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Efficacy of bovine bone mineral for alveolar augmentation: a human histologic study

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Abstract: The purpose of this study was to evaluate the osteoconductivity of bovine bone mineral in humans. Fifteen patients referred to a private specialist surgical practice were treated consecutively for the repair of alveolar defects, and/or ridge maintenance at the site of extraction sockets, prior to implantation. Bio-Oss xenograft (Geistlich Pharma, Wolhusen, Switzerland) was utilized as the principal grafting material. Bone cores were trephined out at the time of implant placement and processed and examined to evaluate the tissue response under the light microscope. A total of 22 trephines were processed for histomorphometric evaluation to calculate the mean percentage of bone, residual graft and connective tissue by area. In addition, the mean percentage bone-to-graft contact was also calculated. The mean percentage area of new bone formation was 26.9%, and the percentage of residual graft and connective tissue as 25.6% and 47.4% respectively. The mean percentage contact length between bone and residual graft was 34%. One implant placed into a site, which was histologically identified as having little new bone and, unusually, an inflammatory infiltrate, failed with mobility at abutment connection. All other implants were restored into function, with a survival rate at baseline of 97%.

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Dental implants have been utilized in increasing numbers since the publication of long-term data on the osseointegrated technique (Adell et al. 1981; Buser et al. 1991; Arvidson et al. 1998). More challenging cases are now routinely addressed, in large part due to significant advances in bone augmentation with the aid of new grafting materials when the volume of dentoalveolar bone would otherwise prohibit implant placement.

Grafting materials are known to encourage new bone formation by a variety of processes. Autogenous bone, the 'gold standard', is known to induce bone formation through osteogenesis, while allogeneic bone is thought to be osteoinductive due to the presence of growth factors. Xenografts, like bovine bone mineral (BBM), and alloplastic substitutes encourage the apposition of new bone by osteoconduction. The use of these materials has found favour for repair of periodontal and alveolar defects (Schepers et al. 1993; Shapoff et al. 1997; Camelo et al. 2001; Hising et al. 2001), because of concerns over morbidity associated with extraoral donor sites for the harvest of autogenous bone.

One product, Bio-Oss (Geistlich Pharma, Wolhusen, Switzerland), has been widely reported to be effective in producing an effective bone/graft matrix (Maiorana et al. 2000; Mellonig 2000; Valentini & Abensur 1997). This xenograft is bovine and its safety has been questioned on the grounds that some trace protein may remain (Schwartz et al. 2000; Taylor et al. 2002). However, in contrast, the complete

absence of protein has been demonstrated by Açil et al. (2000) and Benke et al. (2001), as has its safety with respect to transmission of bovine spongiform encephalopathy (Wenz et al. 2001). In numerous experimental studies, the material has been shown to conduct a propitious growth of new bone (Berglundh & Lindhe 1997; Hürzeler et al. 1997; Haas et al. 1998) and it has also been used successfully in humans for defect regeneration, ridge augmentation, sinus floor elevation and repair of periodontal defects (Wetzel et al. 1995; Valentini et al. 2000; Houser et al. 2001).

The purpose of this study was to investigate the human histology and histomorphometry when Bio-Oss was used in a surgical practice setting for the repair of alveolar defects, ridge maintenance after tooth extraction or for sinus lift procedures.

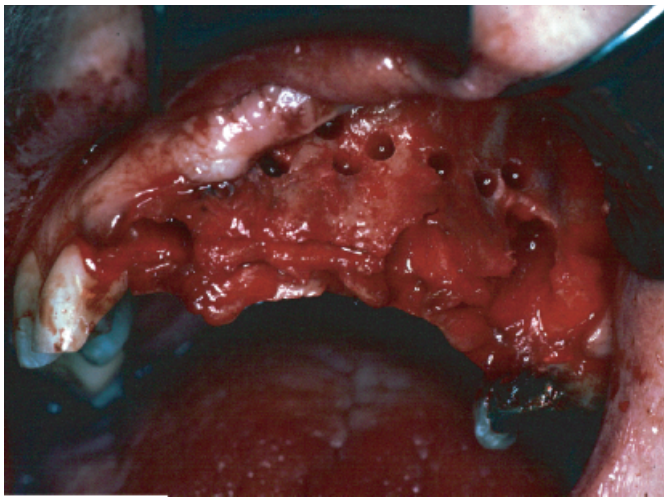

Fig. 1. The loss of labial cortex at the extraction sites and a reduced ridge width necessitates a preliminary graft procedure. Note the intramarrow perforations of the labial cortical plate.

