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Clinical evaluation of demineralized bone allograft in a hyaluronic acid carrier for sinus lift augmentation in humans: a computed tomography and histomorphometric study

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Key words: augmentation, β-TCP, Bio-Oss®, DBM, DBX®, DFDBA, histology, human, sinus lift

Abstract

Objectives: Natural and synthetic graft materials are used routinely in sinus floor augmentations to help support implants in atrophic maxillary ridges. This clinical study was based on the hypothesis that the clinical effectiveness of demineralized freeze-dried bone allograft/demineralized bone matrix (DFDBA/DBM) in sinus lifts varies when used in combination bone graft substitute materials. To test this hypothesis, DFDBA was used together with one of three materials: in saline plus anorganic bone (DFDBA: Bio-Oss®); in hyaluronic acid (DFDBA: HY, 32 : 68, w/w; DBX®) alone; DBX® plus Bio-Oss®; and DBX® plus tricalcium phosphate granules (β-TCP).

Material and methods: Thirty-two sinus lift procedures, eight per group, were performed on 26 patients. Before surgery and at 8 months post-surgery when implants were placed, ridge heights were visualized by computed tomography (CT) and measured by morphometric analysis. Cores of bone were removed by trephine at the sites of implant placement; these biopsies from the graft sites were used for histomorphometric analysis.

Results: All 32 sinus lift elevations were successful when measured by CT, increasing from an average 2.84 ± 0.2 mm before treatment to 15.2 ± 0.6 mm after treatment. The percent of each biopsy that was occupied by new bone and incorporated bone graft materials varied with each treatment: DFDBA + Bio-Oss®, DBX® + Bio-Oss®, or DBX® alone was higher than that for DBX® + β-TCP by approximately 10%. When comparing only newly formed bone, DBX® + β-TCP treatment resulted in 50% less bone than the other three preparations. All grafted sites received implants as per the treatment plan for each patient.

Conclusions: This study confirmed the hypothesis that new bone formation is dependent on the DFDBA formulation used and demonstrated that DBX®, alone or in combination with other materials, can be used successfully for sinus floor elevation.

Date:
Accepted 13 March 2006

To cite this article:
Schwartz Z, Goldstein M, Raviv E, Hirsch A, Ranly DM, Boyan BD. Clinical evaluation of demineralized bone allograft in a hyaluronic acid carrier for sinus lift augmentation in humans: a computed tomography and histomorphometric study.
Clin. Oral Impl. Res. **18**, 2007; 204–211
doi: 10.1111/j.1600-0501.2006.01303.x

In periodontics and oral surgery, the use of bone graft substitutes to enhance bone regeneration has become common practice. These procedures, which include infrabony defect treatments, ridge augmentation, and sinus floor elevations, sometimes make use of a single bone graft substitute, but often they are combined with autogenous bone (Hallman et al. 2005; Zijderveld et al. 2005). Human demineralized freeze-dried bone allograft (DFDBA), also called demineralized bone matrix (DBM), is a bone graft substitute (Libin et al. 1975; Mulliken et al. 1981) that has been used for sinus floor elevation (Groeneveld et al. 1999), but it does not possess ideal handling characteristics or sufficient structural strength for some purposes. For this reason, DFDBA is sometimes combined with materials that result in a putty-like consis-

tency, or with materials that are stiffer, such as non-demineralized bone allograft particles (Cammack et al. 2005), xenograft materials like deproteinized bovine bone (Valentini & Abensur 1997), and synthetic calcium phosphate granules.

Besides proven effectiveness, a clinician desires a bone graft substitute to possess simple handling characteristics. In order to facilitate the use of DFDBA in clinical practice, several commercial suppliers of this bone graft substitute have begun to combine the powder with a carrier. However, the effect of these carriers on the osteoinductivity of the DFDBA is unknown. The repercussions could range from a simple dilution effect to a complete inhibition of the osteoinductivity. In the worst-case scenario, the carrier could be toxic, immunogenic, or both.

In addition to favorable handling characteristics, an optimal material used in sinus lift procedures would have sufficient body to hold the sinus lining in an elevated position and not settle before stabilization by bone fill. For this reason, materials such as deproteinized bovine bone (Tadjoedin et al. 2003), cortical bone particles (Lundgren et al. 1996), tricalcium phosphate (Zijderveld et al. 2005), and bioactive glass (Turunen et al. 2004) are used separately or in combination to confer bulk to the graft. DFDBA provides some structural support but is frequently combined with one or more of these additives to ensure that height is maintained as new bone formation proceeds. When DFDBA is formulated as a putty using hyaluronic acid as the carrier, handling properties are improved but the resulting material has less mechanical stiffness than DFDBA alone, suggesting that it would need to be used with a mineral-containing bone graft substitute in a sinus lift application.

The present study was based on the hypothesis that the amount of bone formed within a sinus lift procedure using DFDBA depends on the formulation used. We also tested a secondary hypothesis that DFDBA in the form of a putty is sufficient to support bone formation and maintain tissue dimensions to a similar extent as can be achieved when DFDBA is used in combination with a mineralized bone graft substitute. To do this, we used a putty consisting of human DFDBA (32% by weight) in hyaluronic acid (DBX®) and compared its effectiveness *in vivo* with that of DBX® plus one of two bone graft substitutes: deproteinized bovine bone granules (Bio-Oss®) and β-tricalcium phosphate granules (β-TCP). In addition, the results were compared with a commonly used clinical combination: DFDBA plus Bio-Oss® (Valentini & Abensur 1997). Outcome measures included the size and quality of sinus elevation, the former by computed tomography (CT) and the latter by histomorphometrics.

