Long Term Follow-Up of Dental Implants Placed in Autologous Onlay Bone Graft

Devorah Schwartz-Arad, DMD, PhD;* Ronen Ofec, DMD, MSc;† Galit Eliyahu, PhD;‡ Angela Ruban, PhD;§ Nir Sterer, DMD, PhD¶

ABSTRACT

Purpose: The aim of this study was to evaluate the efficacy of autologous intraoral onlay bone grafting (OBG) in correlation with long-term survival rates of dental implants placed in the augmented bone.

Materials and Methods: A retrospective study was conducted on 214 patients who received a total of 633 dental implants placed in 224 autologous intraoral block OBG augmentations, combined with Bio-Oss – mixed with platelet-rich plasma (PRP) and covered by platelet-poor plasma (PPP) – as scaffold, with a follow-up time up to 137 months (mean 39.9 ± 30.9 months).

Results: A total of 216 OBG cases were successful (96.4%), and most of the augmentations were uneventful (88.4%). Bone graft exposure was moderately associated with bone graft failure ($\chi^2 = 3.76$, $p = .052$). The healing period after implant placement was 4–6 months (mean 5.6 ± 2.56). The majority of the 591 implants survived (93.4%). The cumulative survival rate of the implants was 83%.

Conclusions: We suggest that augmentation of severely atrophied jaw bone through the placement of horizontal and/or vertical intraoral OBGs in combination with Bio-Oss saturated with PRP and covered by PPP should be considered a reliable, safe, and very effective surgical technique for obtaining high bone graft survival rate and high long-term implant survival rate.

KEY WORDS: autologous bone, bone augmentation, bone grafting, implant survival, long-term survival

INTRODUCTION

Fixed restoration of partially or fully edentulous jaws using dental implants requires sufficient bone volume for their placement. The reconstruction of atrophic alveolar ridges using autologous bone grafting was originally reported in 1975.[1] Today, augmentation of the alveolar bone, via a variety of bone grafting procedures, is a commonly performed surgical solution. Autologous bone is considered as the "gold-standard" bone-grafting material, as it combines all properties required in a bone graft material: osteoinduction (by bone morphogenetic proteins [BMPs] and other growth factors), osteogenesis (by osteoprogenitor cells), and osteoconduction (by acting as a scaffold).[2–5]

Possible sources for autologous bone grafts include extraoral sources such as the calvaria, tibia, and iliac crest.[6] However, the use of intraoral sources, such as the mandibular symphysis[7,8] and ramus,[9,10] is more readily available and offers no cutaneous scarring, minimal discomfort, and less morbidity compared with the extraoral sources. The mandible, as a preferable donor site, has advantages that also include good bone quality, convenient surgical access, minimal volume loss, good incorporation with a short healing time, high biocompatibility, and embryological proximity.[11]

*Head and senior surgeon, Oral and Maxillofacial Surgery, Advanced Implantology, Periodontology & Endodontology, Schwartz-Arad Day-Care Surgical Center, Ramat Hasharon, Israel; †Privet Dental practice, Department of Statistics and Operations Research, Tel Aviv University, Tel Aviv, Israel; ‡researcher, Oral and Maxillofacial Surgery, Schwartz-Arad Day-Care Surgical Center, Ramat Hasharon, Israel; §head, Clinical Research Units, Schwartz-Arad Day-Care Surgical Center, Ramat Hasharon, Israel; ¶former head, Clinical Research Units, Oral and Maxillofacial Surgery, Schwartz-Arad Day-Care Surgical Center, Ramat Hasharon, Israel

Corresponding Author: Ms. Devorah Schwartz-Arad, Oral and Maxillofacial Surgery, Advanced Implantology, Periodontology & Endodontology, Schwartz-Arad Day-Care Surgical Center, Ramat Hasharon 47243, Israel; e-mail: dubi@dsa.co.il

DOI 10.1111/cid.12288

Although the iliac crest is frequently used in major jaw reconstructions, recent studies have reported extensive bone deficiency reconstruction using solely intraoral block bone grafts by means of a multitier technique,[12] possible by reharvesting of bone from the same donor site following its augmentation with bone replacement material in the first procedure.[13]

In order to stimulate the healing process of the grafted bone, the use of platelet-rich plasma (PRP) has been suggested by Marx and colleagues.[14,15] PRP, which provides an enhanced concentration of platelets compared to blood, has gained wide interest as a therapy for both soft and hard tissue injuries. Blood platelets are an invaluable source of growth factors that modulate critical cellular events. Many of the growth factors released from activated platelets are osteoinductive.[16]

Examples of growth factors found in PRP that may aid in bone regeneration are platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factors (IGF-I and II).[17,18] An added benefit of using PRP as a potential therapy for bone loss is that PRP is autologous, nontoxic, and nonimmunoreactive. However, there is some controversy in the literature regarding the effectiveness of PRP in bone regeneration, which might be due to differing protocols for obtaining PRP (with regard to centrifugation) and the low numbers of systematic studies carried out to date.[19] In this study, all patients were treated with PRP combined with bovine bone substitutes as a part of the bone graft procedure.

Platelet-poor plasma (PPP) is the upper layer of plasma, which is formed after centrifugation of whole blood and is composed of acellular plasma containing fibrinogen and growth factors.[20] Few studies have attempted to evaluate the effect of PPP in the bone regeneration process. Hatakeyama and colleagues showed that PPP is an effective material for the preservation of sockets with buccal dehiscence.[20] Yilmaz and colleagues reported a positive clinical effect of PPP in combination with bovine-derived xenograft treatment of patients with intrabony periodontal defect.[21]

In the current study, PPP was used as a biological membrane to cover the entire augmented area and donor site to facilitate healing and angiogenesis. The benefits of PPP are probably due to elevated levels of fibrinogen, which has the ability to form a fibrin-rich clot once activated.[22] The healing process requires cell migration and attachment, which is facilitated by this fibrin clot.[22] The clot within the injured space provides a provisional matrix for cell migration.[23,24] Fibrin has been reported to induce angiogenesis directly.[25,26] Most vascular cells have receptors for fibrinogen, which plays an important role in establishing cell-cell interactions, frequently after receptor activation.[27] The aim of the present retrospective study was to study the effectiveness and safety of ridge augmentation with intraoral-origin onlay bone grafts (OBGs), combined with Bio-Oss (saturated with PRP and covered by PPP) as scaffold, as a method of obtaining high bone graft survival rate and high long-term implant survival rate.