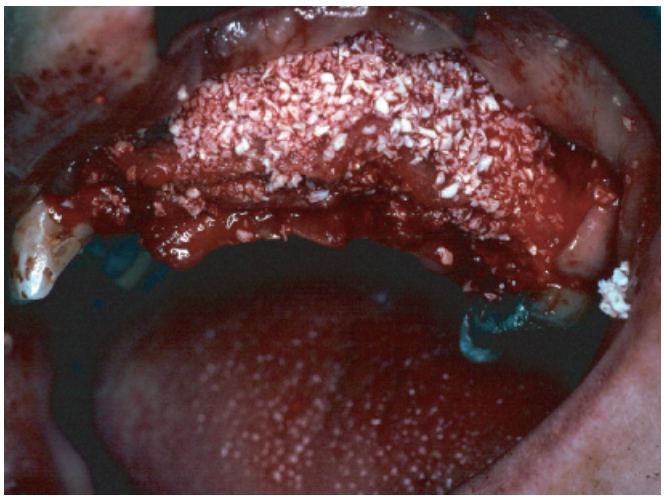

Fig. 2. Spongiosa granules (0.25–1.00 mm) of Bio-Oss have been used to fill the extraction defects and to augment the deficient ridge.

Material and methods

Seven males and eight females, with a mean age of 53 years (26 – 69 years) (Table 1), referred for the extraction of teeth, typically as a result of periodontal disease, endodontic failure, or trauma were recruited chronologically. All patients were systemically healthy at the time of consultation. Diabetics, alcoholics and drug abusers were excluded, but smokers were included. Patients signed a letter of consent for the use of BBM as a graft material and all patients were advised of the results of their histology.

When required, surgery was conducted under intravenous sedation administered by a consultant anaesthetist; otherwise, all procedures were conducted under local anaesthetic.

All extractions, grafting and the implant surgery were carried out under antibiotic prophylaxis of 3 g amoxicillin immediately preoperatively and then 250 mg three times per day (TDS) for 5 days postoperatively. (Patients undergoing sedation were given cefuroxime 750 mg i.v., and one patient who was allergic to penicillin was given Metronidazole 400 mg TDS, p.o.) All patients were asked to rinse with a 0.2% w/v chlorhexidine gluconate mouthwash for 1 min preoperatively and then twice a day for 1 min, for 1 week postoperatively.

Extractions were facilitated by a periotome and gentle elevation and resulted in either intact extraction sockets or sockets with loss of the buccal/labial cortical plate (Fig. 1). All sockets or defects were thoroughly debrided with aggressive curettage, followed by intramarrow perforations with a round bur through the cortical lining of the socket under profuse saline irrigation (Fig. 1). A bleeding bone bed was considered an essential prerequisite to graft placement.

Defects were treated with Bio-Oss spongiosa with a granule size of 0.25 – 1.00 mm (Fig. 2). A bone trap (Astra Tech, Mölndal, Sweden) was used to collect small amounts of bone debris during surgery, which was mixed with the graft. Bio-Gide® porcine collagen membranes (Geistlich Pharma, Wolhusen, Switzerland) were used to cover grafts where sockets lacked a buccal/labial cortical plate (Fig. 3), where primary closure over the sockets could not be effected, or to cover the lateral access window used for sinus lift procedures.

A minimum reentry time of 4 months was set for core trephination and implantation; however, the time between augmentation and implantation was also influenced by clinical appearance of the tissues, wound healing and by the radiographic interpretation of graft incorporation and the trabecular pattern of the grafted area. It was generally apparent when the graft remained poorly consolidated and/or

Table 1. **Clinical details of patients in chronological order of treatment**

	Patient	Age	M/F	Smoker	Type of defect	Position and (no. of Implants)	Bio-Gide	Healing time/ (weeks)	Surgical protocol	Osseointegration (weeks)
1	JW	64	M	N	Socket	14 to 24 (8)	N	17	Submerged	19
2	EM	69	F	N	Sinus	15, 16 (2)	Y	15	Submerged	20
3	CD	48	F	Y	Socket	14 (1)	Y	16	Submerged	32
4	NF	49	M	N	Socket/Sinus	26 (1)	Y-EXP	18	Submerged	33
5	CH	39	F	Y	Socket	45, 46 (2)	Y-EXP	25	Submerged	21
6	JC	64	F	N	Socket	12, 11, 21, 22 (4)	Y	22	Submerged	20
7	DG	26	M	N	Socket	11 (1)	Y	26	Submerged	20
8	NM	60	F	N	Sinus	25, 26, 27 (3)	Y	21	Submerged	30
9	JP	56	M	N	Socket	14 (1)	Y	23	Transmucosal	Failed
10	CC	55	F	N	Socket	36, 37 (2)	Y	40	Transmucosal	26
11	NS	46	M	N	Socket	16 (1)	Y-EXP	44	Transmucosal	0
12	FR	53	F	N	Socket/Sinus	16 (1)	Y-EXP	34	Transmucosal	13
13	RW	44	F	N	Socket	21, 22, 23, 24 (4)	Y	37	Submerged	22
14	BG	65	M	N	Socket	45, 46 (2)	Y	20	Transmucosal	17
15	RM	57	M	Y	Socket	36, 37 (2)	N	33	Transmucosal	19
	Mean data	**53**	**M = 7**	**Y = 12**	**Socket = 13**	**N = 35**	**Y = 13**	**26**	**Two stage – 60%**	**20.86**
			F = 8	**N = 3**	**Sinus = 4**		**N = 2**	**= 6 months**	**One stage – 40%**	**= 4.8 months**

poorly incorporated with the surrounding bone.