Material and methods

Patient selection

Twenty-six patients, 13 of each sex, all non-smokers, age range 29–73 years with an average age of 53.3 ± 1.5 (mean SEM), were included in this study. Patients were excluded from the research if their health was compromised or they suffered from drug abuse. The inclusion criteria for patients were as follows: partially edentulous jaws, with a unilateral or bilateral loss of teeth in the maxillary pre-molar or molar area, severe alveolar atrophy (a residual alveolar ridge height of 5 mm or less) as judged by pre-operative panoramic radiographs, and alveolar ridges that needed no buccal–lingual augmentation. The patients selected had good oral health and no active periodontitis.

All patients were sent for CT (an example in Fig. 1a). From the tomograph of each patient, two cuts were selected that reflected the mesial and distal limits of the proposed sinus elevation, limits dictated by the number of implants to be placed in the site. Measurements were made of the alveolar ridge height at two cuts immediately adjacent to the outer limiting cuts. Another measure was made geometrically between these two cuts. These three measurements were then used to obtain the average alveolar height. For all the patients, the average residual height was 2.84 ± 0.15 mm. In addition, two additional measurements were obtained from the CT scans: the minimum residual alveolar height (1.94 ± 0.15 mm) and the maximum residual alveolar height (3.75 ± 0.19 mm). The minimum and maximum values for the four patient groups are listed in Table 1.

In the population of 26 patients, 20 needed unilateral sinus floor augmentation, and six needed bilateral augmentation. As a result, there were 32 sinus lift surgeries. They were treated as separate procedures and divided into four groups of eight surgical sites. The patient distributions with the pre-operative and post-operative alveolar ridge heights are shown in Table 1.

All patients were fully informed of the research implications of the surgeries, and consent forms were signed prior to the commencement of the treatment. The consent forms were approved by the Ethics Committee of Hadassah Hebrew University and the Ministry of Health Israel.

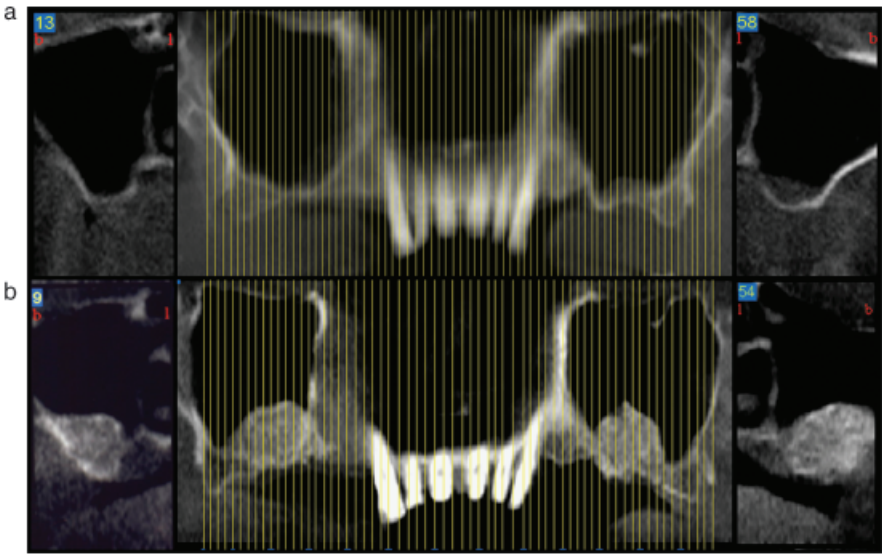

Fig. 1. (a) Computed Tomography scan of a patient before bilateral sinus lift elevation; (b) scan of a patient at 8 months post-surgery, showing new bone mass on the sinus floor.

Table 1. **Patient information and distribution in the study**

Treatment group	Age (years)	Sex		Maxilla side		Alveolar ridge height pre-operative (mm)		Alveolar ridge height post-operative (mm)	
		F	M	Right	Left	Min	Max	Min	Max
DFDBA + Bio-Oss®	56.1 ± 2.4	4	4	4	4	1.9 ± 0.3	3.3 ± 0.2	13.6 ± 2.1	18.0 ± 2.6
DBX + Bio-Oss®	50.8 ± 3.4	5	3	4	4	1.6 ± 0.2	3.5 ± 0.5	11.6 ± 1.3	17.6 ± 1.4
DBX®	56.4 ± 2.5	3	5	4	4	2.4 ± 0.4	4.5 ± 0.5	11.4 ± 0.5	17.8 ± 0.9
DBX® + β-TCP	49.9 ± 3.6	4	4	4	4	1.9 ± 0.2	3.8 ± 0.3	11.6 ± 1.2	17.8 ± 0.6

Min, minimum; Max, maximum; F, female; M, male; β-TCP, β-tricalcium phosphate granules; DFDBA, demineralized freeze-dried bone allograft.

