Association between maxillary sinus fungus ball and sinus bone grafting with deproteinized bovine bone substitutes: a case-control study

SCOLOZZI, Paolo, et al.

Abstract
To evaluate the association between sinus bone graft and the development of fungus ball (FB) of the maxillary sinus.


DOI : 10.1016/j.oooo.2016.01.022
PMID : 26972422
Association between maxillary sinus fungus ball and sinus bone grafting with deproteinized bovine bone substitutes: a case-control study

Paolo Scolozzi, MD, DMD, a Alexandre Perez, DMD, b Raul Verdeja, MD, DMD, c Delphine S. Courvoisier, PhD, d and Tommaso Lombardi, MD, DMD e

Objective. To evaluate the association between sinus bone graft and the development of fungus ball (FB) of the maxillary sinus.

Study Design. The charts of all patients seen for surgical treatment of maxillary sinus FB following sinus bone grafting between 2006 and 2014 were reviewed. The charts of 49 participants were selected from our internal registry for comparison as controls. The association between FB and age, gender, smoking habits, associated co-morbidities, and bone grafting material was evaluated. FB of the maxillary sinus was estimated by using an odds ratio with a Yates’ correction. P values were computed using Fisher’s exact test, and the statistical significance was set at a P value < .05.

Results. All 13 cases (100%) with FB of the maxillary sinus had received anorganic bovine bone as the bone substitute (P = .0001). There were significantly more women in the case group than in the control group (84.6% in the cases vs 40.8% in the controls; P = .01).

Conclusions. This study demonstrated a significant association between a specific deproteinized bovine bone substitute use as sinus bone graft material and subsequent development of FB of the maxillary sinus. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:e143-e147)

Fungus ball (FB) represents the most common form of noninvasive extramucosal fungal infection involving the paranasal sinuses and is encountered in almost 28.5% of patients suffering from chronic maxillary sinusitis. 1-3 Aspergillus fumigatus is, by far, the most frequent causative agent found in Europe, and the root canal overfilling with the passage of zinc oxide endodontic sealers into the maxillary sinus is the most commonly recognized risk factor for the development of FB in up to 84% of patients. 1-6 Although this form of sinusitis typically affects healthy adults and has a striking female predominance, several pathologic conditions, such as diabetes, immunodeficiency diseases, and immunosuppressive and chronic corticosteroid and antibiotic treatments have been pointed out as potential predisposing factors favoring the colonization and subsequent overgrowth of the fungal hyphae. 1-3

Since its first report in 1980 by Boyne and James, grafting of the maxillary sinus floor has rapidly become the most common surgical procedure used to increase the subantral alveolar bone height of the posterior maxilla for subsequent dental implant placement. 7 Although reported as a predictable and reliable procedure, sinus bone graft has, nevertheless, been associated with several intra- and postoperative complications, such as sinus membrane perforation, maxillary sinusitis, wound dehiscence with graft exposure, and graft infection. In most cases, complications resolve with no need for further surgery and with no substantial impact on implant survival; however, in some cases, complications may lead to complete loss of the graft material, thus compromising the subsequent implant-supported dental restoration. 8-17

Although the literature contains many reports describing the use of a myriad of bone substitutes, including allografts, xenografts, and alloplasts, autologous bone graft has been shown to be the only “material” to possess the three fundamental properties...

Statement of Clinical Relevance

Our findings showed a significant association between specific deproteinized bovine bone use as sinus bone graft material and development of fungus ball of the maxillary sinus.
("regenerative triad") of an ideal graft: osteogenesis, osteoinduction, and osteoconduction.\textsuperscript{18-21} For this reason, autologous bone graft remains the gold standard for biologic management of alveolar ridge augmentation despite the risk of donor site morbidity and graft resorption.\textsuperscript{18-21}

Since its first applications to alveolar bone at the end of the 1980s and beginning of the 1990s, Bio-Oss (Geistlich Pharma AG, Wolhusen, Switzerland), a deproteinized bovine bone substitute, is, by far, the most commonly used xenograft. It may be used alone or mixed with cancellous autogenous bone for the reconstruction of limited horizontal alveolar ridge defects, for subantral bone augmentation as part of sinus lift procedures, for periodontal regeneration, and for the healing of extraction sockets.\textsuperscript{22-25} Although only one study has reported on the development of FB of the maxillary sinus following sinus bone grafting, in recent years, we have observed a resurgence of cases presenting with such a calamitous association.\textsuperscript{26}

Thus, the present case-control study was undertaken to assess the possible association between sinus bone graft material and subsequent development of FB of the maxillary sinus. To the best of our knowledge, this is the first comprehensive study that evaluates such a relationship.

