Incidence of Sinus Mucosa Perforations During Healing After Sinus Elevation Using Deproteinized Bovine Bone Mineral as Grafting Material: A Histologic Evaluation in a Rabbit Model

Michihide Miki, DDS[1]/Daniele Botticelli, BMBS, PhD[2]/
Erick Ricardo Silva, DDS, PhD[3]/Samuel P. Xavier, DDS, PhD[3]/Shunsuke Baba, DDS, PhD[1]

Purpose: To examine the reaction of mucosa over time to a close contact with biomaterial after sinus elevation performed with deproteinized bovine bone mineral (DBBM) granules of two different sizes. ***Materials and Methods:*** Bilateral sinus mucosa elevation was performed in 18 New Zealand rabbits through access on the nasal dorsum. DBBM with granule dimensions of either 1 to 2 mm (large group) or 0.250 to 1.0 mm (small group) were used to randomly fill the subantral hollow spaces. Biopsy specimens of the experimental sites from six animals in each group were obtained 2, 4, and 8 weeks after the surgery. ***Results:*** The integrity of the sinus mucosa was clinically evaluated during surgery using a ×2.5 magnifying visual device. The sinus mucosa in contact with the biomaterial granules was found to be thinned compared with the pristine mucosa in all periods examined. Three hundred fifty-two thinned zones were found considering all 36 sinuses treated. Perforations of the sinus mucosa with extrusion of granules toward the sinus were observed, increasing in number over time. In the 8-week healing period, five perforations in three sinuses and eight perforations in four sinuses were found in the large and small groups, respectively. No differences were seen between the large and small groups. The differences between 2 and 8 weeks were statistically significant for the thinned mucosa width in both the large and the small groups and for the number of sinuses and perforations for the small group. ***Conclusion:*** Thinning zones and perforations of the sinus mucosa were seen increasing in number over time in regions in contact with graft granules in both the large and small groups. *Int J Oral Maxillofac Implants 2021;36:660–668. doi: 10.11607/jomi.8580*

Keywords: animal study, bone healing, sinus floor elevation, xenograft, perforation

Sinus floor augmentation through lateral access was proposed to increase bone volume in the atrophic posterior region of the maxilla.[1] This technique is associated with a high success rate[2] but also with complications during and after surgery.[3] The most commonly reported complication was sinus mucosa perforation during the surgical approach.[4–11] In a literature review, risk factors were associated with perforations of the sinus mucosa.[12] Some of these factors were judged to have a high risk for perforations, such as a sinus mucosa thickness < 0.8 mm or > 3 mm, the presence of multiple septa or of a septum ≥ 6 mm in height, the presence of roots into or near the area of treatment, and a residual bone height < 4 mm. Other factors that presented a high risk for perforations were the presence of an angle between the lateral and medial sinus walls < 30 degrees, a palate-nasal recess angle < 90 degrees, the presence of the posterior superior alveolar artery in the zone of the antrostomy, smoking habits, and preoperative chronic sinusitis.[12]

Postsurgical complications have been reported by several articles.[4,5,13–16] In a retrospective study on 359 sinus floor augmentations in 208 patients, the sinus mucosa was perforated in 41.8% of cases.[4] Sinusitis was registered in ~5% of cases, of which 11.3% were associated with perforated mucosae and 1.4% with undamaged mucosae. An overall graft failure rate of 6.7% was reported, of which ~71% were at perforated sinus mucosa sites. The extrusion of biomaterial inside the antral cavity was also reported in clinical studies in which the biomaterial had to be removed endoscopically to achieve the healing.[13,15] In a retrospective study, 198 patients treated with 274 sinus grafts were included.[13] Eight patients (2.3%) presented a sinus graft infection.

[1]Department of Oral Implantology, Osaka Dental University, Osaka, Japan.
[2]ARDEC Academy, Rimini, Italy; Fundación ARDEC, Cartagena de Indias, Colombia.
[3]Depto CTBMF e Periodontia FORP-USP- Faculty of Ribeirão Preto (SP), Brazil.

Correspondence to: Dr Daniele Botticelli, ARDEC Academy, viale Giovanni Pascoli 67, 47923 Rimini, Italy.
Email: daniele.botticelli@gmail.com

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The infected parts of the graft were surgically removed, and all patients recovered.

The presence of graft material within the sinus could be ascribed to a perforation of the mucosa that occurred during the surgical procedures. However, that perforation may have been established in a later stage.

Hence, the aim of the present study was to examine the reaction of the mucosa over time to a close contact with the biomaterial after sinus elevation performed with deproteinized bovine bone mineral (DBBM) granules of two different sizes. The hypothesis was that a close contact to the graft material might damage the mucosa.

MATERIALS AND METHODS

Ethical Statement

The protocol for the present experiment was approved by the Ethical Committee of the Faculty of Dentistry in Ribeirão Preto of the University of São Paulo (USP, SP-Brazil; 2017.1.278.58.9). The ARRIVE guidelines and the SYRCLE risk of bias tool for animal studies were adopted.