Bone graft substitutes

As noted above, the study consisted of four treatment groups. DFDBA and Bio-Oss® together constitute a common clinical bone graft substitute used in periodontology and implant dentistry (Valentini & Abensur 1997), and we elected to use it as the control in this study. Group 1 was a 50–50 (v/v) mixture of 250–800 μm diameter DFDBA particles [Musculoskeletal Transplant Foundation (MTF), Edison, NJ, USA] and deproteinized cancellous bovine bone (Bio-Oss®, Geistlich Sons Ltd, Wolhusen, Switzerland). Group 2 was a 50–50 mix (v/v) of DBX® (32% DFDBA in hyaluronic acid carrier) (MTF) and Bio-Oss®. Group 3 was DBX® alone. Group 4 was a 50–50 mix (v/v) of DBX® and β-TCP (Synthes, Solothurn, Switzerland). The DFDBA in the DBX® used in Groups 2–4 was from the same donor as used in Group 1, and had the same particle size.

Surgical procedures

Patients were given 1750 mg of amoxicillin/clavulanate potassium (Augmentin®, GlaxoSmithKline, Research Triangle Park, NC, USA) 1 h before their surgery. The sinus floor augmentation was then carried out according to a modified Calwell–Luc approach as described by Kent & Block (1989) (Fig. 2). In brief, under local anesthesia the posterior part of the maxilla was exposed via a crestal incision and elevation of a muco-periosteal flap. A buccal window was opened and the sinus mucosa was carefully lifted. The sinus was then filled with one of the graft mixtures, and then a resorbable collagen membrane (Bioguide®, Geistlich Sons Ltd) was positioned over the open window, and a complete wound closure was performed. After the surgery, the patient was prescribed 875 mg of Augmentin® twice a day for a week, and advised to rinse their mouth daily with chlorhexidine (0.2%) for 10 days. The patients were examined 1 week post-surgery when the sutures were removed. All patients were checked regularly to verify healing. After 8 months, implants were placed in the augmentation sites.

Biopsies

The bone samples used for histological evaluation were obtained as a by-product of implant placement. Under local anesthesia, a vertical incision was made buccally in the canine area and continued horizontally and distally at the palatal side of the alveolar crest. A full-thickness flap was raised and mobilized for tension-free closure. After the bone was inspected and the implant position was determined, a trephine hollow drill was used to prepare the cylindrical placement site. The removed bone biopsy, contained within the trephine, measured 10–12 mm in length and 2.8 mm in diameter. The implants were then twisted into the cylindrical sites, and the torque required was recorded. After the implants were seated, complete wound closure was performed.

The biopsied bone was quickly removed from the trephine and fixed in buffered 4% formaldehyde. After a week of fixation, they were decalcified in 5% formic acid for 2 weeks. The decalcified cylindrical specimens were embedded in paraffin. After bisecting the embedded cylinders, 5 μm longitudinal sections were cut on the bisected face. Sections were stained with hematoxylin and eosin for light microscopy.

Morphometric analysis of CT scans and histologic sections

Morphometric analyses were performed on the two CT scans of each patient: one taken before the sinus lift procedure and the other before the biopsy. The height of bone was measured at three points and the mean height was calculated. In addition, the minimum and maximum heights were measured, as described previously.

Histomorphometric analyses were performed on the same longitudinal sections used for histologic analysis. Areas of the sections to be measured were captured at the appropriate magnification by video camera. The following was measured: (I) area of new bone (NB) including any incorporated graft material (G: DFDBA, Bio-Oss® or β-TCP), reported as a % of the area of the whole section, excluding the original cortical bone (%NB + G); (II) % new bone alone (%NB); and (III) % DFDBA, Bio-Oss®, or β-TCP.

All morphometrics were performed using a computerized analysis system (Image-Pro Plus, Media Cybernetics, Silver Springs, MD, USA). Calibrations were performed according to the instructions accompanying the software.

Statistical analysis

The results of the morphometric analyses were calculated as the means ± SEM for each variable. The values for all groups represent findings from eight sinus lifts. Statistically significant differences between groups were tested by ANOVA and the use of Bonferroni's modification of Student's *t*-test. P values ≤ 0.05 were considered significant.

Results

An example of the sinus floor augmentation procedure is presented in Fig. 2. Under local anesthesia, a mid-crestal cut and two vertical buccal release cuts were performed (Fig. 2a). A full-thickness flap was raised, a buccal window was opened to access the sinus, and the sinus membrane was elevated (Fig. 2b). Implant material (DFDBA + Bio-Oss®) was inserted (Fig.

