Timing of Implant Placement and Augmentation with Bone Replacement Material: Clinical Assessment at 8 and 16 Months

Zvi Artzi, DMD;* Carlos E. Nemcovsky, DMD;† Haim Tal, DMD, PhD;‡ Avital Kozlovsky, DMD§

ABSTRACT

Purpose: The purpose of this study is to evaluate implants placed at different times of bone augmentation.

Materials and Methods: Four implants were placed in seven dogs: one at a 6-month bovine mineral grafted site (6-month Bio-Oss® grafted site [6mBio]), one at a grafted membrane-protected simultaneously augmented (Fresh Bio-Oss® grafted site [FrBio]) site, one at a clotted (nongrafted clotted membrane-protected site [Clot]) membrane-protected site, and one at a pristine (nongrafted uncovered site [Cont]) site. Implants were exposed after 6 months. The same protocol was repeated on the contralateral side, at a delay of 8 months. Peri-implant care was performed throughout the hygienic phase (2 and 10 months, respectively) every 48 to 72 hours. Probing depth and bleeding on probing were recorded. Implant stability was determined by a Periotest® (Medizintechnik Gulden, Modautal, Germany). Statistical analysis was conducted using analysis of variance with repeated measures.

Results: Average probing depth at the simultaneously grafted sites was 2.21 mm and 2.03 mm at 8 and 16 months, respectively. At the 6-month grafted sites, it was 1.96 mm and 1.57 mm. At the Clot sites, it was 2.68 mm and 2.07 mm, and 2.21 mm and 1.82 mm at the Cont sites, respectively. The average bleeding on probing was 0.50 and 0.42 at the FrBio sites, and 0.35 and 0.07 at the 6mBio sites during the respective periods. At the Clot sites, it was 0.50 and 0.28, and at the Cont sites, 0.43 and 0.21, respectively. Probing depth significantly reduced over the time at 6mBio, Clot, and Cont sites ($p < .03$). Average implant stability score at the FrBio sites was −0.24 and −0.27, and −0.50 and −0.46 at the 6mBio sites, at 8 and 16 months, respectively. At the Clot sites, it was −0.35 and −0.46. Cont sites averaged −0.37 at both periods. Implant stability was significantly higher ($p < .005$) comparing 6mBio over FrBio, 6mBio over Cont, and Clot over FrBio sites.

Conclusions: Immediate and delayed augmentations are safe modes. Probing depth and bleeding indices gradually improved along time. Implant stability was higher at the delayed mode.

KEY WORDS: bone augmentation, bone grafting, bone replacement material, bovine bone, guided bone regeneration, implant stability, peri-implant healing, periotest

INTRODUCTION

Implant placement in conjunction and/or subsequent with alveolar ridge augmentation has been shown to be a successful modality for long-term functional prosthetic reconstruction.[1,2] Several surgical techniques have been described to achieve this goal with guided bone regeneration (GBR) being one of the most popular and predictable.[3–5] It has recently been reported that long-term success of implant-supported prosthetic rehabilitation is equal for implants placed at regenerated or pristine bone, regardless the timing of implant placement.[6–10] The augmentation procedure may be performed prior to or in conjunction with implant placement where both techniques showing high clinical

*Associate professor and director of Graduate Periodontics, Department of Periodontology and Dental Implantology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel; †associate professor, Department of Periodontology and Dental Implantology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel; ‡professor and chairman, Department of Periodontology and Dental Implantology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel; §associate professor, Department of Periodontology and Dental Implantology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel

Reprint requests: Prof. Zvi Artzi, DMD, Department of Periodontology, School of Dental Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel; e-mail: zviartzi@tau.ac.il

This study was funded by a grant of the Osteology Foundation.

DOI 10.1111/j.1708-8208.2011.00421.x

success rate and long-term function.[3–5,11–14] It has also been claimed that obtaining initial stability of the implant is a prerequisite to successful osseointegration no matter what technique is applied.[12,15–18]

Numerous biomaterials, including allogenic, alloplastic, or xenographic origins, may predictably be used as the bio-filler in GBR procedures. However, the dilemma of the influence of the timing of augmentation on implant's osseointegration and success rates in regard to a distinguishable observation on clinical soft and hard tissue peri-implant parameters has still not been validated in standardized sites.

Soft tissue condition and implant stability are the principal tools in evaluating healing and function. Most researchers and clinicians have used probing depth (PD), bleeding on probing, and implant stability as the main parameters to assess and monitor success or failure.[19–23] Despite the amenable healing response performing implant placement and augmenting bone simultaneously or in a 2-stage mode, it is of great interest to clinically follow-up implants using both techniques using such parameters.

This study aimed to compare the peri-implant soft tissue conditions and implant stability in simulated implant placement and bone augmentation as a combined or staged procedure at 8 and 16 months postimplant placement.

MATERIAL AND METHODS

The study was approved by the Institutional Animal Care and Use Committee at the Tel Aviv University. The study was carried out on seven adult male beagle dogs, weighing on average 17.6 kg (ranging 15.6–19.3 kg). Animals were housed individually at the Tel Aviv University Animal Institute and were kept on commercial diet and water ad libitum. Following each surgical procedure, soft diet was administered for 2 weeks.