Study Design

In the present study, DBBM granules were used for sinus elevation in the rabbits. The histologic healing within the sinus has been described elsewhere.[17] In the present study, further analyses were performed to evaluate the effect of the contact of the DBBM granules with the sinus mucosa during the healing. The number of perforations of the mucosa were assessed, and the width of the mucosa in close contact with the DBBM granules was measured.

Experimental Procedures

The surgical procedures were illustrated in detail in another article that reported the healing within the elevated area.[17] In brief, after sedation and anesthesia, the nasal dorsum was exposed, osteotomies were prepared, and the mucosa of the sinus was elevated using a small elevator (718-EN1, Bontempi Strumenti Chirurgici). The integrity of the sinus mucosa was clinically evaluated during surgery using a ×2.5 magnifying visual device (Ultra Light Optics). Approximately 250 cc of DBBM granules (Bio-Oss, Geistlich Biomaterials), either 1.0 to 2.0 mm (large) or 0.250 to 1.0 mm (small), were randomly used to graft the two subantral hollow spaces. A small screw was placed in the internasal suture between the two access windows as reference for the histologic cutting.

Euthanasia

The animals were first sedated and anesthetized, and then euthanized with sodium thiopental (1.0 g, 2 mL, Thiopentax, Cristália Produtos Químicos Farmacêuticos).

Experimental Animals

Eighteen New Zealand rabbits of 4 to 5 months of age and 3.5 to 4 kg of weight were included in the experiment and divided into three groups of six animals each, according to the periods of healing, ie, 2, 4, and 8 weeks.

Housing and Husbandry

Each animal was maintained in a separated cage in a room with a controlled temperature and light, with free access to water and food. Professionals controlled the wounds, monitored the biologic functions, and provided the necessary drugs after surgery.

Sample Size

The sample size was calculated for the healing in the elevated zone, as reported elsewhere.[17]

Randomization and Allocation Concealment

The randomization of the allocation of the treatments (large or small granules) was performed in blocks of six by an author (D.B.) not involved in the surgery using www.randomization.com. The information was secured in opaque sealed envelopes that were opened by a masked author (S.P.X.) and disclosed to the surgeon (E.R.S.) after the elevation of the mucosa in both sinuses. Moreover, the surgeon was not informed about the timing of the euthanasia.

Microcomputed Tomography Scanning

All specimens were scanned in a microCT 1172 (Bruker). Due to the difficulties in identifying the mucosa, only images reflecting the sharp edges of the biomaterial in the most external region of the elevated space were illustrated.

Histologic Preparation and Analyses

The specimens containing the experimental regions were kept in formalin and then dehydrated and embedded in resin (LR White hard grid, London Resin). After polymerization, two histologic slides representing the central region of the elevated space were sectioned with cutting and grinding equipment (Exakt, Apparatebau) using the small screw as reference for the cutting plane. Each slide was stained with either toluidine blue or Stevenel's blue and alizarin red. High-definition photomicrographs were captured using an EK14 motorized stage connected to an Eclipse Ci microscope (Nikon Corporation).

The following evaluations were carried out on both histologic slides at a magnification of ×200 using the software NIS-Elements D 5.11 (Laboratory Imaging, Nikon Corporation): *(1)* number of sinuses with perforations; *(2)* number and dimensions of perforations; and *(3)* thickness of the sinus mucosa. The thickness of the mucosa was measured in different regions of the sinus mucosa: *(1)* on the lateral and medial sinus walls far from

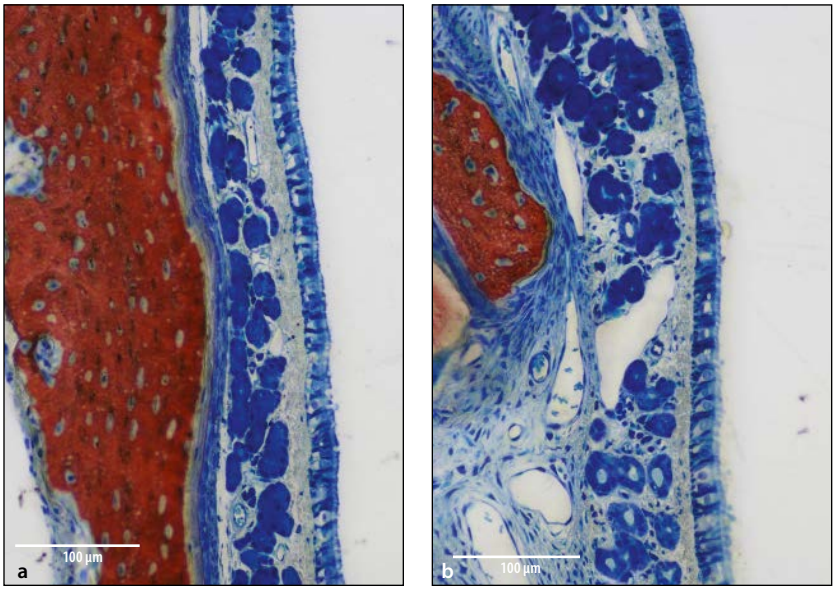

Fig 1 Photomicrographs of ground sections illustrating the pristine mucosa *(a)* presented in all periods lower thickness compared with the elevated mucosa *(b)* in both the large and small groups. Stevenel's blue and alizarin red stain.

