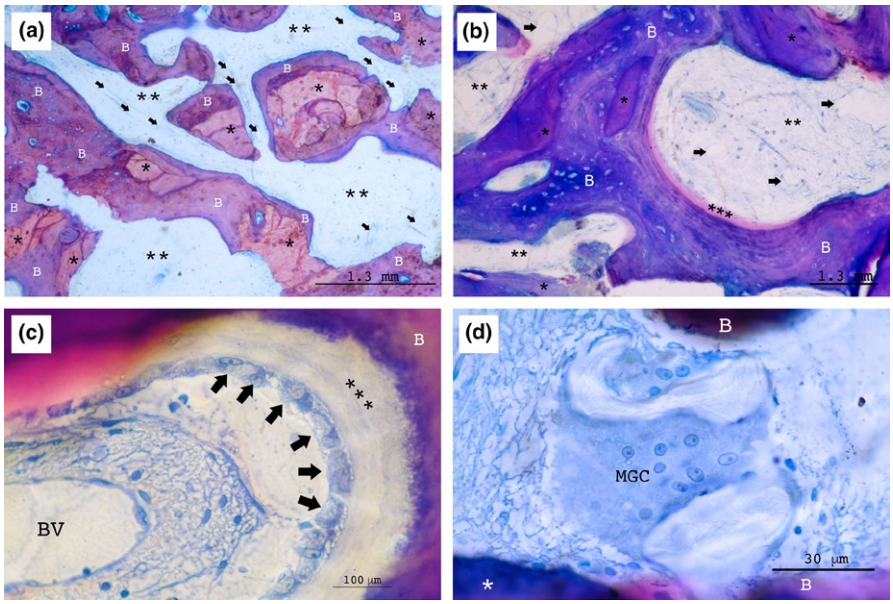

FIGURE 4 Microscopical aspects of specimens retrieved from a sinus <12 mm width and with both lateral and medial walls in contact with the grafting biomaterial. In (a), residual biomaterial particles (*) appeared joined together by new bone (B) to form well-developed bony trabeculae. Inside the marrow spaces (**), several blood vessels were present (black arrows). Toluidine blue and pironine G stain (100× magnification). In (b), the organization of the newly formed bony trabeculae was better defined (toluidine blue and pironine G stain; 400× magnification). Residual small particles of biomaterial (*) appeared completely incorporated by the newly formed bone (B), which is still in formation, as indicated by the presence of an osteoid rim (***) and blood vessels (black arrow). In (c), an active site of bone formation of (b) is represented at higher magnification (1,000×). The close relationships among blood vessel (BV), osteoblastic cells (black arrows), partially mineralized bone matrix (***), and mineralized newly formed bone (B) was visible. Toluidine blue and pironine G stain. In (d), a giant multinucleated cell (MGC) was visible near biomaterial particle surfaces (*). Toluidine blue and pironine G stain (1,000× magnification)