Study Design

The time frame (Figure 1) was kept carefully in accordance to obtain minimal morbidity from the participated animals. At day 0, fourth premolar (P4) and first molar (M1) were extracted (Figure 1, point a) to obtain an edentulous span of approximately 33–35 mm mesiodistally, and natural healing was allowed to occur. At 1 month, one rectangular defect was prepared as the first augmentation phase (Figure 1, point b). At 5 months, second premolar (P2) and third premolar (P3) were extracted (Figure 1, point c), thus establishing an edentulous span of approximately 60 mm (including the previous distal area). One month later (at 6 months), two additional defects were prepared for the second augmentation phase (at one of newly performed sites) concurrent with four implant placement procedures (Figure 1, point d). The exposure phase took place at 6 months postimplant placement (Figure 1, point e). Thereafter, the hygienic phase was commenced for 10 months.

An identical protocol was repeated on the contralateral side, however, at a delay of 8 months.

Consequently, the contralateral hygienic phase lasted 2 months.

Surgical Phases

All surgical procedures were performed under general anesthesia, achieved by presedation with 1.5 cc (20 mg) 2% xylazine base intramuscular (IM), followed by an intravenous (IV) injection of ketamine (Clorketamin® 1000, Vetoquinol, Fort Worth, TX, USA), 5 mg/kg + xylazine base (XYL – M 2, Veterinary), 1 mg/kg. Buccal and lingual local infiltration of lidocaine hydrochloride 2% with norepinephrine (1:100,000) on the vestibular mandibular area was administered for hemostasis and in order to reduce postoperative pain.

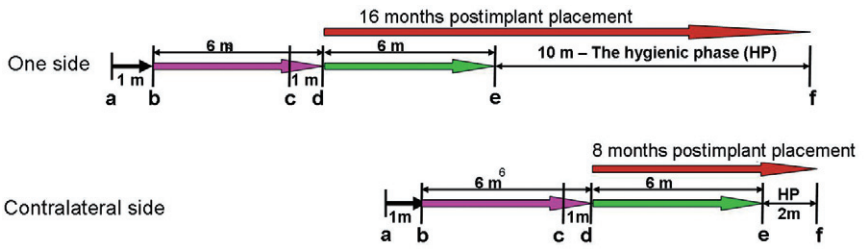

Figure 1 The time line (m – month/second) flowchart on both sides. Point a – extractions of P4 and M1; b – the first augmentation phase; c – extractions of P2 and P3; d – the implant placement, concurrent with the second augmentation phase; e – the exposure phase; f – the day of the euthanizing procedure.M1 = first molar; P2 = second premolar; P3 = third premolar; P4 = fourth premolar.

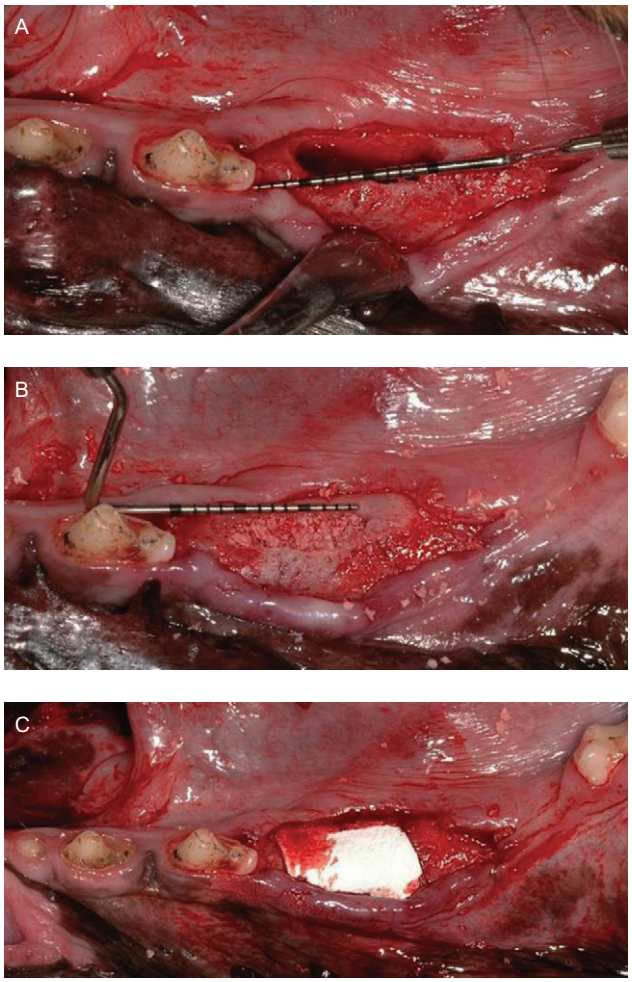

Figure 2 *A*, At 1 month postextraction of P4 and M1, a rectangular four-wall intrabony defect (11 mm M-D, X 5 mm B-L, X 7 mm depth) was established. *B*, The rectangular surgical simulated defect was filled with bovine bone mineral particles. *C*, The grafted defect was covered by an absorbable dual-layer collagen membrane. M1 = first molar; P4 = fourth premolar.