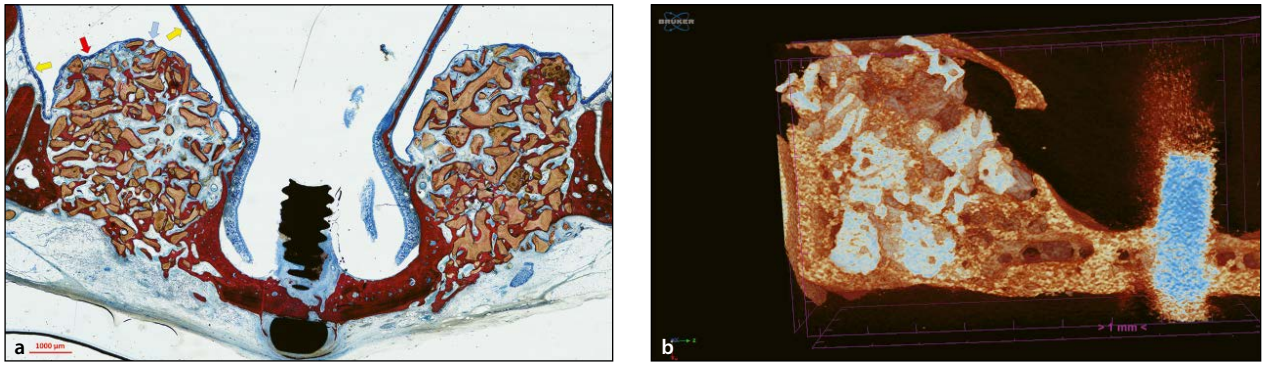

Fig 2 *(a)* Photomicrographs illustrating the healing after 8 weeks. Small (left sinus) and large (right sinus) granules. The arrows illustrate examples of regions used for the measurement of the thickness of the pristine mucosa *(in yellow)*, elevated mucosa *(in red)*, and thinned mucosa *(in light blue)*. *(b)* Coronal view taken in the central region of the elevated space. Note the particle projections of the grafts protruding beyond the dome-shape periphery. Specimens of the large group, 8 weeks of healing.

the elevated area not included in the elevation procedures (pristine mucosa; Figs 1a and 2a); *(2)* in two different zones in the elevated area (elevated mucosa; Figs 1b and 2a) where the lamina propria was not in "close" contact with the biomaterial; and *(3)* in all zones of the mucosa that were in close contact with the DBBM granules and that presented a width < 50 µm (thinned mucosa; Fig 2a). When a perforation was judged to be the same in both the differently stained slides, only that with the larger dimension was taken into consideration for analysis. All data of the mucosa thickness were instead used for analysis, and mean values were calculated.

Calibration for Histometric Evaluations

All histologic measurements were performed by an expert examiner (K.A.A.A.). Previously, calibration was carried out with another expert (D.B.), and the interrater reliability in measurements was $\kappa > 0.90$.

Experimental Outcomes

The primary variable was the incidence of perforations. The secondary variable was the incidence of thinned mucosae.

Statistical Methods

The IBM SPSS Statistics v.19 (IBM) was used for statistical analyses. Differences between 2- and 8-week periods were evaluated using the Mann-Whitney *U* test, differences between the large and small groups were assessed applying the Wilcoxon test, and differences within each period among the three types of mucosae, ie, pristine, elevated, and thinned, were assessed with the Friedman test.

RESULTS

The sinus mucosa of all 18 biopsy specimens was analyzed. The elevated mucosa was thicker in all periods

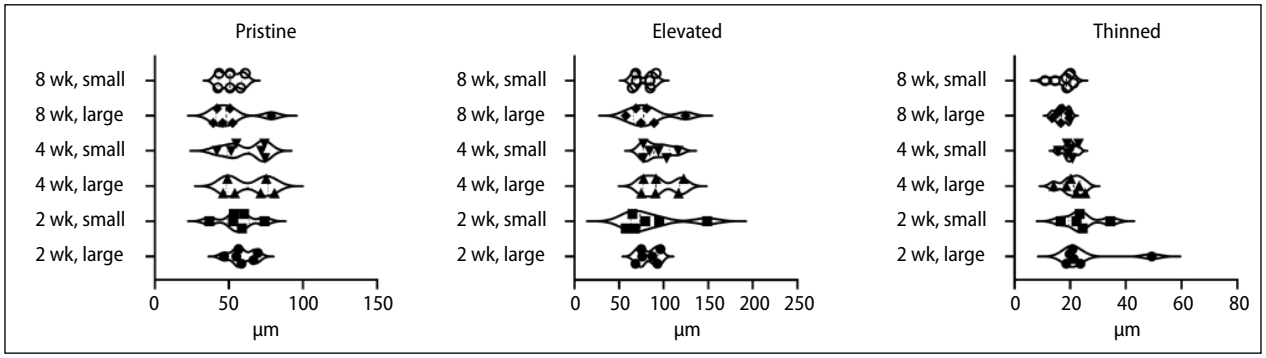

Fig 3 Violin graphs illustrating the thickness of the pristine, elevated, and thinned mucosae in the three periods analyzed. None of the differences between the large and small groups was statistically significant. All the differences among the three sinus mucosa thicknesses were statistically significant in all periods analyzed. The difference between 2 and 8 weeks was statistically significant for the thinned mucosa in both the large and the small groups.