At the time of implantation, 2.5 mm osteotomies were initially made (Fig. 4). Biopsy sites could typically be identified by their granular appearance and by using previous clinical photographs to confirm the original site of grafting. At least one core sample from each patient was immediately fixed in 10% buffered formalin. Typically osteotomies would pass apical to the zone of the graft, so that the apical portion of the implant would engage native bone. In those patients with a sinus lift, the implants were essentially supported by graft (Fig. 5). Osteotomies were completed according to routine protocol (Norton 1995) followed by placement of the appropriate size titanium dental implant (Astra Tech AB, Mölndal, Sweden). A total of 36 implants were inserted with a mean of 2.4 implants per patient.

Trephine cores were orientated, decalcified in 10% formic acid/Duolite C255 ion exchange resin (BDH Ltd, Poole, Dorset, UK) and processed to paraffin wax according to routine methods. Specimens were then sectioned at 5 μm and stained with haematoxylin and eosin for light microscope evaluation.

Each histological specimen was separated into 1 mm^2 regions of interest (ROI). An ROI was only analysed if it contained evidence of Bio-Oss graft since some aspects of the trephine passed through native alveolus and this tissue had to be excluded from the analysis. As a result, some samples yielded more ROIs than others. A digital image was immediately captured of each ROI and analysed histomorphometrically for areas of new bone, graft material and connective tissue/marrow using Q-win software (Leica DMLB Microscope & Micro systems, Milton Keynes, UK). The areas of bone, graft material and connective tissue were delineated manually and expressed as percentage areas. All ROIs were analysed and the mean values were calculated for each sample. The percentage contact between new bone and graft material in each ROI was measured by image analysis. For trephines with more than one ROI the mean percentage bone-to-graft contact was calculated.

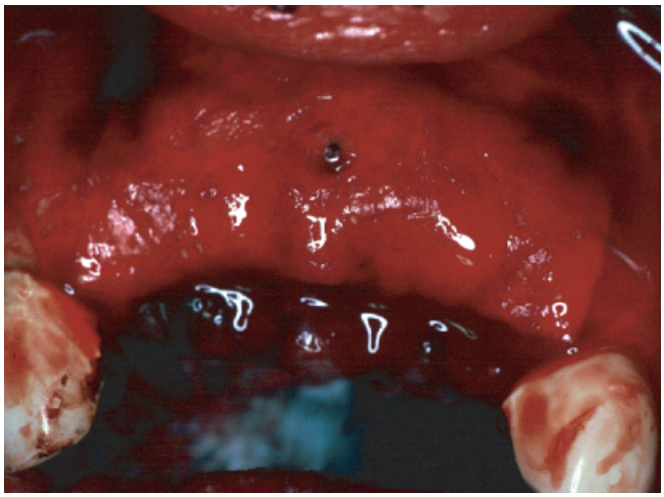

Fig. 3. A Bio-Gide® membrane can be seen draped over the BBM graft and fixed with a resorbable tack (Resorpin®).

After an osseointegration phase, which ranged from 13 to 33 weeks (mean, 21 weeks), all implants were exposed according to routine protocol (Norton 1995), and restored with ceramo-metal prostheses.

Results

In general, patients healed uneventfully, although four membrane exposures were noted (see Table 1). In these cases patients were instructed to continue rinsing with chlorhexidine until the membrane was completely submerged by new epithelium.

Due to differences in healing, radiographic evidence of graft consolidation and patient availability, the time between

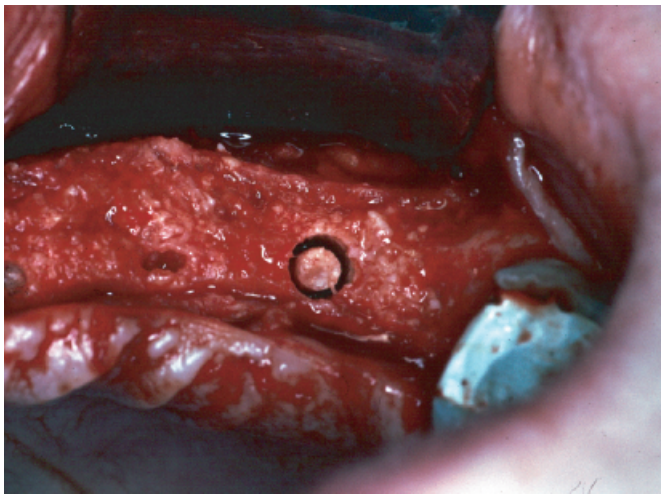

Fig. 4. The consolidated graft of the case shown in Figs 1 and 2 demonstrates repair of the extraction sockets with a significant augmentation of the ridge width. A trephine core has been cut ready for harvesting.

augmentation and implantation ranged from 15 to 44 weeks, with a mean of 26 weeks (Table 1).

In one patient (JP, Table 1) there was a constant tenderness over the apical end of the graft site, which remained throughout the osseointegration period. Clinically, tissues appeared healthy and the graft tissue was dense and bone-like; however, the histology of this case revealed minimal new bone (JP, Chart 1) and, unusually, the presence of an inflammatory infiltrate. It is interesting to note that this was also the only case in which an implant failed at abutment connection. All other implants were immobile at the time of abutment connection, a baseline surgical survival rate of 97%.

