Rehabilitation of Postextractive Socket in the Premaxilla: A 12-Year Study on 27 Titanium Plasma Spray Resorbable Calcium Phosphate Coated Single Implants

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Objectives: *The purpose of this study was to evaluate the peri-implant bone tissue level on postextractive resorbable calcium phosphate coated single implants placed in premaxillary sites grafted with autologous bone, anorganic bovine bone (ABB), platelet-rich plasma (PRP), and keratinized epithelial connective graft over 12 years.*

Materials and Methods: *A total of 27 patients received a postextractive single implant in premaxillary sites grafted with ABB and PRP. Two months later, a keratinized epithelial connective graft was applied and the implants loaded. Clinical and radiographical evaluations were performed at baseline, 6 and 18 months, 4 and 6 years after the implant insertion, and then every 2 years up to the 12th year.*

Results: *After 12 years, a total of 22 implants (81.48%), were available for the final data analysis; the implants achieved a 100% cumulative survival rate, and only a mild degree of periodontal tissue inflammation was recorded. The radiographic evaluation revealed a physiological marginal bone remodeling over the follow-up.*

Conclusion: *Although a good preservation of the residual bone tissue in postextraction implant sites treated with keratinized epithelial connective tissue grafts was observed, the low number of treated cases does not allow us to propose this experimental protocol to all cases of bone defects but it certainly represents a new option. Further studies on a greater number of patients and using implants with different surface characteristics should be conducted for a better understanding of the indications of the proposed treatment. (Implant Dent 2018;27:452–460)*

Key Words: autologous bone graft, keratinized epithelial connective tissue graft, peri-implant bone tissue, postextraction socket

In the anterior region of the jaws and premaxilla, the success of an immediate implant restoration is always linked to the creation of an aesthetic result in harmony with the dental arches. In this way, the surgical procedure plays a key role on the architecture of the peri-implant soft and hard tissues.

The placement of dental implants requires a sufficient volume of bone tissue to allow primary stability, the first step for osseointegration.[1] After tooth loss, the anatomic remodeling of the socket starts because of the lack of nutrition of the fasciculated bone tending to resorption. This tissue is mainly present on the buccal surface.[2] If there are anatomical defects, the remodeling process is faster and massive. In the premaxilla, the buccal plate is thin; the thickness depends on the buccal inclination of the anterior teeth.[3] These factors support the vestibular bone resorption in the maxilla. Some authors have established that in order to obtain an ideal osseointegration, and the support of soft tissues, a 2 mm thick vestibular bone tissue, surrounding the implants is necessary; this amount of bone is useful to reduce crestal bone resorption after the rehabilitation.[4,5] It

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has been shown that a sufficient size of buccal plate is necessary to obtain aesthetic scalloped architecture of premaxillary soft tissues.[6–8]

Several researchers have already described surgical techniques to reduce crestal bone remodeling after tooth loss and immediate implant placement. Over time, changes of peri-implant tissues in postextractive implant sites have been evaluated, and a reconstructive technique able to restore the maxillary buccal bone wall filling the defects in atrophic sockets, using a bone graft harvested from the maxillary tuberosity, was developed.[9] Another surgical technique useful for the reconstruction of the alveolar ridge of postextractive implant sites is the use of bovine xenogenic bone graft together with titanium grids to support the graft and to create a protective curtain effect of the grafted area and prevent excessive resorption during the healing of soft tissues.[10]

For the same purpose, the use of emoderivates and growth factors was also proposed to increase the stability of the soft and hard tissues in the implant restoration in aesthetic regions, where the preservation of bone and gingival architecture takes on a crucial role.[11] Platelet-rich plasma (PRP) is an autologous emoderivate with a high concentration of blood growth factor that mediates and regulates cells events and healing response of the hard and soft tissues.[12] Its high plasticity and application methods allow it to be used in numerous clinical applications and combinations with different biomaterials in regenerative surgery procedures. In the literature, the potential of PRP on bone neoformation is still debated in relation to more evidence about its contribution to early soft-tissue healing.[13]