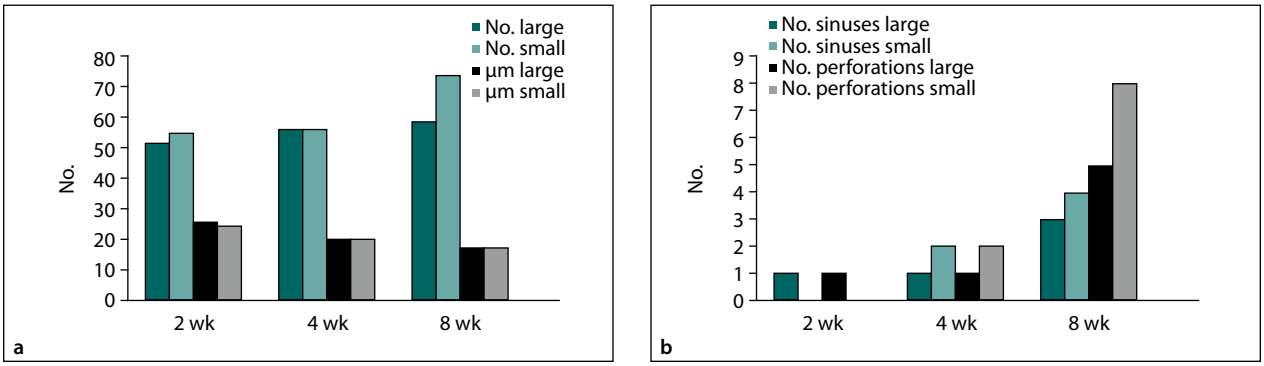

Fig 4 Graphs illustrating for both large and small groups *(a)* number (No.) and thickness of the thinned mucosa zones; *(b)* number of sinuses presenting perforations and number of perforations. The difference was statistically significant between 2 and 8 weeks of healing. No differences were seen between the large and small groups. The differences between 2 and 8 weeks were statistically significant for the thinned mucosa width in both the large and the small groups and for the number of sinuses and perforations for the small group.

compared with the pristine mucosa in both the large and the small groups (Figs 1a and 1b). The mucosa in contact with the biomaterial (thinned mucosa) was thinner compared with both the pristine and the elevated mucosae (Fig 3). The number of zones with thinned mucosa increased over time, while the mean thickness in these zones decreased progressively (Figs 3 and 4).

The histologic features of the thinned mucosa were different from those of the pristine and of the elevated mucosae. Depending on the stage of the damage, the lamina propria decreased in width, and the blood vessels and mucous glands were progressively pushed out from the thinned mucosa zones (Fig 5a). The pseudostratified ciliated columnar epithelium turned out to be thinner (Fig 5b) and vanished in the most compromised sites (Fig 5c). In only few cases, new bone was found interposed between the DBBM granules and the thinner mucosa (Fig 5d).

The sinus mucosa was discontinued in one sinus of the large group after 2 weeks and increased over time in both the large and small groups. The mucosal perforations were located at the granules protruding beyond the dome profile of the elevated space, and they were mainly associated with sharpened edges and cutting projections of the granules of DBBM (Fig 6a). However, in some instances, the mucosa was also discontinued at rounded granules (Fig 6b). The granules penetrating the mucosa sometimes presented new bone adhering to the surface in the side still contained within the elevated space. Repairing attempts carried out by the connective and epithelial tissues surrounding the granules in the perforated region were observed (Fig 6c), as well as healing processes aiming to isolate the grafts and drive them out of the elevated area (Fig 6d). In the 8-week period, some granules perforating the mucosa were incorporated into new bone (Fig 7a).

After 2 weeks, thinned mucosa (< 50 microns) in close contact with biomaterial granules was observed in 52 zones in six sinuses in the large groups and in 55 zones in five sinuses in the small groups (Figs 3 and 4). The mean values of the mucosal thickness were 25.6 ± 11.7 µm and 24.2 ± 6.4 µm, respectively. Only one perforation was seen in the large group with a dimension of 236 µm and without any inflammatory infiltrate.