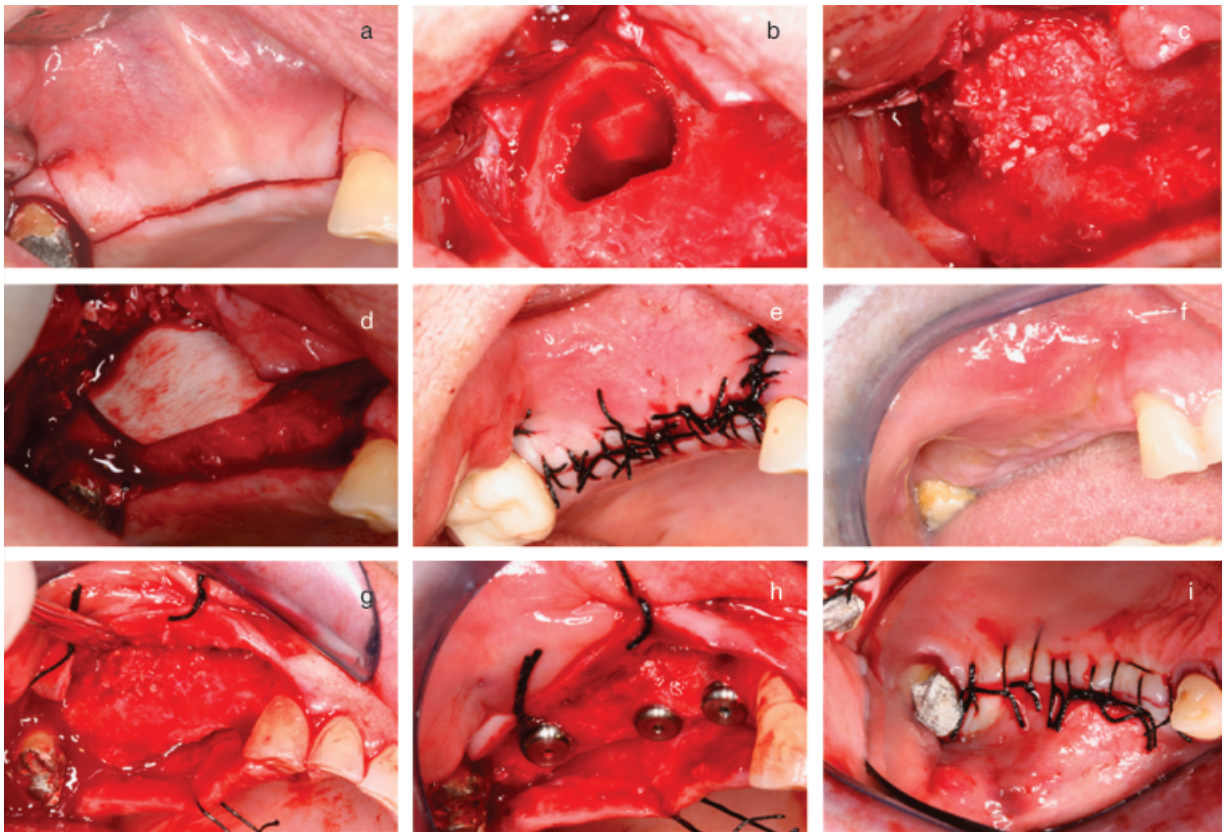

Fig. 2. (a) Crestal and buccal-releasing incisions on edentulous ridge; (b) buccal window in sinus after elevation of a full-thickness flap, bone removal, and lifting of sinus membrane; (c) sinus filled with demineralized freeze-dried bone allograft + Bio-Oss® before closure; (d) entrance to sinus opening covered with collagen membrane; (e) passive closure of surgical site; (f) uneventful healing of surgical site; (g) elevation of flap eight months later, showing full healing of bone; (h) implants placed in biopsy sites; (i) passive closure of implant site.

2c), and a collagen membrane was placed over the entrance to the sinus (Fig. 2d). A passive closure of the area was achieved (Fig. 2e), which healed with no problems (Fig. 2f). Eight months later, a full flap was raised to show complete healing of the bone (Fig. 2g), and after the biopsies were taken, three implants were inserted (Fig. 2h). All the surgeries healed without complications. All grafted sites received an implant, and in all cases sufficient bone height was achieved to insert an implant that was at least 13 mm in length.

The increase in ridge height for every patient as determined from CT scans is presented in Fig. 3a. The responses to sinus augmentation were variable, but in all cases there was a significant increase in ridge height. It is clear that no patient failed to benefit from the procedure, the final minimum ridge height being 13 mm. When the pre- and post-surgery ridge heights were compared for the four treatment groups (Fig. 3b), all of the bone graft materials were found to be effective. While the DFDBA + Bio-Oss® combination appears to be slightly better, there are no statistical differences between the groups.

Insertion of the implants following the augmentation procedure required different levels of torque. Full insertion of implants in patients treated with DFDBA or DBX® with Bio-Oss® was achieved using torque values of 35–40 N. For patients treated with DBX® alone, the torque was 30–35 N, and only 20 N were required for patients treated with DBX® + β-TCP.

The amount of new bone formed within the bone cores was different depending on the graft material used (Fig. 4). The values for DFDBA + Bio-Oss®, DBX® + Bio-Oss®, and DBX® were very similar; 90% of the volume of the bone core removed at the time of implant placement was new bone and associated graft (Fig. 4a). The combination of DBX® with β-TCP resulted in approximately 10% less total new bone plus graft. Measurement of new bone volume alone (Fig. 4b) confirmed that DBX® + β-TCP was less osteogenic than the other three grafts. Measurement of the area of residual graft material in the