Buser et al[14] reported that the lack of 3D implant placement could cause a recession of the buccal mucosa and the formation of headless papillae in postextractive sockets. Some authors have shown that postextractive implants have a survival rate percentage similar to the one of implants placed in mature sites (≥98%).[15,16] On this topic, however, there is still disagreement because experimental animal studies have shown that crestal bone remodeling on postextractive implants was negatively affected by several variables.[17] The presence of different results in the literature and the lack of long-term clinical studies did not allow the development of a therapeutic treatment plan supported by clinical evidence.[18,19]

Last but not least, it is well established that the implant surface characteristics can influence bone to implant contact percentage and therefore osseintegration by increasing the contact surface and the biomechanical interlocking of implant and bone, and eventually affecting cell spreading, differentiation and local factor production.[20]

The aim of the present study was to evaluate the peri-implant bone tissue level over the long time period on postextractive resorbable calcium phosphate (CaP) coated single implants placed in premaxillary sites reconstructed with guided bone regeneration (GBR) technique, autologous bone, anorganic bovine bone (ABB), PRP, and keratinized epithelial connective graft.

Materials and Methods

Between January 2001 and December 2002 at the Unit of Implant Prosthodontics, Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, 27 patients (15 women and 12 men, age ranged between 20 and 66 years) were included in this study. The principles outlined in the declaration of Helsinki on clinical research involving human subjects were adhered to. All patients received thorough explanations and had to provide a written informed consent form before being enrolled in the trial. The study was approved by the Ethics Committee of Sapienza University of Rome (approval number: 3691).

Patients were chosen among a population of 55 subjects having a tooth loss in the premaxilla as a result of trauma, disease, or endodontic therapy

Table 1. Titanium Plasma Spray Implants (Pitt-Easy Bio-Oss, Fbr, Orltronics, Germany) Inserted in the Postextractive Sites of the Premaxilla

Patient Number	Sex	Age	Implant Sites	Implants Dimension (mm)
1	M	45	2.1	3.75 × 12
2	F	25	1.2	3.75 × 16
3	F	32	2.2	4 × 12
4	M	50	1.3	4 × 12
5	M	60	1.1	3.75 × 16
6	F	50	2.1	3.75 × 14
7	F	65	2.3	4 × 14
8	F	30	1.1	3.75 × 12
9	M	48	1.2	4 × 12
10	M	52	2.1	3.75 × 14
11	F	48	2.1	3.75 × 12
12	M	65	2.2	3.75 × 12
13	F	44	1.3	4 × 14
14	M	25	1.1	3.75 × 12
15	M	52	2.1	3.75 × 14
16	F	62	2.2	3.75 × 12
17	F	48	1.2	3.75 × 16
18	F	50	1.1	4 × 14
19	M	55	1.1	4 × 16
20	M	72	2.2	3.75 × 14
21	M	70	1.1	3.75 × 16
22	F	45	1.2	4 × 14
23	F	32	1.1	3.75 × 16
24	M	60	2.1	4 × 14
25	F	58	1.2	3.75 × 16
26	M	71	1.1	4 × 12
27	F	59	1.1	3.75 × 14

failures and were rehabilitated with postextractive implants and gold ceramic crowns. Patients affected by systemic diseases that would contraindicate oral surgical treatment, bruxism and alcoholism, smoking more than 20 cigarettes per day, patients subjected to corticosteroid and bisphosphonates therapy or periodontal treatment, and the ones with poor oral hygiene or contaminated teeth adjacent to the postextractive sites were excluded from the study. The recruited patients were required to have a larger diameter of the bone defect than the inserted implant and were all subjected to GBR with application of autologous bone, ABB (Bio-Oss Geistlich Pharma AG, Wolhusen, Switzerland), and PRP covered by a nonresorbable membrane (W.L. Gore & Associates, Flagstaff, AZ). After 2 months, the membrane was removed and a keratinized epithelial connective graft was applied.