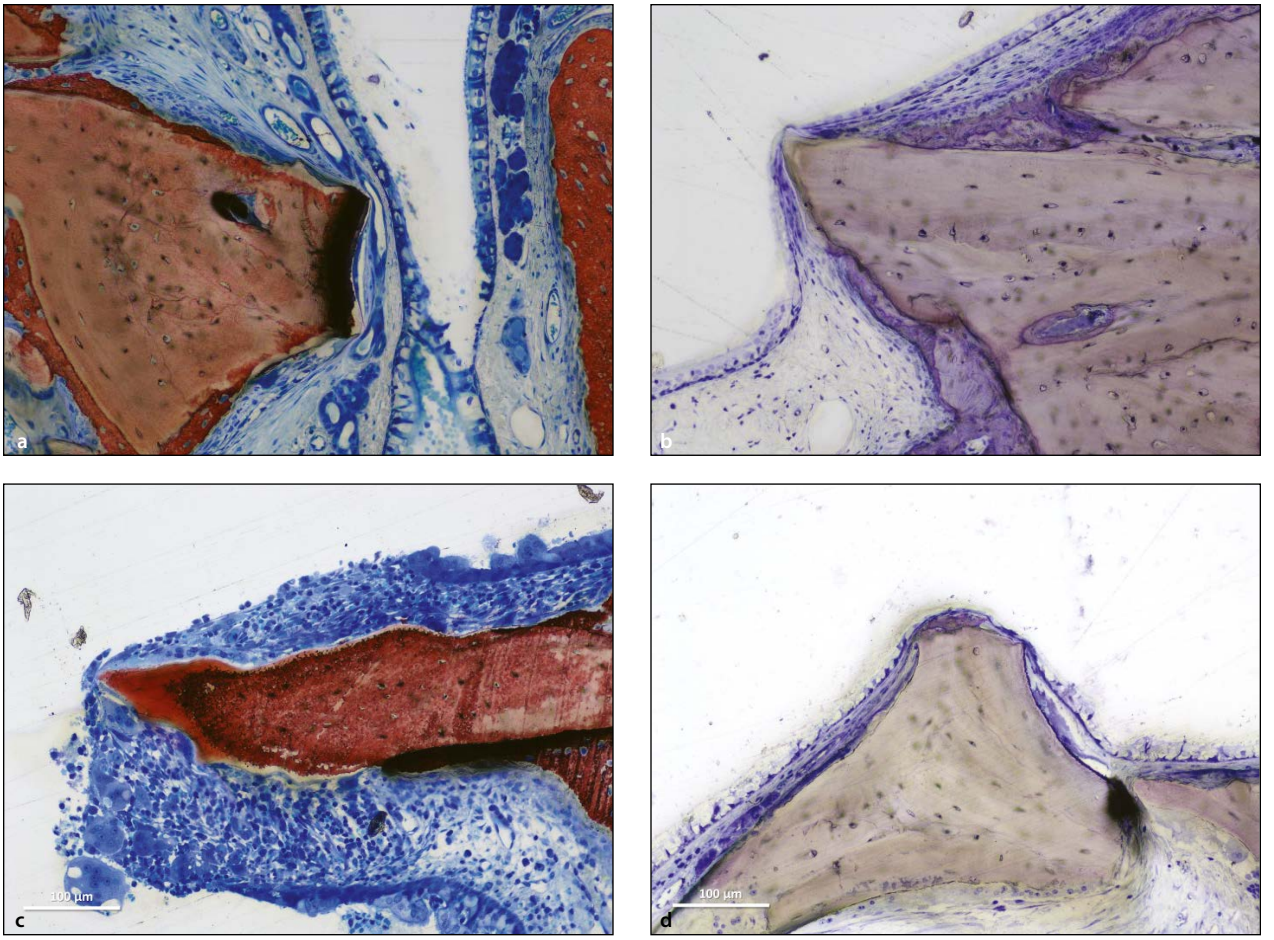

Fig 5 Photomicrographs of ground sections representing thinned mucosa zones. *(a)* Blood vessels and the mucous glands within the lamina propria were progressively dislocated from the thinned mucosa zones. *(b)* The pseudostratified ciliated columnar epithelium turned out thinner. *(c)* The epithelium vanished in the most compromised sites. *(d)* In only few cases, new bone was found interposed between the DBBM granules and the thinner mucosa. *(a, c)* Stevenel's blue and alizarin red stain. *(b, d)* Toluidine blue stain.

After 4 weeks of healing, similar amounts of zones of thinned mucosa were found in both the small and the large groups, presenting, however, a lower thickness (Figs 3 and 4). Three perforations were observed, one in the large group that was 197 µm wide, and two in two different sinuses of the small group (Fig 4) with a mean dimension of 147 µm.

After 8 weeks of healing, 59 zones with thinned mucosa in the large group and 74 in the small group were found (Figs 3 and 4). The mean thickness decreased compared with the previous periods to ~17 µm in both groups, and the differences between 2 and 8 weeks of healing were statistically significant (Figs 3 and 4). Five perforations were observed in three sinuses in the large group, with a mean dimension of 246 µm, and eight perforations in four sinuses in the small group (Fig 4), with a mean dimension of 92.3 µm. The tissues around the granules perforating the mucosa in eight cases presented no or few inflammatory cells. However, four sites presented a large inflammatory infiltrate, mostly limited to the areas around the particles (Fig 7b).

DISCUSSION

The aim of the present study was to examine the reaction of the mucosa over time to a close contact with the biomaterial after sinus elevation performed with DBBM granules of two different sizes.