The roots of the right mandibular P4 and M1 teeth were separated and carefully removed using periotomes and elevators. One month post healing, after complete soft tissue closure over the extraction sites, the edentulous area was exposed by a mid-crestal incision, using a No.15c type blade. A rectangular 4-wall intrabony defect measuring 11 mm mesial-distal, 5 mm buco-lingual, and 7 mm deep was established at either the anterior or posterior previous extraction sites (Figure 2A) using the technique described by Berglundh & Lindhe.[24] The defect was filled with bovine bone mineral particles (BBM; Geistlich Bio-Oss®, Geistlich Pharma AG, Wolhusen, Switzerland) (Figure 2B), followed by a bilayered collagen membrane (Geistlich Bio-Gide®) coverage (Figure 2C). The augmented site was covered by coronally advanced mucosal flaps to achieve primary soft tissue closure, using a 4-0 polyamide monofilament nonabsorbable suture (Ethilon®, Ethicon®, Johnson & Johnson, Somerville, NJ, USA). Postoperatively, surgical sites were swabbed every 48–72 hours with 0.2% chlorhexidine. Antibiotic coverage was continued for the first 10 days postsurgery.

At 5 months, the P2 and P3 were removed on the same mandibular side, with a similar procedure as described, and thus, establishing a 55 to 60-m-long edentulous site. At 6 months, the mandibular edentulous ridge (P2 – M1), was exposed, and two additional intrabony defects were created at the P2–P3 extraction healed site (Figure 3, A and B).

Four dual acid-etched surface implants (Osseotite®, Biomet 3i, Palm Beach Gardens, FL, USA) 3.25 mm (D) × 10 mm (L) were placed; one at the 6-month augmented site (P4/M1), two at the freshly created 4-wall surgical defects, and one at a pristine healed site. The implants in the fresh intrabony defects engaged neither the buccal nor the lingual bony walls and were stabilized at their apical 3 mm end only. All implant necks were placed at the level of the osseous crestal rim, whether at the current created defects or flush with the housing bone. Thereafter, one of the newly made defects was filled with BBM particles, while the other one was left untreated and spontaneously filled with blood (Figure 3C). Both implants/defects were then covered by a collagen membrane (Figure 3D). Subsequently, advanced gingival flaps were coronally positioned to achieve full soft tissue closure using interrupted 4-0 polyamide monofilament sutures (Figure 3E). Thus, four different sites were established differing in the peri-implant tissue: (i) implant placed concurrent with bovine mineral particles – a fresh BBM site (Fresh Bio-Oss® grafted site [FrBio]); (ii) implant placed in a blood clot-filled defect (nongrafted clotted membrane-protected site [Clot]); (iii) implant placed in a 6-month BBM remodeled site (6-month Bio-Oss® grafted site [6mBio]); and (iv) implant placed in a postextraction healed site (nongrafted uncovered site [Cont]). Inter-implant distance was at least 10 mm in order to enable future mesio-distal section cuts. An advancing coronal positioned flap from buccal and lingual aspects ensured nontensional soft tissue closure, using the horizontal internal mattress suture. Six months after implant placement (12 months after the first augmentation), implants were exposed (Figure 4A), and implant healing screws