Histology revealed the BBM to be biocompatible with an absence of inflammatory cells other than for the patient mentioned above. A mix of woven, maturing woven and lamellar bone was typically seen to be associated with graft particles, with a varying degree of contact between graft and bone (Fig. 6A and B). The lamellar nature of new bone was apparent when viewed under polarized light (Fig. 7). In some specimens the bone was not directly related to the graft, although it may well have been the result of specimen preparation.

Histomorphometry revealed 26.9% (mean, range 0–52.8%) of the total trephine area to be occupied by bone, 25.6% by residual graft, and 47.4% by fibrous and other connective tissue (Chart 1). The mean percentage bone per area for grafts

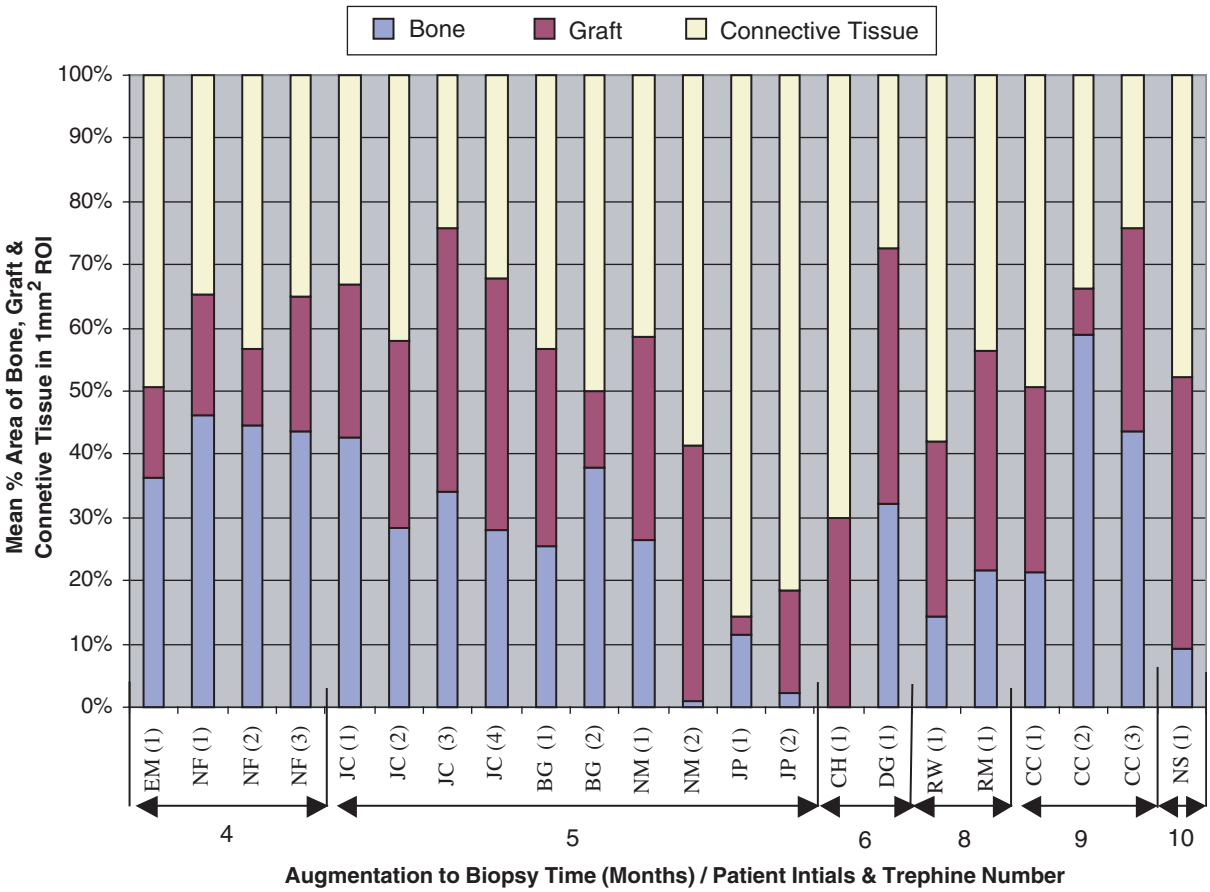

Chart 1. Histomorphometric Data by Patient and Healing Time (Months).

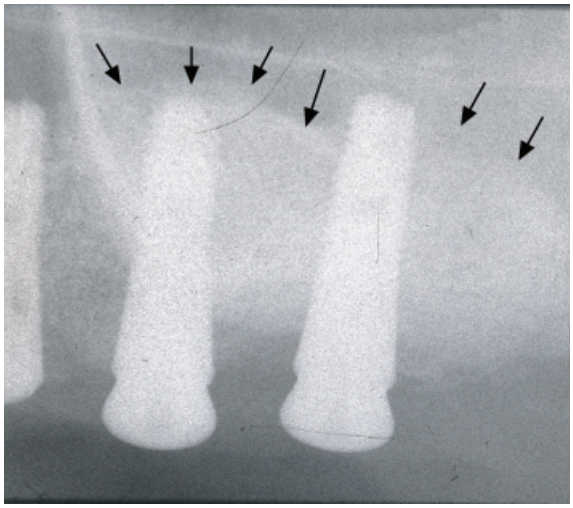

Fig. 5. This intraoral radiograph taken at abutment connection identifies the BBM (arrows) filling the sinus and supporting the two posterior implants.

left to heal for 4–5 months ($n = 14$) measured 28.9% (mean, range 1.1%–46.1%) compared to 23.4% (mean, range 0.0–52.8%) for those left to heal from 6 to 10 months ($n = 8$) (Chart 1).