The elevated mucosa was found to be thicker in a range of ~29% to 38% compared with the pristine mucosa in all periods and presented a lamina propria of increased dimensions containing hypertrophic mucous glands. This agrees with another similar study in rabbits in which similar outcomes were observed.[18] In the present study, the mucosa in contact with DBBM particles was thinner compared with the pristine mucosa in proportions of 56% to 57% after 2 weeks and 66% to 68% after 4 and 8 weeks of healing, in both the large and the small groups.

The thinned mucosa was in zones where the granules were protruding outward from the dome profile of the elevated space. In these zones, the mucosa appeared to be lining the surface of the biomaterial that often presented sharpened edges and cutting projections.

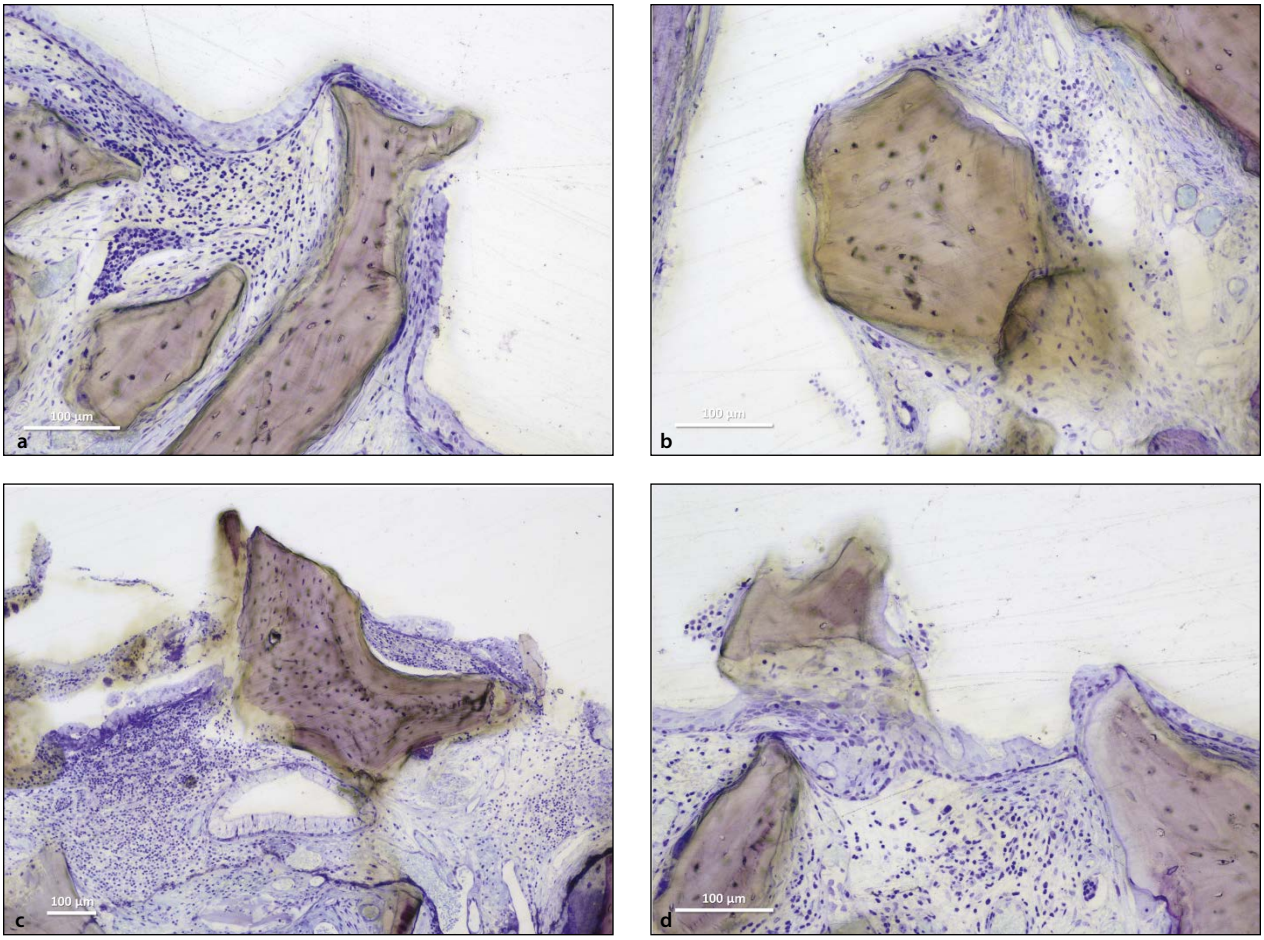

Fig 6 Photomicrographs of ground sections illustrating granules perforating the sinus mucosa. *(a)* The perforations were mainly associated with the sharpened edges and cutting projections of the grafts. *(b)* Rounded granules were also found disrupting the mucosa in some cases. *(c)* Repairing attempts carried out by the connective and epithelial tissues surrounding the perforating granules. *(d)* Healing processes aiming to isolate the grafts and drive them out of the elevated area. Toluidine blue stain.