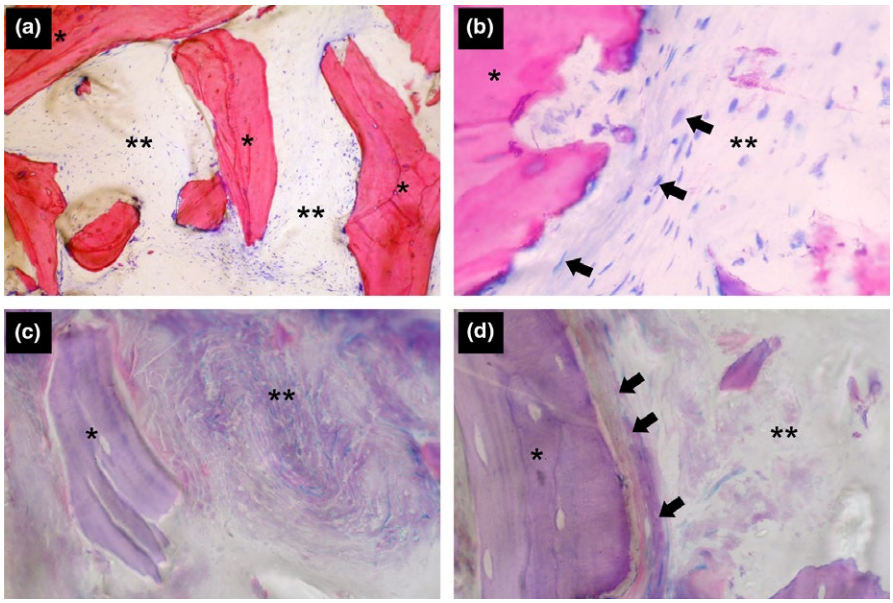

FIGURE 5 Microscopical aspects of specimens retrieved from a sinus >15 mm width and with no contact between lateral and medial walls and the grafting biomaterial. In (a), residual biomaterial particles (*) appeared dispersed inside the marrow spaces (**), encapsulated by soft tissue. Azure II and fuchsine acid stain (100× magnification). In (b), a biomaterial particle (*) appeared in contact with some fibroblasts (black arrows) immersed inside a soft tissue (**) (1,000× magnification). In (c), a biomaterial particle (*) appeared completely surrounded by soft tissue (**). Toluidine blue, methylene blue, and fuchsine acid stain (200× magnification). In (d), a dense soft tissue (black arrows) encapsulated a biomaterial particle (*). The soft tissue far from biomaterial surface appeared less densely organized (**). Toluidine blue, methylene blue and fuchsine acid stain (800× magnification)

TABLE 4 Results of the multiple forward linear regression to estimate association of each explanatory variable with NFB and GR at 6 months (n = 44)

Explanatory variable	β coefficient	*SE*	*t*	Significance
Model 1; Outcome: NFB (%); R^2 = .781				
WGC (1 wall)	.927	0.430	0.184	p = .037; S
WGC (2 walls)	4.115	0.364	0.964	p < .001; S
Model 2; Outcome: NFB (%); R^2 = .793				
SW (mm)	−.567	0.047	−12.018	p < .001; S
Model 3; Outcome: GR (mm); R^2 = .192				
WGC (2 walls)	−.468	0.148	−3.162	p = .003; S
Model 4; Outcome: GR (mm); R^2 = .140				
NFB (%)	−.093	0.036	−2.612	p = .012; S

NFB, percentage of newly formed bone (entered as root-squared data); GR, graft resorption in mm (entered as root-squared data); WGC, sinus walls in contact with graft (entered as dummy variable, WGC = 0 as reference category); SW, sinus width in mm (entered as continuous data). Models 1 and 3 with WGC among the explanatory variables; models 2 and 4 with SW among the explanatory variables. SE, standardized error of the β-coefficient. S, significant; NS, not significant.

Schneiderian membrane isolation from the regeneration area did not influence the healing outcomes at all (Scala et al., 2016).

On these premises, the necessity of an adequate membrane elevation from lateral and medial sinus walls in order to allow a close contact between vital bone and grafting material seems a crucial factor to optimize regenerative outcomes, irrespective of the surgical approach. In the lateral window technique, the membrane must be carefully elevated with manual or ultrasonic instruments under the visual control of the surgeon, until exposing floor, anterior and medial wall of the sinus cavity (Wallace et al. 2012; Lundgren et al., 2017). On the contrary, a direct intra-operative control on membrane elevation during transcrestal procedures is not possible: Schneiderian membrane is indirectly detached following the path of least resistance (Stelzle & Rohde, 2014), irrespective of the selected surgical technique (osteotomes condensing graft with trapped fluids or hydrodynamic tools). Therefore, it seems that sinus conformation and anatomy could play a fundamental role in determining entity and modalities of membrane elevation during transcrestal approach: Recent studies (Jang, Kim, Lee, & Lee, 2010; Lombardi et al., 2017) demonstrated that, after tSFE, the contact between grafting material and both lateral and medial sinus wall occurred predictably only in narrow sinuses. These findings were confirmed in the present study, in which sinus membranes resulted correctly reflected and elevated from both palatal and buccal walls (WGC = 2) in narrow sinuses (mean width of 10.6 ± 1.8 mm), while "dome-shaped" elevations, with the grafting material completely surrounded by the Schneiderian membrane (WGC = 0) occurred in wider ones (mean width of 17.3 ± 2.2 mm). The results of multiple forward linear regression analysis revealed a strong positive correlation between WGC and NFB percentage after six months of healing (R^2 = .781), confirming the importance of this explanatory variable for successful outcomes of tSFE procedure. This finding is in accordance with a recent pilot study (Lombardi et al., 2017) but, unfortunately, no other comparisons are possible as insufficient data on new bone formation after tSFE in humans are present in the literature (two case reports—Bernardello et al., 2014; Trombelli et al., 2015; two case series—Esfahanizadeh et al., 2012; Wainwright et al., 2016). Furthermore, histologic and histomorphometric outcomes of the numerous studies on lateral sinus augmentation should not be automatically extended to tSFE, as the regenerative environment could present significant differences between the two techniques.