The percentage bone-to-residual graft contact ranged from 0% to 75% with a mean of 34%. Fig. 8 shows a typical ROI with the interface between bone and graft highlighted in green.

Discussion

With increasing awareness of dental implants, there is increasing demand for the treatment of more complex cases where preliminary grafting is indicated.

In practice many less-than-ideal sites require preliminary augmentation procedures and while the use of autogenous bone remains the 'gold standard', many clinicians now look to alternatives, in an effort to avoid a second surgical donor site, thereby reducing postoperative morbidity and operator time.

Many studies have reported on the efficacy of a variety of graft materials, and within the group of osteoconductive graft materials the BBM xenograft and the alloplastic bioactive glasses have been the subject of considerable investigation. Bioactive glass is a synthetic, nontoxic, biocompatible material (Wilson et al. 1981), for which there are no concerns for risk of cross infection. These materials have been shown to be highly osteoconductive in

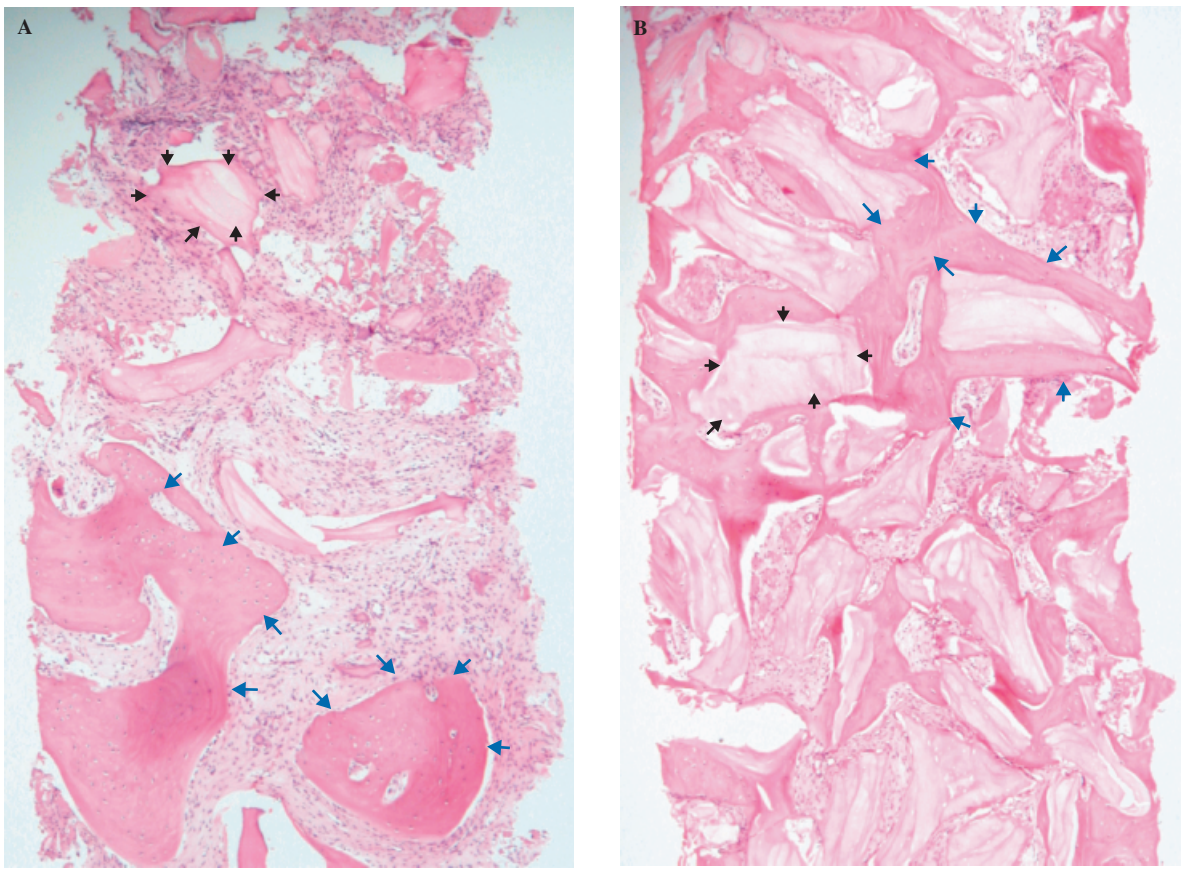

Fig. 6. Light microscopy clearly identifies the graft particles (black arrows) and new host bone (blue arrows) in these two specimens representing poor bone conduction (A) and excellent bone conduction (B).