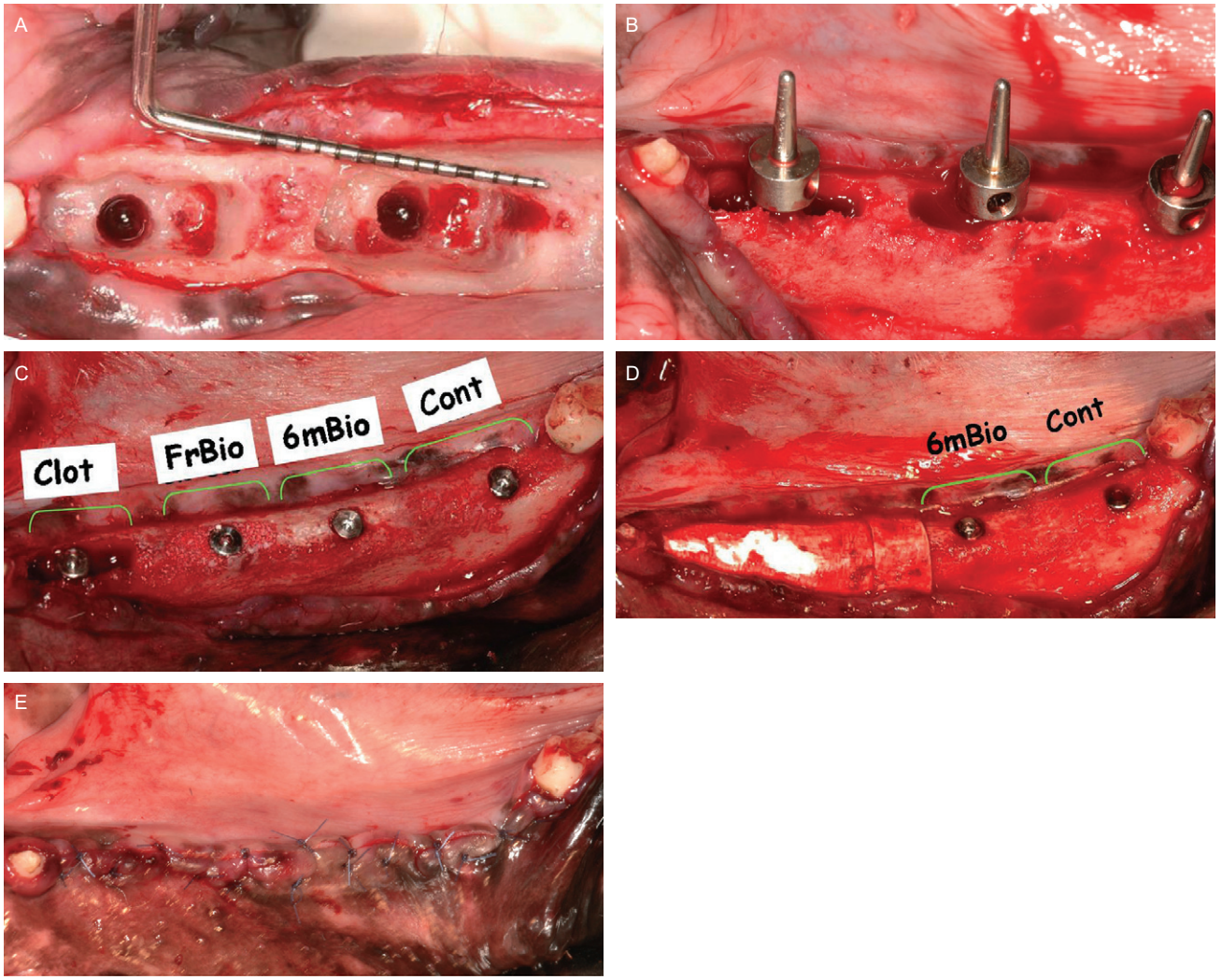

Figure 3 *A*, At 6-month postsurgical phase 1 and 1-month postextraction of P2 and P3, two additional similar intrabony defects were performed. Note the preparation of the apical portion of the implant site at the floor of the defects. *B*, Implant site preparation at the surgically created rectangular defects. Note the mesio-distal distance to the bony wall defects. *C*, Four implants were placed, followed by the filling of one of the defects with BBM particles (FrBio), while the other one was left to be filled with blood (Clot). The other two were placed at the 6-month augmented site (6mBio) and at the pristine one (Cont). Implant stability was achieved at the 3 mm apical end. *D*, An absorbable collagen membrane was applied over the newly established surgical defects, thus covering the fresh grafted and nongrafted implant sites. *E*, Coronally advanced positioned flaps were established to ensure full nontensional soft tissue healing. 6mBio = 6-month Bio-Oss® grafted site; BBM = bovine bone mineral; Clot = nongrafted clotted membrane-protected site; Cont = nongrafted uncovered site; FrBio = Fresh Bio-Oss® grafted site; P2 = second premolars; P3 = third premolars.

(4 mm high) were connected, protruding approximately 2 mm above the surrounding soft tissue (Figure 4B). The same surgical protocol with identical timing of augmentation and implant placement procedures was repeated on the contralateral side of the mandible, however, at a delay of 8 months.

The Hygienic Phase

Implant superstructure healing screws were maintained by brushing periodically three times a week. Clinical examination was performed during checkups in 2-week intervals and under premedication only. Measurements were taken up to the day of euthanizing, at 8 and 16 months postimplant placement, respectively. For credibility and reproducibility, all clinical measurements were recorded twice by two different examiners (ZA and AK), while the identification of the experimental site was masked. PD[25] was recorded on the mesial, mid-buccal, distal, and corresponding lingual sites by using a periodontal probe (University of North Carolina periodontal probe). In order to achieve accuracy and since a reference point such as the cemento-enamel junction

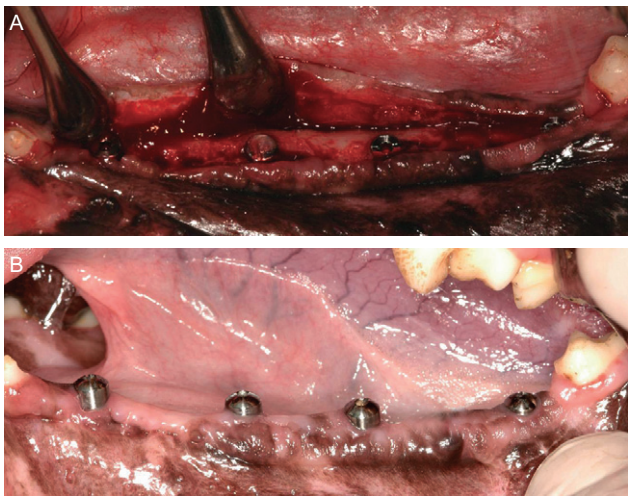

Figure 4 *A*, The implant exposure phase at 6 months postimplant placement. *B*, The implant healing screws during the hygienic maintenance phase.

does not exist, a measurement of the height of the exposed implant superstructure screw was also recorded, respectively. Bleeding on probing (BOP) was determined according to the modification of Mombelli et al.[26] from Herald Löe[27] in natural dentition to be adapted around functional implants, with a ranking of 0–3 (no, pin-point, linear, profuse bleeding). The mucosal marginal level in relation to the implant superstructure screws, which were used to observe any changes and/or events of marginal soft tissue recessions, as well as keratinized mucosal (KM) width (height), were measured with the aid of the periodontal probe. These were recorded on the buccal (Keratinized mucosa – Buccal [KMB]) and lingual (Keratinized mucosa – Lingual [KML]) aspects of each implant. Implant stability was determined by a Periotest® (PT) device (Medizintechnik Gulden, Modautal, Germany).