In the present study, we recorded three membrane perforations (6%): This finding is in accordance with the outcomes of a systematic review on tSFE (Călin, Petre, & Drafta, 2014) and is lower than mean perforation rate reported by recent systematic reviews on the lateral approach (Atieh, Alsabeeha, Tawse-Smith, Faggion, & Duncan, 2015; Stacchi, Andolsek, et al., 2017). However, our data could be underestimated due to the difficulty in detecting small perforations in tSFE: in fact, two patients (4%) presented a late dissemination of the biomaterial, likely due to hidden perforations.

In this study, mean NFB percentage after six months of healing was 21.2%, but with wide variability among samples (range 0%–62.1%). This finding is consistent with the study by Wainwright et al. (2016), in which NFB percentage ranged between 7.6% and 75.1% six months after tSFE, even if performed with hydrodynamic ultrasonic-driven approach. However, multivariate analysis revealed a strong negative correlation between NFB and SW (R^2 = .793, p = .0001), in agreement with the conclusions of recent studies on tSFE, based both on radiographic (Cheng et al., 2017; Spinato et al., 2015; Zheng et al., 2016) and histomorphometric data (Lombardi et al., 2017).

The concept that in large sinus cavities is more difficult to regenerate consistent amounts of vital bone is a biological consequence of the centripetal gradient of bone formation occurring in the maxillary sinus (Busenlechner et al., 2009). Histomorphometric results from Avila et al. (2010) and Soardi et al. (2011) demonstrated the validity of this assumption for lateral sinus augmentation and are in agreement with the analyses performed in the present study on tSFE (Table 2). When SW was stratified in groups, results showed that NFB percentage decreases as SW increases: In the group with the lowest SW (<12 mm), mean NFB was 35.6%, whereas in the two groups where SW was comprised between 12 and 15 mm or was >15 mm, mean NFB were 13.1% and 3.4%, respectively. The linear

regression model demonstrated a strong negative correlation between SW and NFB percentage after 6 months of healing (R^2 = .793, p = .0001).

In previous studies on lateral sinus augmentation, mean NFB percentage at 6 months varied from 13% to 20% in sinuses with SW ≥15 mm (Avila et al., 2010; Soardi et al., 2011): Our findings suggested that the final result in similar anatomical conditions when using tSFE could be considered as a sort of biological failure in terms of new bone formation (3.4%). A possible explanation could be that, in tSFE, an ineffective membrane detachment from lateral and medial sinus walls is a frequent occurrence in wide sinuses, further jeopardizing the already low regenerative potential of large cavities.