**MATERIALS AND METHODS**

The procedure followed in this retrospective case-control study was in accordance with the Helsinki Declaration of 1975, as revised in 2000, and was approved by our local ethical board.

All patients referred to the Hôpitaux Universitaires de Genève and the Hôpital Cantonal de Fribourg, Switzerland, between 2006 and 2014 for surgical treatment of FB of the maxillary sinus following sinus bone grafting were included.

The diagnosis of FB was based on the presence of chronic unilateral maxillary sinusitis with purulent discharge and on typical computed tomography scan features (opacified sinus with disseminate flocculent metal-like bodies). All of the patients were treated by lateral antrotomy with bone flap repositioning and fixation with a titanium plate, according to the technique previously described by Scolozzi et al.\textsuperscript{27} The final diagnosis of FB was made by microscopic examination, which confirmed the presence of *Aspergillus* hyphae in all biopsy specimens. The microbiologic cultures were negative in all the cases.

For each case, we considered age at time of diagnosis, gender, smoking habits, associated co-morbidities, bone grafting material, and pre-existing sinus disease. Co-morbidities were defined as the co-occurrence of any acute and/or chronic diseases.

The charts of 49 participants who underwent sinus bone grafting during the same period were selected from our internal registry for comparison as controls. The control group was selected from the same population as the cases (i.e., same time period, same geographic area, and same indications for sinus bone grafting). The main criterion of selection was that they underwent a sinus bone grafting during the same period as the case-study group.

**Statistical analysis**

Data were analyzed by using R 3.1.1 statistical software (R Development Core Team, Vienna, Austria).

According to our protocol, we expected to select four times more control participants than our 13 cases. Assuming prevalence for each risk factor among the cases of 40%, a Type I error of 5% and power of 80% allowed the detection of a difference of proportion of 40.7%, which means that at least 80.7% of patients with FB were exposed to the risk factor. Note that only 49 controls were then obtained from the internal registry of the Dental School at the University of Geneva.

The association between FB and age at time of diagnosis, gender, smoking habits, associated co-morbidities, bone grafting material was evaluated. FB of the maxillary sinus was estimated by using odds ratio (OR) with Yates’ correction to accommodate the cell with a zero count and its 95% confidence interval. *P*-values were computed by using Fisher’s exact test and the statistical significance was set at a *P* value < .05.

**RESULTS**

Thirteen cases were diagnosed with FB of the maxillary sinus following sinus bone graft. In all of the cases, the disease was diagnosed during the phase of incorporation of the graft material, and thus none of the patients could receive dental implants.

Table I lists the characteristics of both groups. There were significantly more women in the case-study group.

<table>
<thead>
<tr>
<th>Table I. Sample characteristics of cases and control</th>
<th>Cases</th>
<th>Control</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2 (15.4)</td>
<td>29 (59.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Women</td>
<td>11 (84.6)</td>
<td>20 (40.8)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>56.5 (10.5)</td>
<td>62.7 (16.5)</td>
<td>.07</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (7.7)</td>
<td>3 (6.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>12 (92.3)</td>
<td>46 (93.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (100.0)</td>
<td>49 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing sinus disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (100.0)</td>
<td>49 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>
Table II. Number (%) of patients exposed to Bio-Oss among cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (FB)</th>
<th>Controls (No FB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio-Oss</td>
<td>13 (100.0)</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>No Bio-Oss</td>
<td>0 (0.0)</td>
<td>28 (57.1)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>49</td>
</tr>
</tbody>
</table>

FB, fungus ball.