The PT device, which its hand piece is placed horizontally and perpendicular in proximity (1–2 mm) to the implant emergence superstructure part, is a tapping device that measures the braking point when tapping the implant superstructure rigid connected surface.[28] Its scales ranging from –0.8 as the highest stability value to +0.9 as a least stable nonmobile element. Negative PT values (PT < 0), indicated well-osseointegrated implants.

Radiographs were performed from the sectioned blocks on the day of the euthanizing processing. Each block lay on an occlusal film, and an orthoradial angle was obtained.

Statistical Analysis

There were four different experimental sites in this study, each examined at two time points, one on each side, 8 and 16 months postimplant placement. The distribution is normal. Means and standard deviations were calculated for each of the measured parameters, and the differences between mean values were analyzed by analysis of variance with repeated measures, two within factors: (i) site and (ii) time. A statistical significance was identified at $p \leq .05$.

RESULTS

In both the surgical augmentation and implant placement phases, soft tissue healing was immaculate. One dog developed a swelling after the second augmentation phase; however, an additional period of antibiotic administration solved the event with no recurrence. The establishment of buccal and lingual advancing coronal positioned flaps, which obtained a resilient soft tissue closure with the horizontal internal mattress suturing, ensured no spontaneous exposure. Animals showed no sign of mastication distress. Wherever needed rarely loosened superstructures were retightened during soft tissue maintenance (every 48–72 hours).

Clinically, all implants were integrated with the surrounding tissues. At 1 month postimplant cover screw exposure phase, soft tissue healing was established, concurrent with professional plaque control. The marginal masticatory mucosa was maintained and found to be stable/preserved around the implant superstructures, with imperceivable recession. Radiographically, implants were surrounded by radiopaque tissue with no signs of peri-implant radiolucency. Crestal bone level location was maintained at the implant neck or at the roughed surface flat neck coronal to the first thread of the implant body in most sites (Figure 5). Thus, a slight crestal bone resorption was evident, however, to the less than 1.5 mm (the distance of the implant neck to the first thread).

Keratinized mucosal height (KM) at the labial and lingual aspect of the implant superstructures, ranged from 0 up to 8 mm, irrespective of the experimental type site. Since all other statistical examinations between KML and KMB to the other clinical parameters in any of the different sites and at both observation periods were

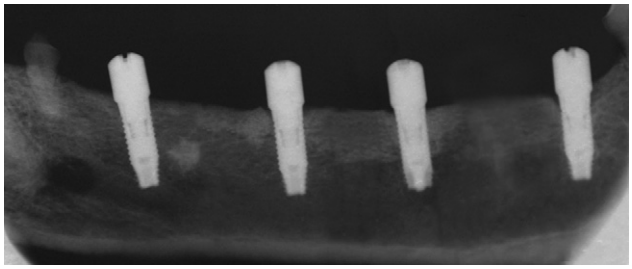

Figure 5 Radiographically, crestal bone level is maintained around the implant necks.

meaningless and unrelated, they were discarded from the summarized table scheme.

Fresh BBM (FrBio) versus 6-Month-Old Remodeled BBM Site (6mBio)

The average PD at the FrBio sites was 2.21 mm ± 0.79 standard deviation (SD) at 8-month observation period and 2.03 mm ± 0.66 SD at 16 months (Table 1). At the 6mBio sites, the average PD was 1.96 mm ± 0.36 SD and 1.57 mm ± 0.37 SD, respectively. The average BOP was 0.50 ± 0.92 SD and 0.42 ± 0.44 at the FrBio sites, and 0.35 ± 0.55 SD and 0.07 ± 0.18 SD at the 6mBio sites during the respective periods. No statistically significant differences were found.

PT recording at the FrBio sites averaged −0.24 ± 0.12 SD and −0.27 ± 0.09 at 8 and 16 months, respectively. At the 6mBio sites, the average PT score was −0.50 ± 0.08 and −0.46 ± 0.07 during the respective observation periods. The stability of the implants at the 6mBio sites was found to be significantly greater than with the FrBio group ($p = .003$).

FrBio and 6mBio versus Nongrafted Clotted Membrane Protected (Clot) and versus Control (Cont)

The average PD at the Clot sites was 2.68 mm ± 0.51 SD and 2.07 mm ± 0.34 SD at 8 and 16 months, respectively. At the control sites (Cont), the average PD was 2.21 mm ± 0.22 SD and 1.82 mm ± 0.59 SD, respectively. The average BOP at the Clot sites was 0.50 ± 0.28 SD and 0.28 ± 0.26, and at the Cont sites, it was 0.43 ± 0.60 and 0.21 ± 0.26 SD during the respective observation periods. When analyzing 6mBio versus Cont groups in regard to PD, there was a statistically significant difference between 8 and 16 months ($p = .017$) in each type of sites.