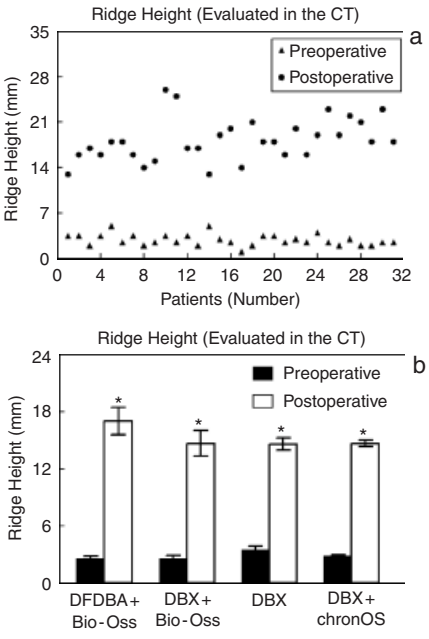

Fig. 3. (a) Pre- and post-operative ridge heights of 32 sinus lift sites as determined by Computed tomography (CT); (b) pre- and post-operative ridge heights for the four treatment groups as determined by CT. Each point is the mean ± SEM of eight patients (b).

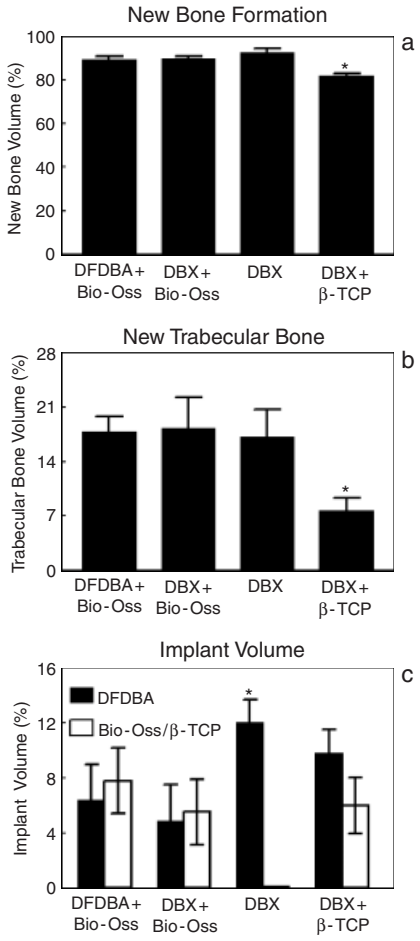

Fig. 4. (a) Comparison of the amount of new bone plus incorporated bone graft material in cylindrical cores removed at the time of implant replacement. (b) Comparison of the amount of new bone found in the four treatment groups as determined by histomorphometry. (c) Residual demineralized freeze-dried bone allograft (DFDBA), Bio-Oss®, or β-tricalcium phosphate granules present in the histologic sections. Data are expressed as percents of the total volume of the core. Each point is the mean ± SEM of eight patients. *$P<0.05$, significantly different from control (DFDBA + Bio-Oss®).

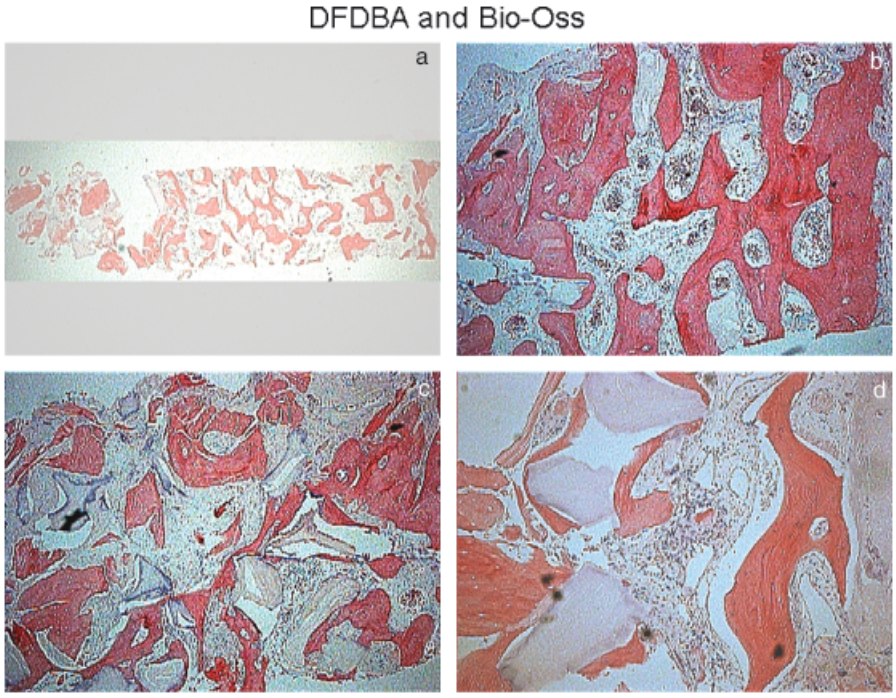

Fig. 5. Histologic sections of biopsies from the demineralized freeze-dried bone allograft (DFDBA) + Bio-Oss® treatment group. (a) Low-magnification photomicrographs of a full-length biopsy showing the focal site distal to the original cortical bone. (b) Specimen with a small amount of DFDBA graft material. (c, d) Low- and high-power magnifications of a specimen dominated by graft material.

sections (Fig. 4c) showed that the combinations of DFDBA + Bio-Oss® and DBX® + Bio-Oss® were resorbed and replaced by new bone at approximately the same rate. The amount of DFDBA remaining in the DBX® group was greater, but it was grafted at twice the amount originally. However, the amount of DFDBA left in the DBX® + β-TCP specimens suggests that β-TCP granules may have delayed the resorption of DFDBA.