MATERIALS AND METHODS

Study Population

A consecutive retrospective study was conducted on patients (mean age at OBG surgery 50.3 ± 15.5 years, 179 females) who received a total of 633 dental implants placed in OBGs from 1999 to 2010. These included a total of 224 augmentations using solely intraoral bone for the block grafts. Patients who were smoking at the time of the surgery were defined as smokers. At time of operation, 175 (81.8%) were nonsmokers and 39 (18.2%) smokers.

All the augmentations and implant placement procedures were performed by a single surgeon (DSA) as described herein. Data collected from the files included medical history and smoking habits, with special attention to conditions that might affect bone and wound healing (e.g., diabetes, osteoporosis), as well as information regarding the areas of surgery, donor sites, implants, bone graft survival, and complications. In the absence of exposed bone graft/sequestrum or exposed bone fixation screw head, OBG was defined as successful. Follow-up time was up to 137 months (mean 39.9 ± 30.9 months). Implant survival was defined as the implant still functioning at the end of the follow-up period. All implants were evaluated by x-ray.

The patient inclusion criterion was the presence of edentulous areas in the mandible and/or maxilla with a degree of atrophy preventing placement of implants of at least 6 mm in height without the risk of damaging anatomical structures such as the inferior alveolar nerve, the maxillary sinus floor, or the nasal floor.

Patient exclusion criteria were (a) severe kidney and/or liver disease, (b) congenital or acquired

immunodeficiency, (c) ongoing chemotherapy at the time of first examination, (d) sequelae of radiotherapy in the head and neck area, (e) connective tissue disease of any kind, (f) poor oral hygiene, and (g) noncompliance.

Preoperatively, panoramic radiography and conventional (previously available) or computerized tomography (CT) scans were used to visualize the region of interest. Immediately after the surgical intervention, only panoramic radiography was performed. Five months after the initial bone graft surgery and before placement of the second tier and/or implants, the patients were examined based on clinical symptoms, panoramic radiography, and CT. Prior to exposure of the implant, panoramic radiography was performed once again. Thereafter, panoramic radiography was performed annually at up to 5 years and then every 2 years.

Documentation for all clinical cases included (a) intraoral photographs of the initial clinical situation, (b) a panoramic radiograph and a complete series of periapical radiographs for partially edentulous patients, and (c) preoperative CT scans.

PRP and PPP Preparation

The preparation of PRP and PPP was performed using Harvest SmartPrep processing techniques (Harvest Technology, Plymouth, MA, USA). Briefly, 20 or 60 ml of blood was drawn from each patient using a sterile syringe containing 2 or 5 ml of anticoagulant citrate dextrose solution A (ACD-A). The blood was then separated into PRP and PPP (lower and upper layers) and red blood cells using sterile chamber containing 1 or 3 mL of ACD-A and centrifuged following manufacturing instructions. The PRP was dropped into a sterile surgical cup using a sterile syringe with a blunt needle. To create the PRP-infused scaffold material, Bio-Oss (Geistlich Pharma AG, Wolhusen, Switzerland) was saturated with PRP (Figure 1A). The CaCl and thrombin mixture was added to form a gel with internalized Bio-Oss particles that were used as a filling material in both the recipient (filling any gaps between the recipient bed and block grafts) and donor sites. The upper layer of plasma (PPP) was gently transferred into a sterile cup using a sterile syringe with blunt needle. To create a membranelike structure from the gel, the PPP was activated by adding a mix of human thrombin and CaCl (Omrix Biopharmaceutical Ltd., Kiryat Ono, Israel) (Figure 1B). Throughout the study, PRP and PPP preparation techniques and manufacture were not modified.

Surgical Procedure: Graft Phase

Premedication was administered as previously described.[12] A midcrest incision was made along the recipient area. A mucoperiosteal flap was reflected. The recipient site was decorticated and recontoured using a round bone bur (Aesculap AG, Tuttlingen, Germany) for better adaptation of the graft and to improve graft-to-recipient bone contact. The bone defect was evaluated to determine the size, shape, and number of the blocks needed. In severe bone deficiency (greater than 5 mm in height), a multitier bone grafting technique was utilized.[13] Bone blocks were harvested from intraoral donor sites (e.g., the mandibular ramus and/or symphysis) (Figure 1C). The ramus area was accessed using an extension of the commonly used envelope flap for third molar extraction. The incision was made in the buccal vestibule, medial to the external oblique ridge, and extended anteriorly and laterally to the retromolar pad, continuing anteriorly into the buccal sulcus of the second molar. A mucoperiosteal flap was reflected, exposing the lateral aspect of the ramus and third molar area. A reciprocating or oscillating saw or piezoelectric surgery device (Mectron Medical Technology, Carasco, Italy) was used to cut through the cortex along the anterior border of the ramus. An anterior vertical cut was made in the mandibular body (the length depended upon the size of the graft needed), and a posterior vertical cut was made on the lateral aspect of the ramus. No inferior osteotomy was performed. The border cuts were made only to the depth where bleeding occurred from the underlying cancellous bone to prevent injury to the underlying neurovascular bundle. A thin chisel was gently tapped along the entire length of the osteotomy, taking care to avoid injury to the inferior alveolar nerve by preventing the cancellous bone from penetrating beneath the cortical layer. Graft splitting from the ramus was then completed. For the symphysis, an intrasulcular incision and two vertical releasing incisions were made posterior to the second premolar regions, reflecting the mucoperiosteal flap at the facial side.