In all other comparisons, no statistically significant differences were found, except for the fact that PD at the Clot and Cont sites was significantly reduced over time ($p = .026$).

The average PT score at the Clot sites was −0.35 ± 0.26 SD at 8 months and −0.46 ± 0.11 SD at 16 months. At the Cont sites, both periods showed identical score of an average of −0.37 ± 0.17 SD. Significant differences were found between the FrBio and Clot sites ($p = .003$), in favor of the nongrafted ones, and between the 6mBio and Cont ($p = .032$), in favor of the 6-month grafted sites. Although the PT scores were higher at the Cont group compared with the FrBio group, differences were not statistically significant ($p = .06$).

DISCUSSION

The present surgical model of an extensive surgical rectangular defect filled with BBM particles, concurrent

TABLE 1 Probing Depth, Bleeding on Probing, and Periotest Measurements at the Different Sites

	Sites					
Indices	Probing Depth (mm)		Bleeding on Probing		Periotest	
Periods (months)	8	16	8	16	8	16
FrBio	2.21 ± 0.79 SD	2.03 ± 0.66	0.50 ± 0.92	0.42 ± 0.44	−0.24*,¶ ± 0.12	−0.27*,¶ ± 0.09
6mBio	1.96** ± 0.36	1.57** ± 0.37	0.35 ± 0.55	0.07 ± 0.18	−0.50* ± 0.08	−0.46* ± 0.07
Clot	2.68† ± 0.51	2.07† ± 0.34	0.50 ± 0.28	0.28 ± 0.26	−0.35¶ ± 0.26	−0.46¶ ± 0.11
Cont	2.21†† ± 0.22	1.82†† ± 0.59	0.43 ± 0.60	0.21 ± 0.26	−0.37 ± 0.17	−0.37 ± 0.17

*,¶$p = .003$.
**$p = .017$.
†,††$p < .03$.
6mBio = 6-month Bio-Oss® grafted site; Clot = nongrafted clotted membrane-protected site; Cont = nongrafted uncovered site; FrBio = Fresh Bio-Oss® grafted site.

with or followed by an implant placement, proved to be a suitable model to clinically examine the soft tissue characteristics over regenerated bone surrounding osseointegrated implants.

Clinically, frequent periodic brushing and close monitoring kept soft tissue appearance well maintained. Implant stability was maintained over the study period at all surgical sites. Proper functioning was observed in accordance with the chewing ability, thus monitoring marginal mucosal soft tissue appearance and performing clear sounding upon gentle percussion on the implant connected superstructures. Animals responded well to the treatment and the healing sites presented no postoperatory infection and/or complications.

To avoid overloading,[29] implants superstructures were kept out of occlusion, allowing functional chewing and physiological/habitual forces.

In regard to the type of the applied biomaterial, BBM has been used for over 20 years and proven very suitable for these procedures.[11,24,30–34]

Regardless of the type of procedure, clinical observations showed similar outcome. Similar findings were also observed in a recent human study.[35] PD differences between different sites did not reach a significant level. After 8 months, PD ranged from 1.96 mm to 2.68 mm at all sites and decreased at 16 months from 1.57 mm to 2.07 mm, at the respective periods. Except for the FrBio, all sites showed significant improvement from 8 to 16 months. Since the marginal soft tissue level was observed to be clinically stable, it can be assumed that the reduction in probing over time is probably more related to the clinical attachment level status rather than to the marginal mucosal recession. Although an improvement was shown at the FrBio site as well, this change did not reach a significant level. It appears that meticulous oral hygiene monitoring and continuous functional osseous remodeling allowed for PD improvement, irrespective of the site type. At 8 months, the average PD at the 6mBio showed the shallowest PD, followed by an identical outcome at the FrBio and Cont with the deepest PD at the Clot sites. During the extended period, at 16 months observation, the delayed regenerated site (6mBio) and Cont groups, showed the shallowest PD in comparison with the FrBio and Clot groups. However, this study did not show statistically significant differences between these sites.

In a human study,[36] evaluating implants placed in BBM augmented and nonaugmented ridge, mean PD was 1.5 mm and mean BOP was 0.1 mm. They also reported that no clinical differences were observed when comparing implants that were placed simultaneously with graft material and those that were placed using the staged technique.

The tendency of clinical improvement was also repeated in regard to BOP. At 8 months, the averages ranged from 0.35 to 0.50 at the different sites and decreased at the extended observed period to ranging from 0.07 to 0.42, respectively. As in PD, the lowest BOP values were found in the 6mBio and Cont groups (in sequence) in both observation periods. However, data dispersion and sample extent may have avoided statistical significance. Although these improvement tendencies were shown in the PD as well as in the BOP, the correlation was not statistically significant.