While there were some differences between groups relative to osteogenesis, there was considerable variation within each group. Figure 5 shows the response in patients from Group 1 who were grafted with DFDBA + Bio-Oss®. In several cases, there was a lack of uniformity in the location of the new bone. In the patient shown (Fig. 5a), the new bone was concentrated away from the original cortical bone. Some patients exhibited only new bone, without any residual graft material (Fig. 5b). Figure 5c (low magnification) and 5d (high magnification) show a specimen with both DFDBA and Bio-Oss® particles but little new bone.

Patients treated with DBX® + Bio-Oss® presented very similar histology. Although all patients formed new bone, there was considerable variation in the amount. Figure 6a shows a case of focal osteogenesis and in Fig. 6b, new bone replaced all of the graft particles. In Figs 6c and d, the remnants of graft material were dominant. The similarities between sites grafted with DFDBA + Bio-Oss® and sites grafted with DBX® + Bio-Oss® suggest that the carrier had no effect on osteogenesis.

DBX® alone was very osteogenic in some of the patients in this treatment group. In Fig. 7A (low power) and 7b (high power), the new bone was so dense that it had the appearance of cortical bone. The specimen in Fig. 7c shows the considerable retention of DFDBA particles, but in 7d, there was considerable bone marrow and few DFDBA particles.

Patients treated with DBX® + β-TCP all showed at least some new bone formation (Fig. 8d). However, in most cases considerable DFDBA and β-TCP particles were observed (Figs 8a–c). The residual graft material was sufficient in some cases to cause sectioning artifacts during the preparation of histologic slides.

Discussion

This study confirmed the hypothesis that the amount of bone formed within a sinus lift procedure using DFDBA depends on the formulation used. One of the strengths of this study was that all graft preparations were from the same batch of DFDBA. We have shown in previous studies that there is great variability in the osteoinductivity of different batches of commercial DFDBA (Schwartz et al. 1998). These differences may be variously ascribed to donor age, method of preparation, and/or sterilization. Thus, any differences in bone formation can be ascribed to the formulation and not to donor variability in the DFDBA component. Like Bio-Oss®, tri-calcium phosphate

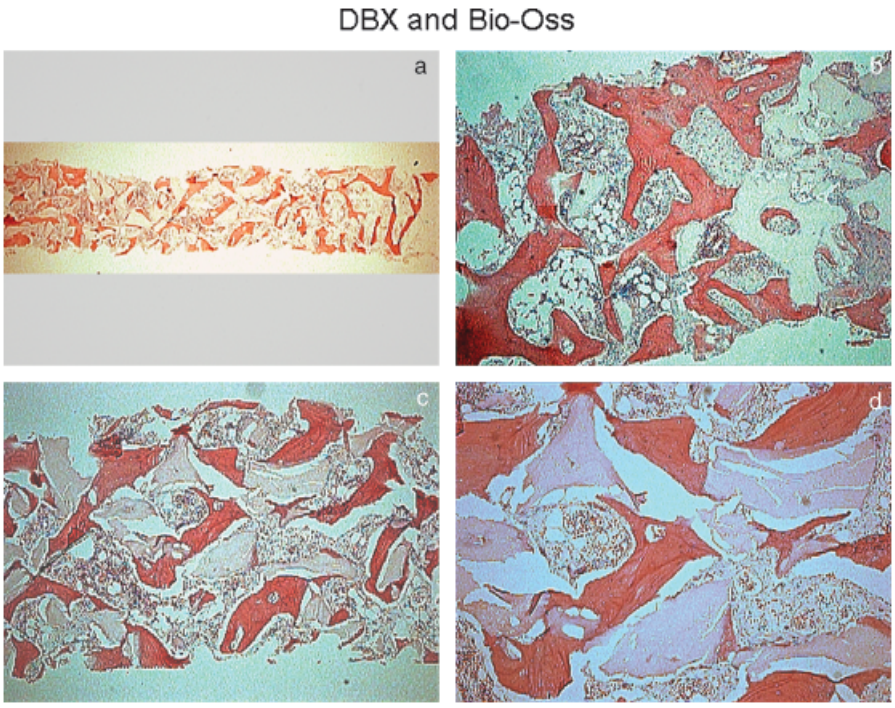

Fig. 6. Histologic sections from the DBX® + Bio-Oss® treatment group. (a) low-magnification picture showing focal osteoinduction. (b) Specimen in which most of the graft material has been replaced by new bone; some remnants of the graft material can still be found. (c, d) Low- and high-power magnification of a section with considerable residual graft material.