Despite the unpredictability of the biological outcomes, systematic reviews analyzing studies on tSFE reported survival rates ranging from 92.8% to 96.1% for implants inserted in combination with this regenerative technique (Călin et al., 2014; Del Fabbro, Corbella, Weinstein, Ceresoli, & Taschieri, 2012; Emmerich, Att, & Stappert, 2005; Tan, Lang, Zwahlen, & Pjetursson, 2008). However, these studies also indicated that reduced crestal height at baseline may negatively impact on implant survival/success rates. It should be considered that, in the studies included in these reviews, the majority of the implants were placed in bone crests with a height >5 mm, making it difficult to discern the real contribution of the newly formed tissue to implant support: In fact, many recent randomized clinical trials reported comparable survival rates using 5- or 6-mm implants inserted in the native bone of posterior maxilla (Bechara et al., 2017; Felice et al., 2015; Pohl et al., 2017; Sahrmann et al., 2016). In the present study, we recorded 93% implant survival rate at 1-year follow-up, in accordance with the aforementioned systematic reviews: However, all the failed implants were inserted in wide sinuses (mean width 18.5 ± 2.0 mm), where graft had no contact with buccal and medial sinus walls.

Residual crestal height has been regarded for many years as the paradigm for choosing between lateral and transcrestal approach. Since the Sinus Consensus Conference of 1996, five to seven millimeters of RBH have been considered as the necessary prerequisite for tSFE procedures (Jensen, Shulman, Block, & Iacono, 1998; Pjetursson & Lang, 2014): In this study, mean RBH at baseline was 3.4 mm and statistical analysis demonstrated that it was not a significant factor in influencing new bone formation and implant survival at 1-year follow-up. Moreover, mean vertical gain after 6 months of healing was 8.6 mm, allowing the placement of implants ≥10 mm in all cases: From these findings, RBH should be regarded only as a predictive factor for immediate implant placement.

In the present study, GH decreased from a mean value of 10.3 mm immediately after surgery to 8.6 mm after 6 months of healing. Mean GR after 6 months was 1.7 mm but with wide variability (range 0.1–7.7 mm): linear regression models suggested very weak negative correlations between GR and NFB (R^2 = .140, p = .012) and between GR and WGC (R^2 = .192, p = .003), in accordance with the studies by Spinato et al. (2015), Zheng et al. (2016) and Cheng et al. (2017). These results are also in accordance with studies conducted on lateral augmentation (Kolerman et al., 2008; Soardi et al., 2011), even if some author contradicts these findings (Favato et al., 2015).

The other evaluated factors (age, sex, and smoking habits) resulted not significant in influencing NFB and GR: This finding is consistent with the outcomes of a previous study on tSFE (Franceschetti et al., 2014).

The present study presents some limitations, which have to be considered in the interpretation of the results. The most important is that biopsies were harvested at a single time point (6 months), so from the data of this study, it is not possible to understand if bone maturation will eventually occur also in wide sinuses after a longer period of time or if large cavities represent an unfavorable environment for new bone formation, such a sort of critical size defect. However, recent studies suggested that, after sinus augmentation, the amount of newly formed bone and residual biomaterial did not vary significantly over time after the first 6 months of healing (Di Stefano et al., 2016; Galindo-Moreno et al., 2013; Lindgren, Mordenfeld, Johansson, & Hallman, 2012). Moreover, this study was conducted using only one biomaterial and membrane elevation was performed without the use of hydrodynamic devices: Further studies investigating these different scenarios are necessary to generalize the results of this research to possible surgical variants of tSFE. Finally, the limited numerosity of the patients treated in this study has to be considered and data must be interpreted with caution: Further clinical trials conducted on an appropriate sample size are necessary to confirm our findings.

The clinical relevance of this study appears mainly related to the possible introduction of new diagnostic criteria for choosing tSFE to augment vertical bone volume in the posterior maxilla: Narrow sinus cavities (SW < 12 mm, measured at 10-mm level, comprising the residual alveolar crest) seemed to represent the most favorable anatomical situation to achieve predictable regenerative outcomes, possibly improving long-term success of implants inserted in the newly formed tissue.

5 | CONCLUSIONS

To the best of our knowledge, the present study represents the first confirmation based on histomorphometric data that a substantial amount of new bone regenerated after tSFE is a predictable outcome only in narrow sinus cavities. During presurgical planning, bucco-palatal sinus width should be regarded as a crucial parameter when choosing sinus floor elevation with transcrestal approach as a treatment option.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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