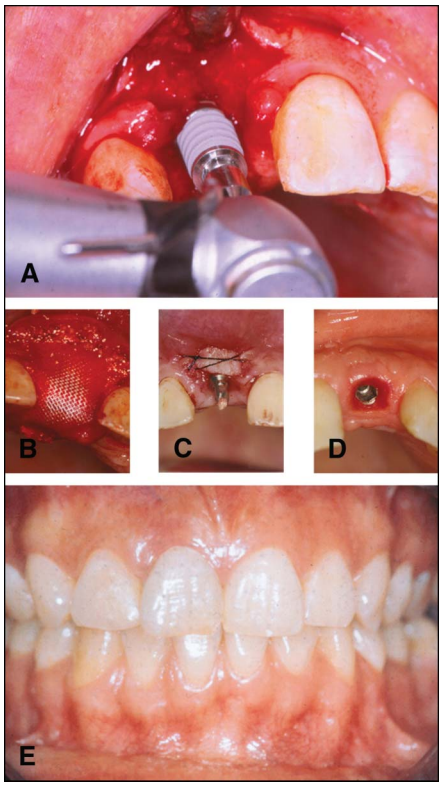

Fig. 1. A, Implant Placement; (**B**) the peri-implant buccal defect and socket gap is augmented with a combination of autologous bone, anorganic bovine bone, PRP, and covered by a membrane; (**C**) an epithelium-connective graft with keratinized gingiva is stabilized with a cross suture on the buccal aspect of the implant site; (**D**) healing of the implant site 2 months after surgery; and (**E**) 1.1 gold-ceramic crown restoration.

During the first visit, the patients were subjected to x-ray examinations: periapical radiographs, dental panoramic radiographs, or CT. In addition, all patients enrolled in this present study underwent at least 1 session of professional oral hygiene 1 month before the surgery. An antibiotic therapy was administered (Augmentin 1gr; Smithkline Beecham, New York, NY) twice a day for 5 days starting 1 hour before the surgery. Local anesthesia was induced by infiltration with articaine-epinephrine1:100,000. In each of the 27 patients, a single implant (PITT-EASY BIO-OSS FBR-coated; Oraltronics, Bremer, Germany), with 3.75 to 4 mm diameter and length ranging from 12 to 16 mm, was placed (Table 1). These were tapered self-tapping implants with a 2-mm machined collar and a titanium plasma spray (TPS) surface modified by electrochemical deposition of 20 ml of CaP coating made of Brushite. This coating had the property to be completely resorbed after 6 to 8 weeks, supporting a fast bone regeneration (FBR).[21,22] To make easier the extraction of the hopeless teeth, a horizontal full-thickness flap extending mesially and distally up to the adjacent teeth was reflected with 2 vertical incision on the vestibular mucosa to facilitate the flap mobilization up to the distal root surface height of the adjacent teeth. The implants were inserted using a surgical template allowing a palatal inclination to obtain a good primary stability while the implant platform was positioned 2 mm below the enamel-cementum junction of the 2 adjacent teeth to reach good aesthetics (Fig. 1A). The trapezoidal flap, once detached, allowed a better stratification of the mixture formed by platelet concentrate, anorganic bovine bone (50%), and autologous bone picked up from the maxilla tuberosity (50%). The bone graft was covered by a Gore-Tex membrane (W.L. Gore & Associates, Flagstaff, AZ), which extended for at least 3 mm on the vestibular and palatal crest where it was fixed on the bone tissue of the postextractive socket (Fig. 1B). Patients were instructed to maintain a liquid or semiliquid diet for the first 3 days and then gradually return to a normal diet. As postsurgical analgesic therapy, Nimesulide in granules for oral solution (Aulin, 100 mg, Roche, Monza, Italy) was suggested. The oral hygiene was maintained with chlorhexidine 0.2% (Dentosan 0.2%; Johnson & Johnson, New Brunswick, NJ) for 15 days. All the implants were placed with a torque wrench device and showed an insertion torque of 35 N/cm.