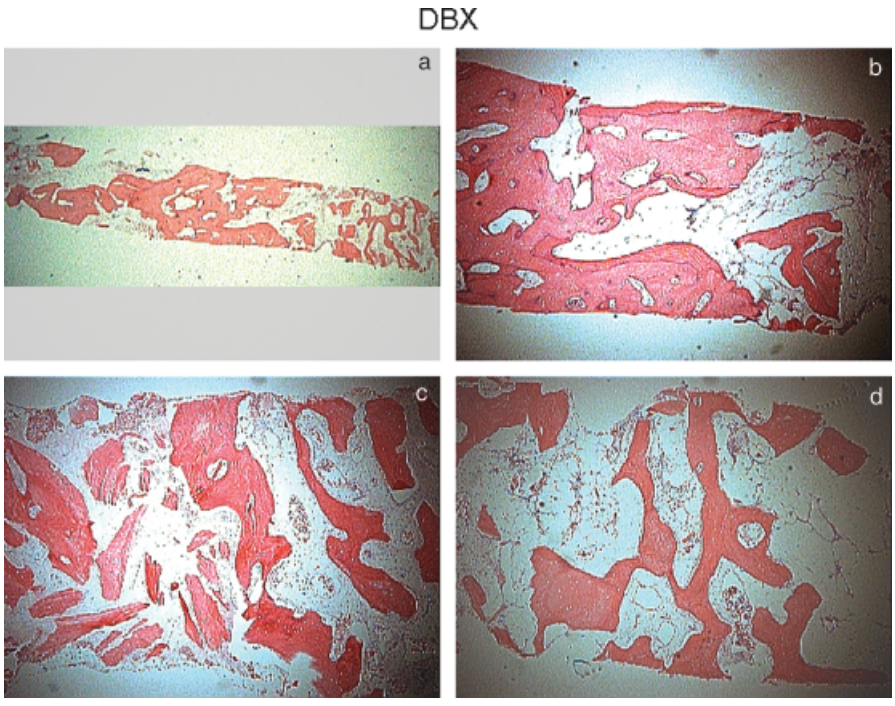

Fig. 7. Histologic sections from the DBX® treatment group. (a, b) low- and high-power photomicrographs showing very dense bone elicited by DBX® alone. (c) Specimen with retained demineralized freeze-dried bone allograft particles. (d) Section showing considerable bone marrow and little retained graft particles.

has been shown to be successful as a sinus graft (Zijderveld et al. 2005). Our results show that the additive used to improve the stiffness properties of a combination allograft material can affect the osteogenic properties of DFDBA *in vivo*: the combination of DBX® with β-TCP was less effective than the combination with Bio-Oss®.

This study also confirmed the hypothesis that DFDBA in the form of a putty is sufficient to support bone formation and maintain tissue dimensions to a similar extent as can be achieved when DFDBA is used in combination with a mineralized bone graft substitute. The combination of DFDBA + Bio-Oss® supported considerable amounts of new bone, possibly explaining the results of an earlier study that reported a high survival rate of implants placed into sinuses grafted with these materials (Valentini & Abensur 1997). Interestingly, the combination of DBX® + Bio-Oss® was just as effective, even though the hyaluronic acid carrier reduced the absolute amount of DFDBA from 50% of the mix to 17.5%. This result shows that the carrier in no way inhibited the osteogenic properties of the diluted DFDBA.

DBX® placed without other material elicited a similar volume of bone fill as the other combinations, but more striking was the quality of the bone. In many of the sections, the bone was so dense as to resemble cortical bone. Insertion torque values were similar to those seen in patients treated with DFDBA or DBX® plus Bio-Oss®. Another study (Valentini & Abensur 1997) used DFDBA by itself in sinus lift procedures, but no data were provided on the extent of the bone fill or how well DFDBA by itself could be handled.

Autogenous bone is considered by many to be the gold standard for grafting, but for several reasons, it is usually extended with other graft materials, natural or synthetic. Despite the fact that most of these combinations have demonstrated excellent results, many clinicians wish to find an alternative to autogenous bone. Obtaining this bone often requires a secondary surgery, either iliac crest (van den Bergh et al. 1998) or mandibular scrapings (Lundgren et al. 1996). The morbidity from these added procedures is not trivial (Kalk et al. 1996) and obtaining sufficient autogenous bones for extensive sinus augmentation further complicates the matter. An effective substitute for autogenous bone would be a welcome addition to the clinician's armamentarium.

The carrier for DBX® is hyaluronic acid, a biocompatible, biodegradable, and nontoxic natural polymer. DBX® alone or in combination with Bio-Oss® was as effective as DFDBA + Bio-Oss®, even though the hyaluronic acid carrier reduced the