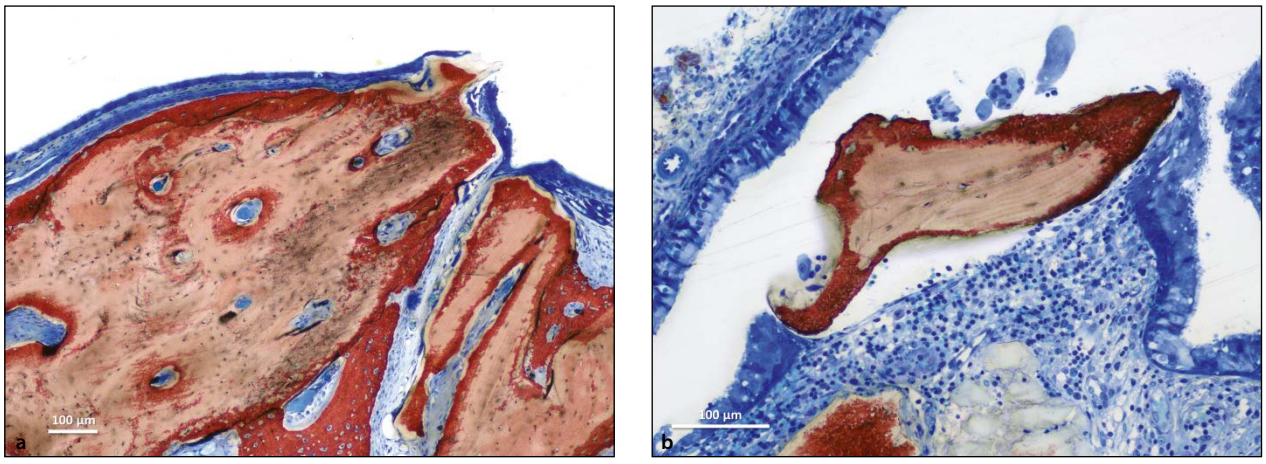

Fig 7 Photomicrographs of ground sections illustrating *(a)* a granule incorporated into new bone and perforating the sinus mucosa; *(b)* large inflammatory reaction that resulted in the elimination of the granules from the elevated area through the perforated mucosa. Stevenel's blue and alizarin red stain.

After an elevation procedure, the sinus tends to re-pneumatize so that the volume gained in the subantral space might decrease over time. This was shown by an overview,[16] systematic reviews,[19,20] human studies,[8–11,21,22] and animal experiments.[18,23–31] In a clinical study, implants were placed simultaneously with a sinus

elevation procedure performed without biomaterials.[22] After 1 to 6 years of follow-up, the tips of the implants, especially the most distal, were found protruding beyond the augmented space. In that study, the reaction of the mucosa around these protruding implants was not evaluated, and no complications such as sinusitis were reported. Nevertheless, in a retrospective study on nine patients,[32] a sample of 24 implants, protruding for > 4 mm within the sinus in nonaugmented sites, did not present signs of sinusitis in the CT analysis.

Also, animal studies showed the tendency of the sinus to regain its original volume after sinus elevation. In an experiment in rabbits,[23] sinus elevation was performed and the subantral hollow space was filled with coagulum, and the healing was studied after 1, 3, and 6 weeks. At the test sites, a sponge was used to occlude the nasal ostium, while that at the control sites was left open. After 6 weeks of healing, while at the control sites, the sinus regained its original volume and the new bone that formed in the previous periods was almost completely resorbed, at the occluded sites, the volume was maintained. The occlusion of the ostium altered the air exchange with the nasal cavity and contributed to decrease the oxygen pressure within the sinus[33] or even to establish a negative pressure in the short time.[34] This might explain the maintenance of the elevated volume in the occluded ostium site in the aforementioned study.[23]

In another similar experimental study in 20 rabbits,[24] the subantral hollow spaces were filled either with DBBM or a clot. The healing was studied after 2, 4, 6, 8, and 10 weeks. While at the DBBM sites, the volume obtained was maintained over time, at the clot sites, most of the new bone formed in the earliest periods of healing was progressively resorbed, and the augmented height of the elevated space decreased noticeably.

Similarly, experimental studies also showed that with implants placed simultaneously in sinuses elevated without placing any filler material, after healing, the tips of the implants were only covered by a layer of sinus mucosa without interposed bone.[27,35] Also, when space-making devices were placed to maintain the subantral volume after sinus elevation, the sinus mucosa was found in the lining in direct contact with the devices after 3 to 9 months of healing.[25,26,28]