Two months after the insertion of the implants, a second surgery was performed to remove the Gore-Tex membrane, and at the same time, the connective graft covered with keratinized gingiva taken from the whole thickness of the palate was inserted and fixed with suture all around the prosthetic abutment connected to the fixture (Fig. 1C). In addition, a temporary crown not in contact with the opposing dentition was applied to condition the grafted tissue and to shape a scalloped-free gingiva (Fig. 1D). The rehabilitation therapy ended after 4 months with the final application of a gold-ceramic crown (Fig. 1E). All the necessary procedures for the implant prosthetic restorations of the 27 patients were performed by 2 operators (A.Q. and G.P.). Oral

Table 2. Implant Success and Survival Rate According to ICOI Pisa Consensus Conference Congress (21)

	Health Scale				
Time Points	I	II	III	IV	Available Implants
6 mo (T1)	27	0	0	0	27
18 mo (T2)	5	20	1	0	26
4 y (T3)	0	25	1		26
6 y (T4)	0	24	1		25
8 y (T5)	0	24	0	0	24
10 y (T6)	0	23	0	0	23
12 y (T7)	0	22	0	0	22

I = success; II = satisfactory survival; III = compromised survival; IV = clinical or absolute failure.

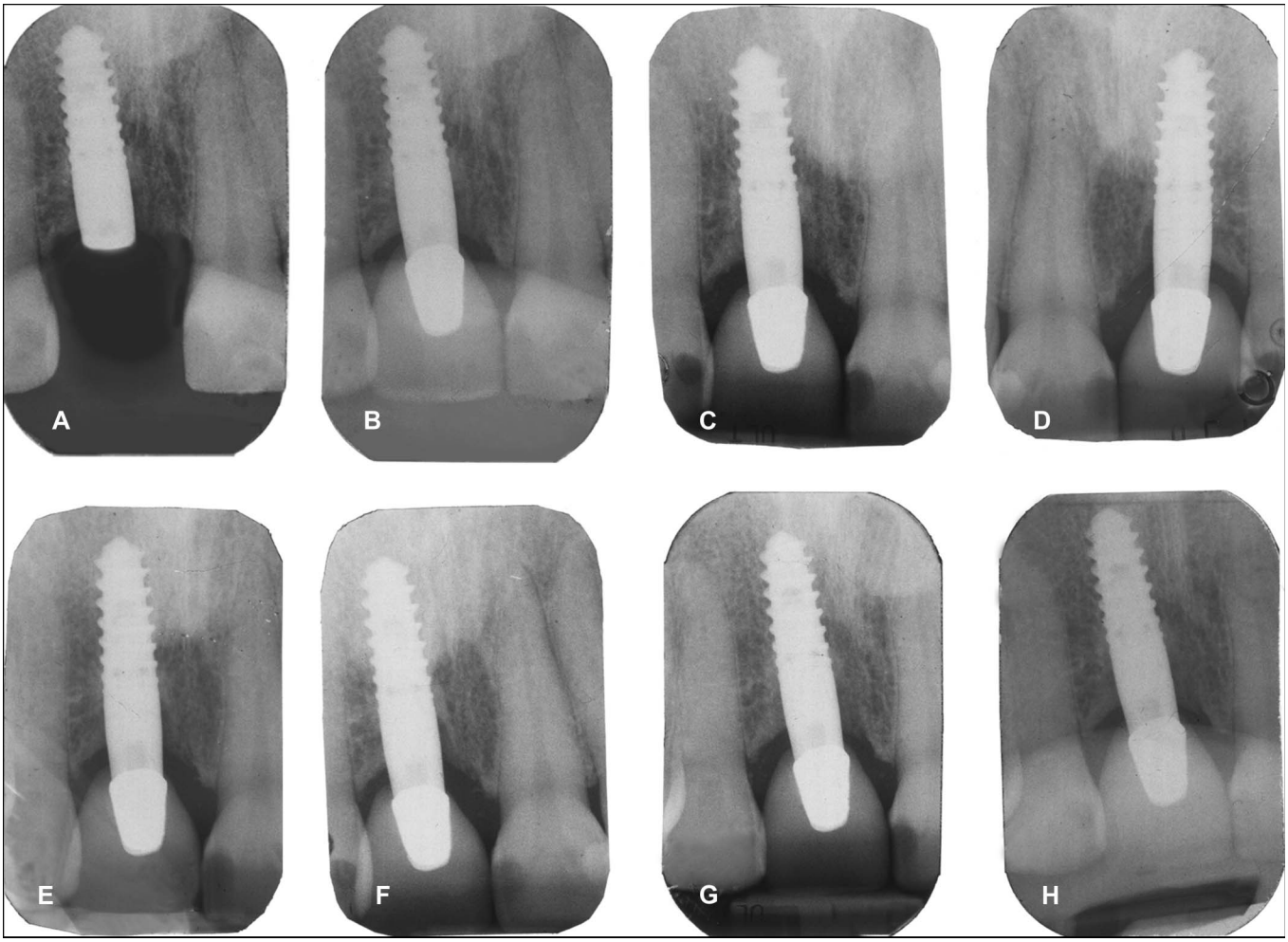

Fig. 2. Standard periapical x-rays measured for 12 years of follow-up. A, X-ray of the implant inserted at baseline T0; (**B**) x-ray after 6 months (T1); (**C**) x-ray after18 months (T2); (**D**) x-ray after 4 years (T3); (**E**) x-ray after 6 years (T4); (**F**) x-ray after 8 years (T5); (**G**) x-ray after 10 years (T6); and (**H**) x-ray after 12 years (T7).

hygiene instructions were also provided. Each patient was enrolled in a strict personal tailored recall system and was followed up every 2 to 4 months during the first 2 years and subsequently every 3 to 6 months up to 12 years after the surgery. During these control sessions, the patient's oral hygiene was assessed and brushing and flossing instructions reinforced. Supragingival and subgingival plaque removal was performed very delicately with plastic or titanium manual instruments. This recalling protocol has already been experimented in another study.[23]