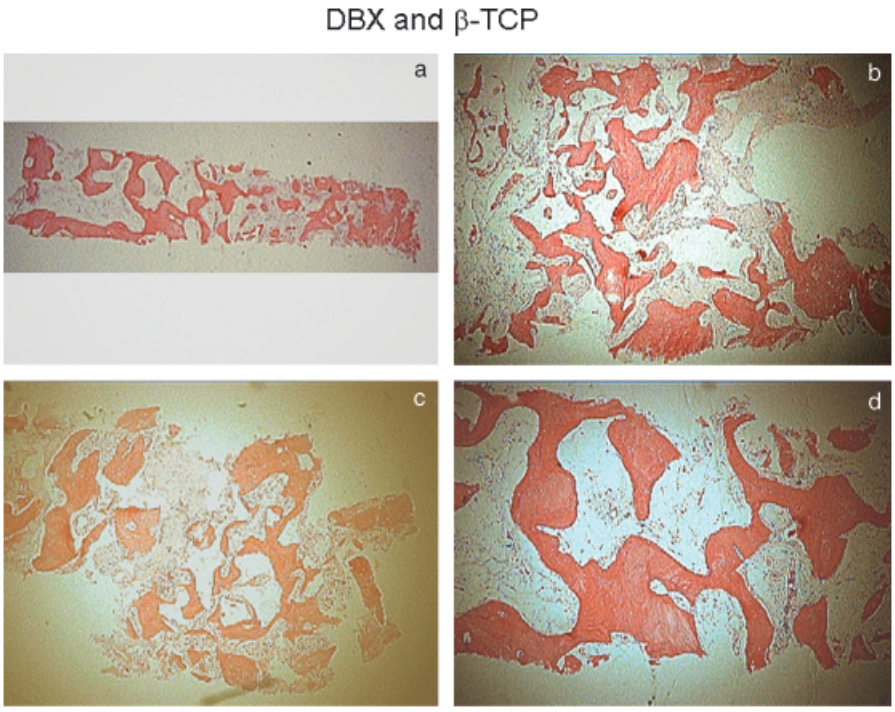

Fig. 8. Histologic sections from the DBX® + β-tricalcium phosphate granules treatment group. (a–c) Micrographs of specimens showing considerable residual demineralized freeze-dried bone allograft. (d) A section showing a small amount of new bone formation.

absolute amount of DFDBA to 16%. Hyaluronic acid has been used successfully in other areas of medicine such as treatment of skin disease (Weindl et al. 2004) and joint maladies (Fukuda 2004), and relative to this study, hyaluronic acid has been used successfully as a carrier of biologics (Fukuda 2004). Our results show that it can also be used as a carrier for DFDBA without reducing the clinical effectiveness of the demineralized bone allograft.

Differences in the required torque to insert the implants fully following augmentation suggested that the clinical result achieved depended on the type of bone graft material used. Insertion torque is an indicator of primary stabilization and does not necessarily indicate the amount of new bone that has formed. The low torque values needed to insert implants in patients treated with DBX® + β-TCP suggested low resistance with less primary stabilization. This may indicate that better clinical results may be seen when implants are inserted into sites treated with the materials used in Groups 1–3.

Hyaluronic acid is composed of different-sized polymers, and the one selected for DBX® in combination with DFDBA provides a mixture with a putty-like consistency. The clinicians involved in the sinus lift surgeries felt that granules of the other materials could be easily incorporated, but that DBX® by itself exhibited good handling characteristics and sufficient body to fill the sinus space without sagging. The added dimension of a putty-like consistency for easier handling earmarks it as a welcome addition to dento-facial and orthopedic surgery. Moreover, because it can be used without mixing with other bone graft substitute materials, procedure times can be reduced.

Acknowledgements: The authors thank Dr Perry Raz (Department of Periodontics, Hebrew University Hadassah Faculty of Dental Medicine, Jerusalem, Israel) for her contributions to the work described in this paper. This research was supported by the Musculoskeletal Transplant Foundation, the Price Gilbert, Jr. Foundation, the Georgia Research Alliance, and the Georgia Tech/Emory Center for the Engineering of Living Tissues. The authors also thank MTF and Synthes for the gifts of materials that were used in the study.

要旨

目的：萎縮した上顎堤にインプラントを埋入するために、上顎洞底増生術において天然または合成の移植材料がルーティンに用いられている。本臨床研究は、サイナス・リフトにおける脱灰凍結乾燥同種骨（DEDBA/ DBM）の臨床的効果には、骨移植代替材料と併用した場合ばらつきがあるという仮説に基づいて行った。この仮説を試験するために、DEDBA を３つの材料のいずれかと併用した；すなわち生食水プラス無機質骨（DFDBA:Bio-Oss®）；ヒアルロン酸（DFDBA : HY、３２：６８：w/w）（DBX®）単独；DBX® プラス Bio-Oss® 及び DBX®プラス燐酸３カルシウム粒子（β - TCP）である。

材料と方法：患者２６名において、各群８回、計３２回のサイナス・リフトを行った。術前と術後８ヶ月後のインプラント埋入時に顎堤の高さをコンピュータ断層撮影（ＣＴ）によって確認し、形態測定分析を行った。インプラント埋入部位からトレファンで骨栓を採取し、移植部位から取ったこれらの生検組織を用いて組織形態測定分析を行った。

結果：３２回の上顎洞挙上術は全て成功し、術前の 15.2±0.6ｍｍから平均 2.84±0.2ｍｍ増加した事がＣＴ測定で確認された。各生検組織に占める新生骨と骨移植材料の比率は各術式によってばらついていた：DFDBA+ Bio-Oss®、DBX® +Bio-Oss® あるいは DBX®単独は、 DBX® +β-TCP より約１０％が高かった。新生骨のみを比べると、DBX® +β-TCP は他の３つの処置に比べて５０％少なかった。全ての移植部位は、各患者の治療計画に基づいてインプラントを入れることができた。

結論：本研究は新生骨の形成は使用する DFDBA の調剤に依存するという仮説を確認し、DBX®単独あるいは他の材料との併用は、上顎洞底挙上術に成功裏に使用できることを示した。

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