After exposing the symphysis and locating the mental foramina, a reciprocating saw or piezoelectric surgery device was used to outline a rectangle the size of the exposed defect. The superior aspect of the rectangle was at least 3–5 mm below the tooth apices, and

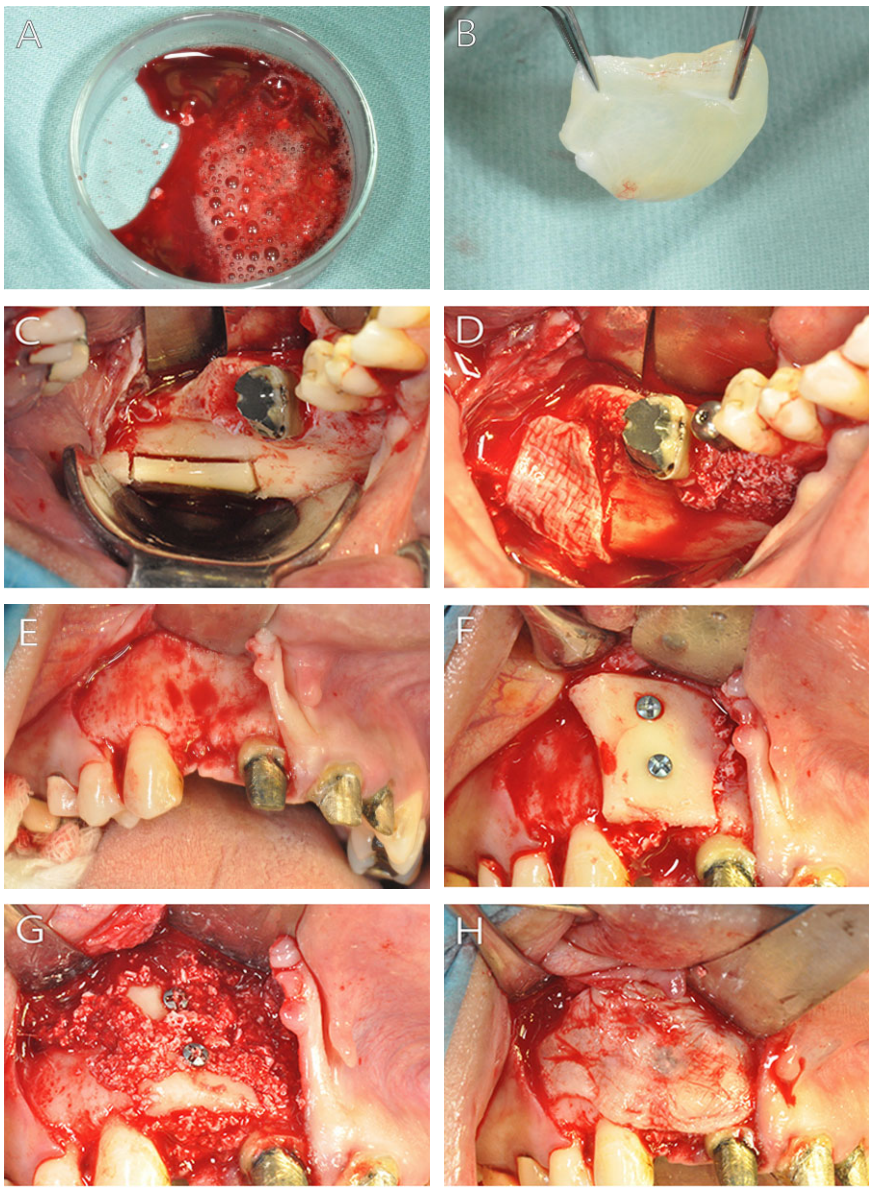

Figure 1 Onlay bone graft augmentation technique: the main steps. (A) Bio-Oss saturated with platelet-rich plasma (PRP) and human thrombin. (B) Platelet-poor plasma (PPP) used as biological membrane. (C) Donor site (right mandibular ramus) prior to block separation. (D) Donor site (right mandibular ramus) filled with combination of Bio-Oss and PRP covered by PPP. (E) Bone defect at recipient site (right maxillary lateral incisor). (F) The harvested autologous bone block graft fixed to the recipient site. (G) The harvested autologous bone block graft at the recipient site, with gaps between graft and recipient bed filled with combination of Bio-Oss and PRP.(H) The entire augmented site covered by PPP.

medially to the mental foramina, the integrity of the lower border of the mandible was maintained. Osteotomes were used to free the block graft and harvest cancellous bone. In selected cases, a vestibular incision was performed, no vertical incisions were needed, and the free-gingival line of the lower teeth was left unharmed.

The bone blocks were restored in a sterile cold sodium chloride 0.9% solution (TEVA Medical Ltd., Ashdod, Israel) for a minimal time before fixation in the recipient site. The block graft was positioned over the recipient site in a vertical dimension (i.e., "saddle" augmentation) and/or horizontal dimension (i.e., "veneer" augmentation) with the endosteal side of the graft facing the cortical bone. The blocks were adapted to fit close to the site. To ensure immobilization, the grafts were fixed to the recipient site using titanium self-tap screws 1.6 mm in diameter (KLS Martin LP, Jacksonville, FL, USA), to be removed during the second-tier operation or implant placement (Figure 1, E and F). Any sharp

angles in the block segment that could perforate the overlying flap were eliminated, leaving a smooth outline. Corticocancellous particles and Bio-Oss saturated with PRP were used to fill the gap between the graft and recipient bed site (Figure 1G). PPP was used to cover the entire augmented area (Figure 1H). The periosteum at the base of the facial flap in the recipient site was carefully incised to allow stretching of the mucosa and tension-free adaptation of the wound margins. The flap was sutured with a 4-0 rapid polyglactin suture (Intromedix, Natanya, Israel) and removed 2 weeks later. Treatment of the donor site was completed only at the end of the procedure, after the fixation of the bone graft and the suturing of the recipient site.

The donor defect was filled with Bio-Oss saturated with PRP and covered with PPP or resorbable membrane (Bio-Gide, Geistlich Sons, Wolhusen, Switzerland) and sutured with the same sutures (Figure 1D). The intraoral donor sites for harvesting autologous bone block included the mandibular ramus (72.8%), symphysis (24.6%), both the mandibular ramus and symphysis (1.8%), and the sinus window (0.9%). Most augmentations (57.1%) were horizontal, or veneer-type; 25% were vertical (saddle-type); and 17.9% were combined (two dimensions, horizontal and vertical). The marginal bone level was measured on panoramic radiographs using the implant threads as an internal standard, a technique formerly suggested by Haas and colleagues.[28] The number of threads unsupported with bone at implant exposure was subtracted from the number of threads unsupported with bone at the most recent follow-up and the total multiplied by the implant pitch (in millimeters) to determine the amount of bone loss (in millimeters). The accuracy level of this method is half a pitch (0.35–0.375 mm) of the implant thread. The number of threads was converted to millimeters using the millimeters per thread for that particular implant (one pitch = 0.7–0.75 mm, according to the manufacturer). Total bone resorption following implant placement greater than 1.5 mm (i.e., more than half a pitch per year; mean follow up time 39.9 ± 30.9 months) was defined as marginal bone loss.