In the present study, in the 2-week period, the mucosa was only displaced beyond the dome-shaped periphery of the subantral space by the projections of the DBBM granules. Neither inflammatory responses nor changes in the histologic structures within the mucosa were noted. In the more advanced stages of healing, the mucosa became thinned, and the glands and vessels were found to be dislocated and deformed by the contact with the biomaterial (Fig 5a). Subsequently, glands and vessels disappeared, and only an epithelial layer with cells of reduced height was observed lining the biomaterial. These effects on the sinus mucosa were especially observed at the sites where the biomaterial presented sharp projections toward the periphery of the elevated subantral space. The mean number of thinned mucosa zones for each sinus ranged between ~8 to 12 in the various periods examined. A progressive thinning of the mucosa was observed, with the difference between 2 and 8 weeks of healing being statistically significant. It might be argued that the thinning of the mucosa could eventually result in a perforation of the mucosa. In fact, the number of perforations found in the present study increased over time. After 2 weeks, only one perforation was found in the histologic analysis. This perforation could have occurred during the surgical procedures or as a consequence of the thinning process suffered by the mucosa in contact with the biomaterial. However, it is not possible to refer the cause to the former or to the latter option. It is known that, during sinus floor elevation with a crestal approach, inadvertent and not-recognized perforations can occur during the placement of biomaterial or of implants, as shown both in human[36,37] and in ex vivo[38,39] studies. Moreover, the perforations might be so tiny that it makes them clinically undetectable.

In the present experiment, the number of perforations increased over time in both groups, and comparing the occurrences at the three periods examined, it might be supposed that most of those perforations occurred during the healing period and not at the surgery. It might be likewise supposed that the perforations were preceded by damaging processes that led to the progressive thinning of the mucosa. After 2 weeks of healing, only one perforation was found, while after 8 weeks of healing, 50% of the sinuses in the large group and 67% in the small group were affected by single or multiple perforations, with the differences being statistically significant for the number of both sinuses involved and perforations in the small group. Moreover, it should be kept in mind that the histologic slides represented only the central region of the elevated space, so that all the remaining parts of the biopsy were not included in the histology and thus were excluded from the analysis. This, in turn, means that higher amounts of thinned mucosa zones and perforations should be expected if the mucosa of the whole elevated region were examined. This was also confirmed by the micro-CT 3D reconstructions that revealed many sharp ridges and projections of the DBBM granules protruding from the subantral elevated space toward the sinus cavity in all parts of the dome-shape elevated space (Fig 2b).

Sinusitis with the presence of biomaterial extruded inside the sinus cavity was also reported in human studies. In a retrospective study,[15] 14 patients who presented sinusitis 4 months to 2 years after sinus elevation, and who did not respond to medical treatment,

underwent functional endoscopic sinus surgery. In all patients, a hydroxyapatite graft was used as filler. The computed tomography revealed the presence of biomaterial within the sinus in six patients. A middle meatal maxillary antrostomy was carried out and the infected biomaterial was removed, and the patients recovered from the infection. In another retrospective case series article,[40] 11 patients presented sinusitis from 3 months to 11 months after sinus elevation. In the computed tomography, remnants of biomaterial were detected in four patients. It can be argued that the perforations might have occurred accidentally when the biomaterial or the implants were placed in the subantral space during sinus elevation. However, it cannot be excluded that damage to the sinus mucosa (ie, incidences of thinned mucosae) and late perforations might have occurred after the surgery. The sinus mucosa in humans is thicker (~0.45 to 1 mm at the histologic examination[41]; ~0.9 to 3.1 mm at the CBCT examination)[42] compared with that of rabbits (~0.08 mm).[18] Nevertheless, it could be a matter of time that the sinus mucosa is damaged to such a level to allow a perforation and an extrusion of the biomaterial into the sinus cavity. Indeed, the extrusion of biomaterial inside the antral cavity has been documented in clinical studies, situations that required endoscopic removal of the biomaterial.[13,15] The present study reported the presence of multiple micro perforations. However, the presence of large perforations protected by a collagen membrane did not negatively influence the healing, as reported by various clinical studies.[43–46] It has also been documented that no adverse outcomes occurred regarding implant failures when no attempt was made to protect the sinus mucosa perforation, allowing the displacement of large amounts of graft material through the perforations. Nevertheless, higher intraoperative and postoperative complications were registered in that group of patients compared to the group with no perforation of the sinus mucosa.[14]

In the present study, repairing processes performed by the sinus mucosa were observed around the perforations, either in a hopeless attempt to once again include the granules within the elevated space or, mostly, driving them outside the subantral zone to allow healing of the procured wound (Figs 6c and 6d).

The animal model used in the present study was a modification of the original design proposed previously.[47] The major limitation of the present study was represented by the use of this rabbit model that suggests using caution when the outcomes are inferred to human beings due to the different width of the sinus mucosa[18,41,42] and the rate of healing.[48] Nevertheless, the literature available is mostly directed to the outcomes of the implants placed in the augmented sinusal region. A longer interval period should have also been considered to evaluate possible wound repairs after the expulsion of the graft granules (Figs 6c and 6d). Moreover, a control at time 0 should have been included to evaluate how the surgical trauma could directly affect thinning and perforation of the sinus mucosa. More studies should be performed to evaluate the healthy conditions of the sinus mucosa over time, not only with radiographic assessments, but also with specialist visits followed by endoscopic check-ups if needed. Experimental studies using biomaterial with different characteristics and resorbability should be performed to evaluate the effect on the sinus mucosa over time.

CONCLUSIONS

Thinning zones and perforations of the sinus mucosa were seen increasing in number over time in regions in contact with graft granules in both the large and small groups.

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