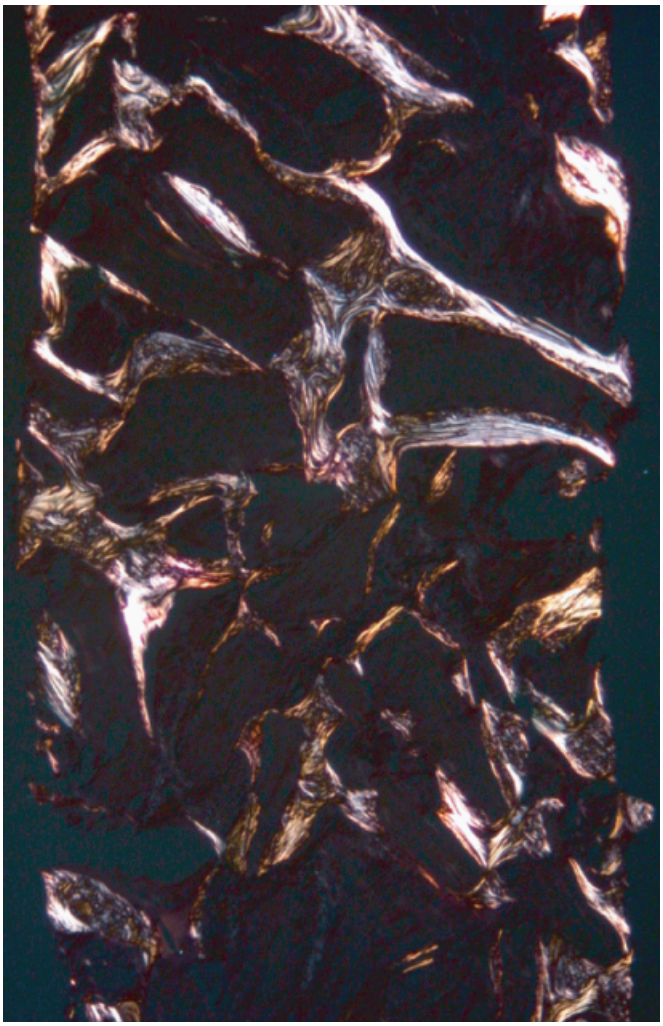

Fig. 7. Viewed under polarized light, it is possible to demonstrate the form birefringence of lamellar bone within the speciment (light areas).

animal studies (Wilson & Low 1992; Johnson et al. 1997; Turunen et al. 1997). However, a recent publication reported a worryingly low percentage of new bone found within the Bioglass graft in humans even after 6 months of healing (Norton & Wilson 2002). In this study it was concluded that in contrast to the animal studies, the material conducted limited new bone formation in humans, at least for the first 6 months.

In contrast, the xenograft BioOss has been the subject of human histological analysis in a number of studies, although only a small number provide the combination of a consecutive series of patients with both histological and histomorphometric analysis (Piatelli et al. 1999; Yildirim et al. 2000; Artzi et al. 2001; Yildirim et al 2001; Artzi et al. 2002; Proussaefs et al. 2002). Like the bioactive glasses, its osteoconductivity has been evaluated by numerous experimental studies (Berglundh & Lindhe 1997; Hürzeler et al. 1997; Haas et al. 1998) and clinical studies (Camelo et al. 2001; Hising et al. 2001; Yildirim et al. 2001); however, the evaluation of a consecutive series of human specimens provides additional important evidence to support its efficacy as an osteoconductive material in humans.

Unlike the synthetic Bioglass, BBM does raise concerns for cross infection. Recent studies have provided conflicting evidence for the presence or absence of protein (Açil et al. 2000; Benke et al. 2001; Schwartz et al. 2000; Taylor et al. 2002), with suggestions that residual growth factors may be present, which would impart osteoinductive properties giving rise to its apparent osteopromotive ability (Schwartz et al. 2000). It is currently unclear whether proteins are present in BBM, and further studies are vital to determine this.

In a study by Piatelli et al. (1999), a total of eight cores evaluated after 6 months of healing revealed that 40% of the trephine area comprised marrow spaces, approximately 30% newly formed bone and 30% residual BioOss graft. In two separate studies by Yildirim et al. (2000, 2001), comparable histomorphometry of 22 and 23 cores respectively after 6–7 months of healing yielded values for new bone of 14.7% and 18.9%. Values for residual graft were 29.7% and 29.6% and for marrow and/or connective tissue 55.6% and 51.5%, respectively.

This study adds to the body of human histomorphometric data, with a further 22 trephines evaluated from 15 patients consecutively treated with BBM for the repair of extraction sockets with an additional four sites requiring a sinus lift procedure. Histology revealed a predictable response, with the formation of new bone of both woven and lamellar types, weaving its way around embedded particles of residual graft in over 80% of the cases. In four specimens the bone growth was very poor, with less than 10% bone per area. Furthermore, in three of these specimens, the percentage of bone measured was less than 5% per area, indicating that in these specimens the graft had effectively failed. In one specimen there was a significant inflammatory infiltrate and the implant placed at this location failed to osseointegrate. These negative findings are also likely to be the result of intrinsic patient variability.