Surgical Procedure: Implant Phase

Following orthopantomographs and CT examinations, dental implant placement was performed 5 months following the OBG augmentation (mean 4.52 ± 2.55 months). These included 246 one-tier (94%) and 16 two-tier (6%) augmentations. Patients were treated under local anesthesia. A total of 633 screw-type implants were placed (Screw-Vent and Spline, Zimmer Dental Inc., Warsaw, IN, USA; NobelActive and Replace Select, Nobel Biocare, Göteborg, Sweden; Implant Direct, Implant Direct LLC, Zurich, Switzerland). Length and diameter of the implants were chosen according to the area to be rehabilitated, the prosthetic indications, and the bone shape and volume available in each implant site.

All patients underwent submerged healing according to the authors' two-stage augmentation and implantation protocol. The healing period was 4–6 months (mean 5.6 ± 2.56), after which panoramic radiography was performed and the implants were uncovered. The implants were followed up by clinical examination and panoramic radiography annually up to 5 years after implantation, then every 2 years.

Postsurgical Care

Patients received prophylactic antibiotics during the 10 days after graft surgery and the 5 days after implantation, specifically amoxicillin (Moxypen Forte, Novopharm, Toronto, ON, Canada; 500 mg ×3). Dexamethasone (first dose 8 mg, then 4 mg) was given as well, once per day for 3 days after graft surgery and implantation. Patients were prescribed nonsteroid anti-inflammatory drugs as analgesia. Denture use was avoided during the first month following the grafting procedure and for 10 days after implant placement.

Statistical Analysis

Descriptive statistical analysis was performed at three levels: patient ($n = 214$), bone graft ($n = 224$), and implant ($n = 633$). The cumulative survival rate (CSR) was calculated by Kaplan-Meier life-table analysis. In order to examine differences with regard to CSR between categories of our investigated variables, we used the Cox proportional-hazards regression model. We applied the Grambsch-Therneau test in order to ensure that the proportional-hazards assumption was not violated. In our models, we combined robust standard errors, which accounted for possible correlation between implants of the same patients. All statistical tests were two-tailed with a significance level of 0.05. Statistical analysis was performed with IBM SPSS Statistics 19 (IBM, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Summary of Recipient Sites

Site	Number	Percentage
Anterior maxilla	64	28.6%
Mid-maxilla	30	13.4%
Posterior maxilla	15	6.7%
Anterior mandible	27	12.0%
Posterior mandible	88	39.3
Total	224	100%

TABLE 3 Complications Following Bone Graft Augmentation Prior to Implantation

Complication	Number	Percentage
None	198	88.4%
Exposed bone graft/sequestrum	9	4.0%
Exposed bone-fixated screw head	8	3.6%
Infection/inflammation	9	4.0%
Total	224	100%

RESULTS

A total of 224 OBGs were performed, out of which 216 were diagnosed as successful (96.4%). In 100% of the cases, the donor site was filled by Bio-Oss saturated with PRP and covered with PPP as a biological membrane. The various locations of augmentation are summarized in Table 1. Whereas the mandible was divided into two areas of interest (anterior and posterior to the mental foramen) according to anatomy, bone shape, and quality, the maxilla was divided into three areas: anterior (incisor area), which relates to the nasal floor; posterior (second premolar and molar area), which relates to the maxillary sinus; and the middle portion, normally characterized by higher quality of available residual bone. The main site for onlay bone augmentation was the posterior mandible (39.3%), followed by the anterior maxilla (28.6%), while the ramus was the main source for the bone blocks (72.8%) (Table 2). Up to nine blocks were grafted per augmentation site, and in the majority of the cases one to three blocks were used per site. Bio-Oss saturated with PRP was used to fill the gap between the graft and recipient bed site in 100% of augmentations.

Most of the augmentations were uneventful (88.4%). However, following bone grafting a few complications were observed; the two most frequent were exposure of bone graft/sequestrum and inflammation/infection, which occurred in 9 patients (4%) (Table 3). Of the complications, only bone graft exposure was moderately associated with bone graft failure ($\chi^2 = 3.76$, $p = 0.052$). In total, only 8 bone grafts (3.6%) were defined as failed: 6 one-tier and 2 two-tier grafts (Table 4). No significant correlations between OBG failure and medical history or smoking status of the patients were found (Tables 5 and 6); among smoking patients, only 1 bone graft was defined as failed. A few complications in the donor site were observed, including inflammation/infection (3.1%) and lack of closure (2.2%). Both cortical bone from the ramus and cortico-spongy bone from the symphysis region were used, while no differences in donor site morbidity were observed (11% in the ramus vs 10% in the symphysis). Treatment included combination of irrigation with 0.5% chlorhexidine solution and oral administration of antibiotics according to bacterial flora examination.

The present study includes 633 dental implants placed in OBGs, with an average of 2.9 ± 1.77 implants per patient. Complications following implant placement were observed in 17.2% of the total implants, with inflammation/infection (5.8%) and exposed implant (5.2%) being the most common (Table 7). Treatment included the same protocol: combination of irrigation with 0.5% chlorhexidine solution and oral administration of antibiotics according to bacterial flora examination. Nevertheless, total marginal bone loss ≤1.5 mm accompanied by inflammation occurred only in 2.5% of

TABLE 2 Summary of Donor Sites

Site	Number	Percentage
Ramus	163	72.7%
Symphysis	55	24.6%
Ramus and symphysis	4	1.8%
Sinus window	2	0.9%
Total	224	100%

TABLE 4 Bone Graft Success

		Number	Percentage
Valid	Successful	216	96.4%
	Failed tier 1	6	2.7%
	Failed tier 2	2	0.9%
	Total	224	100%

TABLE 5 Implant Failure by Patient Medication Status

Subject Medication Status		Implant Failure: No	Implant Failure: Yes	Total
None	Number	482	30	512
	Percentage of implant failures	81.6%	71.4%	80.9%
Hypertensive	Number	68	7	75
	Percentage of implant failures	11.5%	16.7%	11.8%
Osteoporosis	Number	18	1	19
	Percentage of implant failures	3.0%	2.4%	3.0%
Hypertensive diabetes	Number	12	0	12
	Percentage of implant failures	2.0%	0.0%	1.9%
Diabetes	Number	11	4	15
	Percentage of implant failures	1.9%	9.5%	2.4%
Total	Number	591	42	633
	Percentage of implant failures	100.0%	100.0%	100%

the cases during the follow-up period (mean follow up time 39.9 ± 30.9 months).