*P-value based on Fisher exact test is .0001.

than in the control group (84.6% in the cases vs 40.8% in the controls; $P = .01$). None of the patients in either group was a regular smoker. In none of the patients in either group was a perforation of the Schneiderian membrane reported during the surgery. Three patients in the control group presented co-morbidities (one patient had Crohn disease, one had type 2 diabetes and hypertension, and one had systemic lupus erythematosus). One patient in the case-group had had a liver transplantation. However, according to the patient file analysis, none of the patients had pre-existing sinus disease.

All 13 cases (100%) with FB of the maxillary sinus had received Bio-Oss as the deproteinized bovine bone substitute. By contrast, only 21 of the 49 (42.9%) controls received Bio-Oss (Table II). Thus, a strong association has been established between the sinus bone graft procedure with Bio-Oss and the subsequent development of FB of the maxillary sinus, with an OR of 35.79 calculated by using Yates’ correction (95% confidence interval 2.01-636.12; $P = .0001$). The difference in risk of exposure to Bio-Oss between cases and controls was large (0.57).

DISCUSSION

In this case-control study, we determined a highly significant association between the use of Bio-Oss as a sinus bone graft material and the subsequent development of maxillary sinus FB. The occurrence of such a severe complication was also found to be significantly more prevalent in women. It should be emphasized that although the relatively high prevalence of Bio-Oss use in the control group (43%) would tend to mitigate the impact of the present study, the results remain highly significant, with large measures of association (OR = 35.8; difference in risk of exposure 57.1%). Unfortunately, our findings could not be compared with other published results, given the absence of similar studies. Note that we could not determine the incidence rate of FB among all patients receiving Bio-Oss. However, given the frequent use of Bio-Oss, and the fact that we only found 13 cases, we can expect the incidence rate to be very low. Thus, even though the risk of a FB is greatly increased by the use of Bio-Oss, this risk remains very low.

Although the literature is replete with clinical studies reporting on the use of Bio-Oss as grafting material for maxillary sinus augmentation, few references have focused on the surgical complications, which often are generic.12,14,25 Therefore, the incidence and treatment of the specific subset of patients with postoperative maxillary sinusitis have to be carefully extrapolated and evaluated. In 2012, a systematic review of 35 studies assessing the outcome of maxillary sinus floor augmentation with Bio-Oss alone or mixed with autogenous bone graft material revealed only one study reporting an acute postoperative maxillary sinusitis, which had led to the loss of the simultaneously placed implants.12 Recently Schwarz et al., in a series of 407 sinus lift procedures with a mixture of Bio-Oss and autogenous bone found an overall maxillary sinusitis prevalence of 8.4%, which increased up to 26.2% in smokers.17 Others have reported that significant risk factors for postoperative maxillary sinusitis include perforation of the Schneiderian membrane and age of patient, with the risk increasing for each additional year.8-11 Interestingly, they showed a significant association between intraoperative perforation of the sinus membrane and subsequent occurrence of sinusitis, which was, nevertheless, found also in cases with an intact membrane.8-11 Moreno Vazquez et al. reviewed 200 consecutive sinus lift procedures, and they found postoperative sinusitis in 3.9% of the patients and intraoperative membrane perforation in 25.7% of the cases.15 In contrast to the previous study, they did not find a relation between sinus membrane perforation and sinusitis.15 Among the patients who had experienced membrane perforation, none developed sinusitis; however, a previous history of maxillary sinusitis was found in half of the patients who developed postoperative sinusitis.15 Thus far, to the best of our knowledge, the development of postoperative maxillary sinusitis has mainly been reported following sinus lift procedures using allografts, xenografts, and alloplasts.12-17 Interestingly, the few cases of acute sinus infection related to autogenous sinus bone graft were associated with a simultaneous alveolar onlay bone graft.9