Another potential variable is the use of autogenous bone, which has been shown to improve graft response. In this study an attempt was made to collect bone in a trap to mix with the graft. However, the amount of bone collected in the absence of a specific harvesting procedure was very small, contributing less than 10% of the graft, and as such is unlikely to be contributory.

To assess the interrelationship between graft and new bone, the percentage contact at the interface was measured within each ROI. In the current series of biopsies this ranged from 0% to 75%, with a mean of 34%. The overall mean figure is skewed by

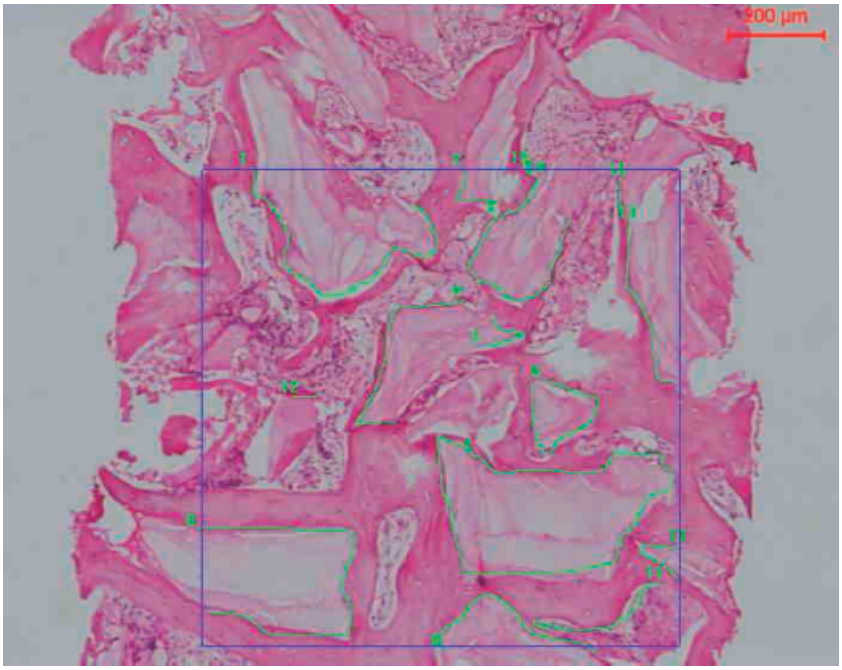

Fig. 8. The 1 mm² ROI outlined in blue with the interface length between graft and new bone highlighted in green.

four specimens where there was essentially no bone/graft contact (Chart 1: JP1, JP2, CH1, NM2) due to the very low bone incorporation.

For the specimen NM2, no implant was placed at this location, as it was clinically apparent that the graft had failed. For the specimen CH1, an implant was placed since the residual socket was small and the implant could effectively engage native alveolar bone apical to the graft zone. This implant successfully osseointegrated and has been retained in function for 18 months.

Only one implant failed to osseointegrate, yielding a baseline figure of 97% for implant survival. While all the implants passed through a zone of grafted tissue, many will have benefited from apical anchorage in native alveolus. It is therefore difficult to ascertain the influence of the graft on implant integration. However, in the case where osseointegration failed (JP), there was poor conduction of new bone formation and, unusually, an inflammatory infiltrate was noted histologically.

It is worthy of note that the relative percentage of new bone within grafts harvested after 4–5 months was comparable to that within grafts left to heal for 6–10 months. While the sample size is too small for statistical analysis to be meaningful, the implication in this particular series was that 4–5 months of healing was adequate to conduct a comparable formation of new bone for implant placement.

In addition, studies that have been able to evaluate the histology of small numbers of cores harvested after 3 years demonstrate that the relative percentages of bone and graft do not vary over time, with little evidence of active graft resorption (Skoglund et al. 1997; Piatteli et al. 1999).

Conclusion

In this study bovine bone mineral was shown to conduct the formation of new bone within extraction defects and within the sinus cavity. Consistent amounts of woven and, more importantly, mature lamellar bone could be demonstrated close to or in contact with particles of the xenograft. There was a relatively equal distribution, with both bone and graft contributing approximately 25% of the total specimen area and with a direct bone-to-graft contact measuring 34%.

On this basis, the bovine derived bone mineral would seem to be a suitable material for grafting of alveolar defects prior to implant placement.

Résumé

Le but de cette étude a été d'évaluer l'ostéoconductivité du minéral osseux bovin chez les humains. Quinze patients envoyés vers une pratique spécilisée ont été traités pour la réparation de lésions alvéolaires et /ou du maintien du rebord osseux au site des alvéoles d'extraction avant le placement d'implants. La xénogreffe Bio-Oss® a été utilisée en tant que matériel de greffe principal. Des carottes osseuses ont été prélevées au moment du placement des implants et examinées au microscope optique. Vingt-deux carottes ont été analysées histomorphométriquement pour calculer le pourcentage moyen d'os, de greffon résiduel et de tissu conjonctif par zones. De plus le pourcentage moyen de contact os-greffon a également été calculé. L'aire moyenne d'os néoformé était de 27%, les pourcentages de greffon résiduel et de tissu conjonctif étaient respectivement de 26 et 47%. La longueur de contact moyenne entre l'os et le greffon résiduel était de 34%. Un implant placé dans un site identifié histologiquement comme possèdant peu de nouvel os et, évènement rare, un infiltrat inflammatoire, a échoué en ayant une mobilité au moment du placement du pilier. Tous les autres implants ont été restaurés avec un taux de survie au départ de 97%.