In total, 591 implants survived (93.37%), while 9 implants failed at the surgical phase (1.4%) and another 33 failed at the prosthetic phase (5.2%) following rehabilitation, on average within 4 years of follow up (Table 8). Out of 42 implant failures, 9 occurred in smokers.

The survival rate in the first year was 97%, followed by 94% and 91% in the next 2 years (Figure 2). The 137-month CSR of the implants was 83%. There was a difference between the CSR of dental implants placed at the anterior parts of the maxilla/mandible and those placed in the posterior areas (Table 9). These differences were found to be statistically significant (HR = 2.51, $p = .03$) using the Cox regression analysis (Table 10). Furthermore, implants that were placed within a two-dimensional bone graft augmentation (horizontal plus vertical) had a 2.49-fold greater risk of failure ($p = .02$) as compared with implants that were placed within a one-dimensional bone graft augmentation (horizontal or vertical). Interestingly, there is a strong, statistically significant relation between bone graft failure and implant failure (HR = 16.47, $p < .01$) (Table 10). Table 11 summarizes the cases in which OBG failure occurred. Although statistically insignificant (due to the small proportion of failures), these data show a common denominator for these cases, with most OBG failures following implant failure at the prosthetic phase.

Furthermore, the posterior portion of the mandible seems to be typically involved, with a somewhat greater failure for vertical (saddle-type) augmentation.

DISCUSSION

The use of autologous transplants from varying donor sites is a preferred method, especially in cases with severe

TABLE 6 Implant Failure by Smoking Status

Smoking Status at Time of Surgery		Implant Failure: No	Implant Failure: Yes	Total
No	Number	459	33	492
	Percentage of implant failures	77.7%	78.6%	77.7%
Yes	Number	132	9	141
	Percentage of implant failures	22.3%	21.4%	22.3%
Total	Number	591	42	633
	Percentage of implant failures	100%	100%	100%

TABLE 7 Summary of Complications Following Implant Placement

	Number	Percentage
None	524	82.8%
Marginal bone loss	7	1.1%
Premature spontaneous implant exposure	33	5.2%
Infection/inflammation	37	5.9%
Inflammation with marginal bone loss	16	2.5%
Bone graft exposure	16	2.5%
Total	633	100.0%

TABLE 8 Summary of Implant Status After 137 Months' Follow-Up

	Number	Percentage
Survival	591	93.4%
Failed at surgical phase	9	1.4%
Failed at prosthetic phase	33	5.2%
Total	633	100.0%

TABLE 9 Cumulative Implant Survival Rate (%) According to Location

Middle	Posterior		Anterior		Follow Up (Months)
Maxilla	Mandible	Maxilla	Mandible	Maxilla	
97	97	89	100	99	12
97	89	74	96	99	36
94	86	65	96	99	60
94	86	65	69	99	84
94	77	—	—	99	108
94	77	—	—	—	132

atrophy of the jaw, due to their osteoinductive and osteogenous properties.[29,30] After extensive reconstruction of the atrophic jaw with bone grafts and dental implants, long-term stability is desirable. The high long-term survival rate of dental implants situated in OBGs presented in this retrospective study indicates the safety and efficacy of this method for restoration of severely atrophic alveolar ridges. This survival rate (93.4%) was similar to the long-term survival rate reported previously for dental implants situated in OBGs,[3,4,31,32] thus giving further support to the effectiveness and predictability of utilizing bone grafts of intraoral origin to support dental

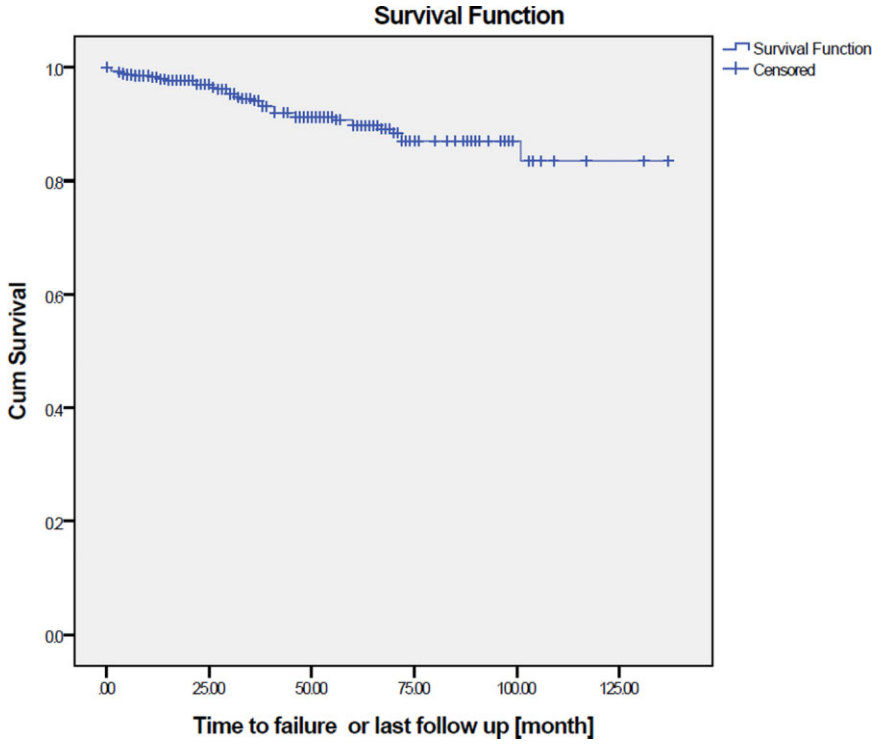

Figure 2 Cumulative implant survival rate (137 months' follow-up).