The most probable primum movens mechanism leading to the development of maxillary sinusitis is the violation of the sinus membrane, which together with specific local rhinosinus predisposing factors (e.g., nasal septum deviations, inferior turbinate enlargement, nasal polyposis, chronic rhinosinusitis, allergic rhinitis, decreased patency of the osteomeatal complex) allows for bacterial and/or fungal proliferation.8,28,29 According to some studies, it would seem that such factors play the predominant role in increasing the prevalence of maxillary sinusitis rather than the intraoperative membrane perforation itself.8,28,29 Conversely, no
systemic disease has been associated with an increased risk of developing sinusitis. To date, the perforation of the Schneiderian membrane is, by far, the most prevalent complication reported in up to 85% of cases and has been associated with residual subantral bone height (<3.5 mm), presence of sinus septa, and a smoking habit. Therefore, on the basis of these findings, some authors strongly suggest evaluating the patient’s history in detail, searching for signs and/or symptoms related to pathologic chronic rhinomaxillary conditions as well as prescribing routine computed tomography in the preoperative workup of maxillary sinus floor procedures and dental placement.11,15

Thus far, only one case of FB following sinus bone grafting—with irradiated cancellous bone as filling material—has been reported in the literature.26 Although the exact etiopathogenesis of FB still remains obscure, there are two main coexisting theories: aerogenic and odontogenic theories.1,3 The aerogenic theory is almost exclusively related to the endemic maxillary sinusitis found in the Sudan associated with the inhalation of high quantities of Aspergillus flavus spores over a very long period.1,3 The odontogenic theory is mainly explained by three interdependent factors related to the use of endodontic sealers containing zinc oxide.1-6 The first factor is the creation of an oroantral communication, which acts as a route for the maxillary sinus contamination with the Aspergillus species. The second factor is the impairment of the normal ventilation and drainage clearance system, which is caused by the physical excess of the sealers within the sinus.1-6 And the third factor is Aspergillus overgrowth, which is chemically elicited by the zinc itself. The explanation of the underlying mechanism leading to the development of FB related to Bio-Oss, as found in our study, can be only speculative and extrapolated by analogy to what has been previously mentioned for zinc oxide. A priori, Bio-Oss is a deproteinized natural bovine cancellous bone with a crystalline structure that is very similar to human bone. The deproteinization process should thus eliminate any immunogenicity concerns. However, studies have demonstrated that Bio-Oss can contain osteoinductive proteins, such as transforming growth factor-β and bone morphogenic protein bone morphogenetic protein-2, which can elicit an immune response.30 Moreover, one case report presented a foreign body reaction in a patient who had undergone alveolar ridge augmentation with a mixture of Bio-Oss and autogenous bone.31 The most plausible explanation for such a reaction is an interaction between residual proteins within the Bio-Oss particles with adhesion receptors present on monocyte/macrophage inflammatory cell populations. In one case in our series, polarization microscopy revealed birefringence, strongly suggesting the presence of residual of collagen fibrils. These findings raise doubts concerning the ability to obtain de facto pure anorganic bovine bone. We can hypothesize that similar to the mechanism of a foreign body reaction, the residual proteins could stimulate an immune response to the xenograft and that this immune response could promote the Aspergillus growth within the maxillary sinus leading to FB formation.

The main limitation of the present study is inherent to the retrospective case-control design. Case-control designs are necessary in the case of very rare complications because the number of patients required to detect even a few cases in a prospective study would be too high. For instance, if the incidence of FB was one for each 10,000 bone grafts when using Bio-Oss and one for each 100,000 bone grafts (incidence rate = 10), the sample size needed for a randomized controlled trial to detect this difference would be 255,680. However, there is always the possibility that the controls selected in our study differ from the cases in some way that was not measured, and this could cause a bias resulting from confounding factors. In this study, the controls were selected from the same period and the same geographic region, and they had the same indications for sinus bone grafting.

CONCLUSIONS
The present study has demonstrated a significant association between specific deproteinized bovine bone use as sinus bone graft material and FB of the maxillary sinus. However, it should be kept in mind that given the limitations of an observational study, an evidence of causality between the use of Bio-Oss in female patients and the development of a sinus FB can only be suspected and not compellingly confirmed. These results suggest that particular attention should be paid to using Bio-Oss with women who are candidates for a sinus bone grafting procedure because they could have a higher risk of developing FB of the maxillary sinus in comparison to using other bone graft substitutes.

REFERENCES


Reprint requests:
Paolo Scolozzi, MD, DMD
Division of Oral and Maxillofacial Surgery
Department of Surgery
University of Geneva & University Hospitals of Geneva
Geneva
Switzerland
Paolo.scolozzi@hcuge.ch