Zusammenfassung

Die Nützlichkeit eines Rinderknochenminerals beim Alveolarkammaufbau: eine histologische Studie.

Das Ziel dieser Studie war es, die Osteokonduktivität eines Rinderknochenminerals am Menschen zu untersuchen. Bei 15 Patienten, die einer privaten Spezialpraxis für Oralchirurgie zugewiesen worden waren, wurde vor der Implantation ein alveolärer Knochendefekt aufgefüllt und/oder eine Kammerhaltungstherapie nach Extraktion durchgeführt. Als Füllmaterial setzte man das Xenotransplantat Bio-Oss (Geistlich Pharma, Wolhusen, Schweiz) als Hauptbestandteil ein. Während der Implantation entnahm man mit einem Trepanbohrer die als Nebenprodukt anfallenden Knochenzapfen, bereitete sie auf und untersuchte die Gewebsantwort unter dem Lichtmikroskop.

Für die histomorphometrischen Untersuchungen bereitete man 22 Knochenzapfen auf. Dann rechnete man in einem vorgegebenen Feld den mittleren prozentualen Anteil Knochen, übriggebliebenes Transplantat und Bindegewebe aus. Zusätzlich bestimmte man den mittleren prozentualen Kontakt zwischen Knochen und Transplantat. Die mittlere prozentuale Fläche neu gebildeten Knochens betrug 26.9%, beim zurückgebliebenen Transplantatmaterial betrug der Wert 25.6% und beim Bindegewebe 47.4%. Die durchschnittliche prozentuale Kontaktfläche zwischen Knochen und verbliebenem Transplantatmaterial betrug 34%.

Ein Implantat, das an einer Stelle implantiert worden war, die sich später histologisch als Stelle mit wenig neuem Knochen entpuppte und ein entzündetes Infiltrat aufwies, ging bei der Sekundärteilmontage infolge Beweglichkeit verloren. Alle anderen Implantate wurden mit funktionierenden Rekonstruktionen versehen und hatten bis zu diesem Zeitpunkt eine Überlebensrate von 97%.

Resumen

La intención de este estudio fue evaluar la osteoconductividad del mineral óseo bovino en humanos. Se trató a quince pacientes consecutivos remitidos a una consulta quirúrgica privada especializada para la reparación de defectos alveolares y/o mantenimiento de la cresta en el lugar de los alvéolos de extracción previamente a la implantación. Se utilizó xenoinjerto Bio-Oss (Geistlich Pharma, Wolhusen, Suiza) como material principal de injerto. Se trepanaron núcleos de hueso en el momento de la colocación de los implantes y procesados y examinados para evaluar la respuesta tisular bajo microscopía óptica.

Se procesaron un total 22 trepanaciones para evaluación histomorfométrica para calcular el porcentaje medio de hueso, injerto residual y tejido conectivo por área. Además se calculó también el porcentaje medio de contacto hueso-injerto. El porcentaje medio de área de formación de hueso nuevo fue del 26.9%, el porcentaje de injerto residual y tejido conectivo fueron del 25.6% y 47.4% respectivamente. El porcentaje medio de longitud de contacto entre hueso e injerto residual fue del 34%. Un implante colocado en un lugar, que se identificó histológicamente por tener poco hueso nuevo e, inusualmente, un infiltrado inflamatorio, fracasó con movilidad al colocar el pilar. Todos los demás implantes se restauraron en función, con un índice de supervivencia del 97% al inicio.

要旨

本研究では、ヒトにおいてウシ骨ミネラルの骨伝導能を評価した。専門医の個人外科診療所に紹介された連続１５名の患者に対して、インプラント埋入前に、歯槽骨欠損の再建及び／または抜歯窩の顎堤維持の治療を行い、Bio-Oss 異種移植材料（Geistlich Pharma, Wolhusen, スイス）を主たる移植材料として用いた。をインプラント埋入時に生検用骨コアをトレファンで採取し、処理をして、光学顕微鏡下で組織反応を評価した。

合計２２コの標本を処理し、組織形態測定の評価を行い、骨、残存移植材料、結合組織の平均面積率を計算した。さらに骨と移植材料の平均接触率も計算した。新生骨形成の平均面積率は、２６．９％、残存移植材料と結合組織の比率は各々２５．６％と４７．４％であった。骨と残存移植材料の平均接触長の比率は３４％であった。

埋入した１本のインプラントは、組織学的に新生骨の量が少なすぎ、炎症浸潤物が認められ、アバットメント連結時に動揺性があり失敗と判定された。他の全てのインプラントは補綴物を装着することができ、ベースライン時の生存率は９７％であった。

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