TABLE 10 Cox Regression Analysis of Variables Affecting the Survival of Implants Placed in Onlay Bone Grafts

Variable	Hazard Ratio	Robust SE	*p* Value
Location*	2.51	0.42	.03
Bone graft dimension†	2.49	0.38	.02
Bone graft failure‡	16.47	0.36	<.01

The final model is presented, with significant variables only.
*Posterior versus anterior.
†Vertical plus horizontal versus vertical or horizontal.
‡Failed versus survived.

implantation. The healing process after autologous bone transplantation is well researched and takes place in several distinct steps. At first, resorptive processes dominate in the context of inflammation. In the course of further healing, the graft is vascularized, and the proliferating cells can penetrate the transplanted bone. The transplanted bone is resorbed and replaced successively with new bone.[33,34] As applied to our study results, this process seems to lead to successful bone graft integration and bone formation with a relatively low rate of complications and a high survival rate.

Infection and bone graft exposure, two main factors that play a critical role in bone graft survival, were observed in only 18 cases, with only 8 bone grafts defined as failed. In the current study, most of the augmentations, both at donor and augmented sites, in addition to bone graft or bone supplement, were filled with PRP following PPP coverage (Figure 1, D and H).

There are contradicting reports in the literature regarding the effectiveness of PRP in bone regeneration process, most probably a result of differences between protocols for obtaining PRP (with regard to centrifugation) and the low numbers of systematic studies carried out to date.[35–37]

The first evidence of the clinical benefits of PRP in implant osseointegration was reported in 1998 by Marx and colleagues,[6] who studied 88 patients with mandibular defects treated with platelet concentrate and cancellous cellular marrow bone graft. Results showed that use of PRP allowed a radiographic graft maturation rate of 1.62 to 2.16 times higher than nonuse of PRP at 6 months, as well as greater bone density. Since then, the use of PRP has been broadened to augmentation procedures for several applications. It has been shown that PRP in combination with bovine bone substitutes manifests a positive effect on bone formation.[38–40] Several studies have suggested autologous bone use in combination with PRP to improve bone implant integration.[13,41,42] Consolo and colleagues reported the regenerative potential of PRP when used with autologous bone, but this effect appeared to be restricted to shorter treatment times: 16 patients underwent bilateral sinus floor augmentation, using autologous bone on one

TABLE 11 Summary of Onlay Bone Graft Failures

Comments	Implant Status	Direction	Area	Gender	Age
Bone replacement augmentation succeeded (second tier)	Successful	Vertical	Posterior mandible (#46, 47)	Female	69
Implant failure resulted in bone graft failure	Failed (prosthetic phase)	Vertical	Posterior mandible (#46, 47)	Female	43
Implant failure resulted in bone graft failure	Failed (prosthetic phase)	Horizontal	Posterior mandible (#45, 46)	Female	44
Bone graft failed, bone replacement augmentation succeeded	Failed (prosthetic phase)	Horizontal	Posterior mandible (#36)	Female	65
Implant failure resulted in bone graft failure	Failed (prosthetic phase)	Vertical	Posterior mandible (#35, 36, 37)	Male	52
Implant failure resulted in bone graft failure	Failed (prosthetic phase)	Vertical	Posterior mandible (#45, 46, 47)	Female	77
Implant failure resulted in bone graft failure	Failed (prosthetic phase)	Combined	Posterior mandible (#35, 36)	Female	54
Repeated onlay bone graft successful	Successful	Horizontal	Mid-posterior maxilla (#14, 15)	Male	33

side and PRP plus autologous bone contralaterally[43]; at 4 months, the PRP group showed higher bone activity as documented by histological analysis. Taking together previous reports and our results, we suppose that the use of PRP as a source of growth factors, in combination with PPP, which plays the role of a biological membrane, contribute to better integration of the graft. Furthermore, we believe that this is the first study that reports using PPP as a biological membrane in bone augmentation surgery. PPP has elevated levels of fibrinogen, which has an ability to form a fibrin-rich clot once activated. The clot provides a matrix scaffold for the recruitment of tissue cells to an injured site.[44] Migrating cells use integrin receptors that recognize fibrin, fibronectin, and vitronectin to interact with the clot matrix.[45,46] Since extracellular matrix molecules can provide signals for gene expression through integrin receptors, the integration of these tissue cells with the matrix might be expected to alter cell phenotype and function and significantly improve the healing process of both soft and hard tissues.[47] Few studies have attempted to evaluate the effect of PPP in the bone regeneration process. Hatakeyama and colleagues showed that PPP is an effective material for the preservation of sockets with buccal dehiscence.[20] An animal experimental study provides evidence of the positive role of PPP as a potential osteoinductive biological tissue adhesive.[48] The high survival rate of the OBG in the current study supports our previous finding that using PPP membrane in combination with PRP improves bone graft integration and new bone formation.

Out of the 224 OBGs that were evaluated, 214 were successful, and only 8 had to be completely removed and defined as failed, yielding a success rate of 96.4%.

A closer look at these 8 cases reveals some shared characteristics. Most of them occurred in the posterior mandible at the prosthetic phase (i.e., following rehabilitation). These results suggest that unlike the failure of implants placed in native bone, in which the bone damage is typically limited to the close vicinity of the implant, the failure of an implant placed in an onlay augmentation more often results in the complete destruction of the grafted bone block, especially in the posterior mandible. One can assume that restorations that apply ischemic pressure to the soft tissue (i.e., causing gum "bleaching"), which worsens the impaired blood supply brought about by scarring and repeated surgery, propagate these failures and therefore should be avoided. However, no conclusions can be made, as no statistical comparison with bone damage following implant failure in native bone was carried out in this study.

Causes for implant failure are multifactorial and include patient-related factors (such as general health status, smoking habits, individual differences in tissue and bone remodeling, and oral hygiene), implant-related factors (implant architecture, surface, location, etc.) and prosthesis-related factors (occlusal forces, implant loading, etc.).[36,49] Implants in this large retrospective cohort were of different types and from different manufacturers. Thus, distribution and analysis of failures according to implant type was not feasible in this work. In this long-term study, no significant correlation between health status and rate of implant failure was found. Although smoking has been shown to be a risk factor in OBG complications,[50] in the present study it did not appear to be significant in promoting bone graft or implant failure. However, out of the 8 implants that failed at the surgical phase, 5 had been placed in smokers. This suggests that smoking has an effect on the early aspects of implant survival within OBGs and warrants further investigation.

Significant differences in implant survival rate were observed between the anterior and posterior portions of the jaws. The higher success rate of the anterior area might be attributed to factors such as functional forces, oral hygiene, and bone quality. Furthermore, it was demonstrated that two-dimensional augmentations (horizontal and vertical) were more common in the posterior regions and more prone to failure compared with single-dimension augmentations (horizontal or vertical).