Significant data were appreciated in regard to implant stability, as measured by the PT. These findings draw a special attention in light of the critical role of this factor as a prerequisite for long-term success.[18] In both observation periods, the recording of the PT at the prior remodeled augmentation site (6mBio) was significantly higher (greater minus PT values) when compared with the combined (FrBio) sites. This is probably the most striking finding, in regard to clinical parameters. Apparently, this is not due to the delayed placement per se but rather to the remodeled healing stage of the surrounding osseous housing at the time of PT value recording by the PT. However, since the significant difference was repeatedly observed at 16 months, it can be implicated that, in regard to implant stability as graded by the PT, the delayed placement mode showed a greater PT values. Furthermore, the 6mBio implants were even superior in PT values in comparison with the Cont group. It can be speculated that the fact that BBM particles did not resorb substantially but rather amalgamated with the newly formed bone over a long period of time,[37] enhanced the solid support around the implant body to show high negative value of the PT. A prolonged healing time of regenerated ridge by BBM was also shown by Rodriguez et al.,[38] who recommended a delayed implant placement in order to allow bone maturation.

Despite the different established defects, clinical healing was immaculate and similar in all site types.

In conclusion, from a clinical point of view, implant placement and bone augmentation showed excellent adaptation with the embraced mucosal and underlined tissues, regardless of the timing of augmentation.

Under professional hygiene, PD was reduced over time, although at the immediate implant placement and bone augmentation sites, this was not statistically significant. PT values showed that implant stability proved to be higher when the delayed technique took place.

ACKNOWLEDGMENTS

This study was funded by the Osteology Foundation. The study was also supported by the Gerald A. Niznick Chair of Implant Dentistry and a grant from Alpha Omega Research Fund, Tel Aviv University. The authors are indebted to Biomet3I for providing the implants; Geistlich Pharma AG for providing the biomaterials; to Dr. Naam Kariv, Mr. Haim Barki, and Mr. Neria Davidov for the animal care; and to Mrs. Ilana Gelerntner for the statistical analysis. The authors declare no conflict of interest at any part of the study.

REFERENCES

1. McAllister BS, Haghighat K. Bone augmentation techniques. J Periodontol 2007; 78:377–396.
2. Tonetti MS, Hämmerle CH. European workshop on periodontology group C. Advances in bone augmentation to enable dental implant placement: consensus report of the sixth European workshop on periodontology. J Clin Periodontol 2008; 35(Suppl):168–172.
3. Buser D, Dula K, Lang NP, Nyman S. Long-term stability of osseointegrated implants in bone regenerated with the membrane technique. 5-year results of a prospective study with 12 implants. Clin Oral Implants Res 1996; 7:175–183.
4. Buser D, Ingimarsson S, Dula K, Lussi A, Hirt HP, Belser UC. Long-term stability of osseointegrated implants in augmented bone: a 5-year prospective study in partially edentulous patients. Int J Periodontics Restorative Dent 2002; 22:109–117.
5. Simion M, Jovanovic SA, Tinti C, Benfenati SP. Long-term evaluation of osseointegrated implants inserted at the time or after vertical ridge augmentation. A retrospective study on 123 implants with 1-5 year follow-up. Clin Oral Implants Res 2001; 12:35–45.
6. Buser D, Halbritter S, Hart C, et al. Early implant placement with simultaneous guided bone regeneration following single-tooth extraction in the esthetic zone: 12-month results of a prospective study with 20 consecutive patients. J Periodontol 2009; 80:152–162.
7. Blanco J, Alonso A, Sanz M. Long-term results and survival rate of implants treated with guided bone regeneration: a 5-year case series prospective study. Clin Oral Implants Res 2005; 16:294–301.
8. Juodzbalys G, Raustia AM. Kubilius R A 5-year follow-up study on one-stage implants inserted concomitantly with localized alveolar ridge augmentation. J Oral Rehabil 2007; 34:781–789.
9. Donos N, Mardas N, Chadha V. Clinical outcomes of implants following lateral bone augmentation: systematic assessment of available options (barrier membranes, bone grafts, split osteotomy). J Clin Periodontol 2008; 35(Suppl): 173–202.
10. Dahlin C, Simion M, Hatano N. Long-term follow-up on soft and hard tissue levels following guided bone regeneration treatment in combination with a xenogeneic filling material: a 5-year prospective clinical study. Clin Implant Dent Relat Res 2010; 12:263–270.
11. Hammerle CH, Chiantella GC, Karring T, Lang NP. The effect of a deproteinized bovine bone mineral on bone regeneration around titanium dental implants. Clin Oral Implants Res 1998; 9:151–162.
12. Lundgren S, Rasmusson L, Sjostrom M, Sennerby L. Simultaneous or delayed placement of titanium implants in free autogenous iliac bone grafts. Histological analysis of the bone graft-titanium interface in 10 consecutive patients. Int J Oral Maxillofac Surg 1999; 28:31–37.
13. van Steenberghe D, Callens A, Geers L, Jacobs R. The clinical use of deproteinized bovine bone mineral on bone regeneration in conjunction with immediate implant installation. Clin Oral Implants Res 2000; 11:210–216.
14. Christensen DK, Karoussis IK, Joss A, Hammerle CH, Lang NP. Simultaneous or staged installation with guided bone augmentation of transmucosal titanium implants. A 3-year prospective cohort study. Clin Oral Implants Res 2003; 14:680–686.
15. Wikesjo UM, Nilveus R. Periodontal repair in dogs: effect of wound stabilization on healing. J Periodontol 1990; 61:719–724.
16. Rasmusson L, Meredith N, Cho IH, Sennerby L. The influence of simultaneous versus delayed placement on the stability of titanium implants in onlay bone grafts. A histologic and biomechanic study in the rabbit. Int J Oral Maxillofac Surg 1999; 28:224–231.
17. Becker W, Sennerby L, Bedrossian E, Becker BE, Lucchini JP. Implant stability measurements for implants placed at the time of extraction: a cohort, prospective clinical trial. J Periodontol 2005; 76:391–397.
18. Lioubavina-Hack N, Lang NP, Karring T. Significance of primary stability for osseointegration of dental implants. Clin Oral Implants Res 2006; 17:244–250.
19. Lang NP, Lindhe J. Maintenance of the implant patient. In: Lindhe J, Karring T, Lang NP, eds. Clinical periodontology and implant dentistry. Oxford, UK: Blackwell Munksgaard Publication, 2003:1024–1030. Chapter 45.