Onlay bone grafts are attached by titanium screw to the recipient site, which may result in soft tissue ingrowths between the grafted bone blocks. In order to avoid this situation, the space was filled with Bio-Oss saturated with PRP. We suggest that PRP stimulates the healing process of the grafted bone by local delivery of growth factors that help promote the healing process and eventually prevent resorption. In fact, we demonstrated low rates of marginal bone loss alone (1.1%) or accompanied by inflammation (2.5%) following implant placement.

There is an ongoing debate in the literature regarding whether a barrier membrane should be applied to cover autologous bone grafts in jaw augmentation.[51–53] A

membrane might or might not prevent graft remodeling with resorption and enhance graft incorporation.[54] We hypothesized that membrane coverage does have a positive effect on resorption and incorporation of autologous OBGs. We believe that PPP has an advantage for use as an autologous biological "membrane," as it contains fibrinogen, growth factors, and cytokines that can contribute to the bone regeneration process. To the best of our knowledge, there have been no previous studies of using PRP in combination with PPP or PPP alone with PPP serving as a biological membrane.

In summary, augmentation of severely atrophied jaw bone through the placement of horizontal and/or vertical autologous OBGs following the technique described in this study should be considered reliable, safe, and very effective in obtaining a high bone graft success rate and a high long-term implant survival rate.

REFERENCES

1. Brånemark PI, Lindstro J, Hallen O, Breine U, Jeppson PH, Ohman A. Reconstruction of the defective mandible. Scand J Plast Reconstr Surg 1975; 9:116–128.
2. Misch CM. Ridge augmentation using mandibular ramus bone grafts for the placement of dental implants: presentation of a technique. Pract Periodontics Aesthet Dent 1996; 8:127–135.
3. Nystrom E, Ahlqvist J, Gunne J, Kahnberg KE. 10-year follow-up of onlay bone grafts and implants in severely resorbed maxillae. Int J Oral Maxillofac Surg 2004; 33:258–262.
4. Nyström E, Nilson H, Gunne J, Lundgren S. A 9–14 year follow-up of onlay bone grafting in the atrophic maxilla. Int J Oral Maxillofac Implants 2009; 38:111–116.
5. Dimitriou1 E, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. BMC Med 2011; 9:66–76.
6. Clementini M, Morlupi A, Agrestini S, Ottria L. Success rate of dental implants inserted in autologous bone graft regenerated area: a systemic review. Oral Implantol 2012; 4:3–10.
7. Zouhary KJ. Bone graft harvesting from distant sites: concepts and techniques. Oral Maxillofac Surg Clin North Am 2010; 22:301–316.
8. Misch CM, Misch CE, Resnik RR, Ismail YH. Reconstruction of maxillary alveolar defects with mandibular symphysis grafts for dental implants: a preliminary procedural report. Int J Oral Maxillofac Implants 1992; 7:360–366.
9. Montazem A, Valauri DV, St-Hilaire H, Buchbinder D. The mandibular symphysis as a donor site in maxillofacial bone grafting: a quantitative anatomic study. J Oral Maxillofac Surg 2000; 58:1368–1371.
10. Proussaefs P, Lozada J, Kleinman A, Rohrer MD. The use of ramus autogenous block grafts for vertical alveolar ridge augmentation and implant placement: a pilot study. Int J Oral Maxillofac Implants 2002; 17:238–248.
11. Aalam AA, Nowzari H. Mandibular cortical bone grafts. Part 1: anatomy, healing process, and influencing factors. Compend Contin Educ Dent 2007; 28:206–212.
12. Schwartz-Arad D, Levin L. Multitier technique for bone augmentation using intraoral autogenous bone blocks. Implant Dent 2007; 16:5–12.
13. Schwartz-Arad D, Levin L. Symphysis revisited: clinical and histological evaluation of newly formed bone and reharvesting potential of previously used symphysial donor sites for onlay bone grafting. J Periodontol 2009; 80:865–869.
14. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85:638–646.
15. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg 2004; 62:489–496.
16. Nauth A, Giannoudis PV, Einhorn TA, et al. Growth factors: beyond bone morphogenetic proteins. J Orthop Trauma 2010; 24:543–546.
17. Anitua E, Tejero R, Zalduendo MM, Orive G. Plasma rich in growth factors promotes bone tissue regeneration by stimulating proliferation, migration and autocrine secretion in primary human osteoblasta. J Periodontol 2013; 84:1180–1190.
18. Gao C, Harvey EG, Chua M, et al. MSC-seeded dense collagen scaffolds with a bolus dose of VEGF promote healing of large bone defects. Euro Cell Mater 2013; 26:195–207.
19. Del Fabbro M, Bortolin M, Taschieri S. Is autologous platelet concentrate beneficial for post-extraction socket healing? A systematic review. Int J Oral Maxillofac Surg 2011; 40:891–900.
20. Hatakeyama I, Marukawa E, Takahashi Y, Omura K. Effects of platelet-poor plasma, platelet-rich plasma, and platelet-rich fibrin on healing of extraction sockets with buccal dehiscence in dogs. Tissue Eng Part A 2013; 20(3–4):874–882.
21. Yilmaz S, Kabadayi C, Ipci SD, Cakar G, Kuru B. Treatment of intrabony periodontal defects with platelet-rich plasma versus platelet-poor plasma combined with a bovine-derived xenograft: a control clinical trial. J Periodontol 2001; 82:837–844.
22. Clark RF. Fibrin and wound healing. Ann N Y Acad Sci 2001; 936:355–367.
23. Knox S, Crooks S, Rimmer CS. Role of fibronectin in the migration of fibroblasts into plasma clots. J Cell Biol 1986; 102:2318–2323.
24. Brown F, Lanir J, McDonagh J, Tognazzi K, Dvorak AM, Dvorak HF. Fibroblast migration in fibrin gel matrices. Am J Pathol 1993; 142:273–283.