20. Salvi GE, Lang NP. Diagnostic parameters for monitoring peri-implant conditions. Int J Oral Maxillofac Implants 2004; 19(Suppl): 116–127.
21. Gerber JA, Tan WC, Balmer TE, Salvi GE, Lang NP. Bleeding on probing and pocket probing depth in relation to probing pressure and mucosal health around oral implants. Clin Oral Implants Res 2009; 20:75–78.
22. Karbach J, Callaway A, Kwon YD, d'Hoedt B, Al-Nawas B. Comparison of five parameters as risk factors for peri-mucositis. Int J Oral Maxillofac Implants 2009; 24:491–496.
23. Adibrad M, Shahabuei M, Sahabi M. Significance of the width of keratinized mucosa on the health status of the supporting tissue around implants supporting overdentures. J Oral Implantol 2009; 35:232–237.
24. Berglundh T, Lindhe J. Healing around implants placed in bone defects treated with Bio-Oss. An experimental study in the dog. Clin Oral Implants Res 1997; 8:117–124.
25. Lang NP, Wetzel AC, Stich H, Caffesse RG. Histologic probe penetration in healthy and inflamed peri-implant tissues. Clin Oral Implants Res 1994; 5:191–201.
26. Mombelli A, van Oosten MA, Schurch E Jr, Lang NP. The microbiota associated with successful or failing osseointegrated titanium implants. Oral Microbiol Immunol 1987; 2:145–151.
27. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol 1967; 38(Suppl):610–616.
28. Aparicio C, Lang NP, Rangert B. Validity and clinical significance of biomechanical testing of implant/bone interface. Clin Oral Implants Res 2006; 17(Suppl 2):2–7.
29. Kozlovsky A, Tal H, Laufer BZ, et al. Impact of implant overloading on the peri-implant bone in inflamed and non-inflamed peri-implant mucosa. Clin Oral Implants Res 2007; 18:601–610.
30. Skoglund A, Hising P, Young C. A clinical and histologic examination in humans of the osseous response to implanted natural bone mineral. Int J Oral Maxillofac Implants 1997; 12:194–199.
31. Artzi Z, Nemcovsky CE. The application of deproteinized bovine bone mineral for ridge preservation prior to implantation. Clinical and histological observations in a case report. J Periodontol 1998; 69:1062–1067.
32. Carmagnola D, Berglundh T, Araujo M, Albrektsson T, Lindhe J. Bone healing around implants placed in a jaw defect augmented with Bio-Oss. An experimental study in dogs. J Clin Periodontol 2000; 27:799–805.
33. Hämmerle CH, Jung RE, Yaman D, Lang NP. Ridge augmentation by applying bioresorbable membranes and deproteinized bovine bone mineral: a report of twelve consecutive cases. Clin Oral Implants Res 2008; 19:19–25.
34. Pieri F, Corinaldesi G, Fini M, Aldini NN, Giardino R, Marchetti C. Alveolar ridge augmentation with titanium mesh and a combination of autogenous bone and anorganic bovine bone: a 2-year prospective study. J Periodontol 2008; 79:2093–2103.
35. Meijndert L, Raghoebar GM, Meijer HJ, Vissink A. Clinical and radiographic characteristics of single-tooth replacements preceded by local ridge augmentation: a prospective randomized clinical trial. Clin Oral Implants Res 2008; 19:1295–1303.
36. Mayfield LJ, Skoglund A, Hising P, Lang NP, Attström R. Evaluation following functional loading of titanium fixtures placed in ridges augmented by deproteinized bone mineral. A human case study. Clin Oral Implants Res 2001; 12:508–514.
37. Artzi Z, Weinreb M, Givol N, et al. Biomaterial resorption rate and healing site morphology of inorganic bovine bone and beta-tricalcium phosphate in the canine: a 24-month longitudinal histologic study and morphometric analysis. Int J Oral Maxillofac Implants 2004; 19:357–368.
38. Rodriguez Y, Baena R, Zaffe D, Pazzaglia UE, Rizzo S. Morphology of peri-implant regenerated bone, in sheep's tibia, by means of guided tissue regeneration. Minerva Stomatol 1998; 47:673–687.