25. Dvorak HF, Harvey P, Estrella P, Brown LF, McDonagh J, Dvorak AM. Fibrin containing gels induce angiogenesis. Implications for tumor stroma generation and wound healing. Lab Invest 1987; 57:673–686.
26. Nehls V, Herrman R. The configuration of fibrin clots determines capillary morphogenesis and endothelial cell migration. Microvasc Res 1996; 51:347–364.
27. Brooks R, Clark F, Cheresh A. Requirement of vascular integrin αvβ3 for angiogenesis. Science 1994; 264:569–571.
28. Haas R, Mensdorff-Pouilly N, Mailath G, Watzek G. Brånemark single tooth implants: a preliminary report of 76 implants. J Prosthet Dent 1995; 73:274–279.
29. Wiltfang J, Schultze-Mosgau S, Nkenke E, Thorwarth M, Neukam FW, Schlegel KA. Onlay augmentation versus sinus lift procedure in the treatment of the severely resorbed maxilla: a 5-year comparative longitudinal study. Int J Oral Maxillofac Surg 2005; 34:885–889.
30. Chiapasco M, Zaniboni M, Rimondini L. Autogenous onlay bone grafts versus alveolar distraction osteogenesis for the correction of vertically deficient edentulous ridges: a 2–4-year prospective study on humans. Clin Oral Implant Res 2007; 18:432–440.
31. Elo JA, Herford AS, Boyne PJ. Implant success in distracted bone versus autogenous bone-grafted sites. J Oral Implantol 2009; 35:181–184.
32. Kim JW, Cho MH, Kim SJ, Kim MR. Alveolar distraction osteogenesis versus autogenous onlay bone graft or vertical augmentation of severely atrophied alveolar ridges after 12 years of long-term follow-up. Oral Surg Oral Med Pathol Oral Radial Endod 2013; 116:540–549.
33. Burchardt H. Biology of bone transplantation. Orthop Clin North Am 1987; 18:187–196.
34. Buckwalter JA, Glimcher MJ, Cooper RR, Recker R. Bone biology. II: formation, form, modeling, remodeling, and regulation of cell function. Instr Course Lect 1996; 45:387–399.
35. Plachokova AS, Nikolidakis D, Mulder J, Jansen JA, Creugers NH. Effect of PRP on bone regeneration in dentistry: a systematic review. Clin Oral Implants Res 2008; 19:539–545.
36. Thor A, Wannfors K, Sennerby L, Rasmusson L. Reconstruction of the severely resorbed maxilla with autogenous bone, platelet-rich plasma, and implants: 1-year results of a controlled prospective 5-year study. Clin Implant Dent Relat Res 2005; 7:209–220.
37. Roffi A, Filardo G, Kon E, Marcacci M. Does PRP enhance bone integration with grafts, graft substitutes, or implants? A systematic review. BMC Musculoskelet Disord 2013; 14:330–341.
38. Camargo PM, Lekovic V, Weinlaende M, Vasilic N, Madzarevic N, Kenney M. Platelet-rich plasma and bovine porous bone mineral combined with guided tissue regeneration in the treatment of intrabony defects in humans. J Periodontal Res 2002; 37:300–306.
39. Lekovic V, Camargo PM, Weinlaender M, Vasilic N, Aleksic Z, Kenney EB. Effectiveness of a combination of platelet-rich plasma, bovine porous bone mineral and guide tissue regeneration in the treatment of mandibular grade II molar furcations in humans. J Clin Periodontol 2003; 30:746–751.
40. Kassolis JD, Reynolds MA. Evaluation of the adjunctive benefits of platelet-rich plasma in subantial sinus augmentatioin. J Craniofac Surg 2005; 16:280–287.
41. Fennis JPM, Stoelinga PJW, Jansen JA. Mandibular reconstruction: a histological and histomorphometric study on the use of autogenous scaffolds, particulate cortico-cancellous bone grafts and platelet-rich plasma in goats. Int J Oral Maxillofac Surg 2004; 33:48–55.
42. Schwartz-Arad D, Levin L, Aba M. The use of platelet rich plasma (PRP) and platelet rich fibrin (PRP) extracts in dental implantology and oral surgery. Refuat Hapeh Vehashinayim 2007; 24:51–55, 84. In Hebrew.
43. Consolo U, Zaffe D, Bertoldi C, Ceccherelli G. Platelet-rich plasma activity on maxillary sinus floor augmentation by autologous bone. Clin Oral Implants Res 2007; 18:252–262.
44. Yamada KM, Clark RAF. Provisional matrix. In: Clark RAF, ed. Molecular and cellular biology of wound repair. New York: Plenum, 1996:51–93.
45. Huhtala P, Humphries MJ, McCarthy JB, Tremble PM, Werb Z, Damsky CH. Cooperative signaling by α5β1 and α4β1 integrins regulates metalloproteinase gene expression in fibroblasts adhering to fibronectin. J Cell Biol 1995; 129:867–879.
46. Newman D, Clark RAF, Honaken L. Human dermal microvascular endothelial cells use α5β1, as well as avb3, to interact with the major fibrinogen breakdown product E1. J Invest Dermatol 1996; 106:823a.
47. Schwartz MA, Schaller MD, Ginsberg MH. Integrins: emerging paradigms of signal transduction. Annu Rev Cell Dev Biol 1995; 11:549–599.
48. Abiraman S, Varma HK, Umashankar PR, John A. Fibrin glue as an osteoinductive protein in a mouse model. Biomaterials 2002; 23:3023–3031.
49. Montes CC, Pereira FA, Thome G. Failing factors associated with osseointegrated dental implant loss. Implant Dent 2007; 16:404–412.
50. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II). Etiopathogenesis. Eur J Oral Sci 1998; 106:721–764.
51. Levin L, Herzberg R, Dolev E, Schwartz-Arad D. Smoking and complications of onlay bone grafts and sinus lift operations. Int J Oral Maxillofac Implants 2004; 19:369–373.
52. Chiapasco M, Abati S, Romeo E, Vogel G. Clinical outcome of autogenous bone blocks or guided bone regeneration with

e-PTFE membranes for the reconstruction of narrow edentulous ridges. Clin Oral Implants Res 1999; 10:278–288.

53. Donos N, Kostopoulos L, Karring T. Augmentation of the mandible with GTR and onlay cortical bone grafting. Clin Oral Implants Res 2002; 13:175–184.

54. Gielkens PFM, Bos RRM, Raghoebar GM, Stegenga B. Is there evidence that barrier membranes prevent bone resorption in autologous bone grafts during the healing period? A systematic review. Int J Oral Maxillofac Implants 2007; 22:390–398.