Clinical and Radiographic Evaluations

Clinical evaluations and periapical x-rays were performed at baseline (T0), 6 months (T1), 18 months (T2), 4 years (T3), 6 years after the implant insertion (T4), and then every 2 years up to the 12th year (T5, T6, T7). Over the 12-year observational period, the clinical measurements of the peri-implant tissues and periapical x-rays were performed by 3 operators previously calibrated (G.P., A.Q., and I.V.). A cone beam CT was performed to show the vestibular bone remodeling around implants at the 12-year follow-up. The following clinical parameters were collected on each implant:

1. Mobility: measured by applying a small transverse force with 2 opposed handles of manual instruments;
2. Presence/absence of pain, inflammation, infection signs;
3. Modified gingival index (mGI)[24];
4. Modified Plaque Index (mPI)[24];
5. Probing depth (PD);
6. Implant failure (specifying the reasons for failure);
7. Survival rate during the time interval;
8. Cumulative survival rate;
9. Success rate during the time interval;
10. Cumulative success rate.

At the 12-year follow-up, implant success, survival, and failure rates were evaluated according to the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference criteria.[25] Radiographic evaluation was performed with standardized periapical x-rays, taken using a customized bite record fabricated with acrylic resin on a Rinn XCP Ring positioner (Dentsply,

Konstanz, Germany) and a beam guiding rod to allow parallelization between the x-ray tube and the film and to standardize all the radiographs. The radiographs were performed with a dental x-ray machine (TM 2002 Planmeca Proline CC; Planmeca Group, Helsinki, Finland) equipped with a long tube that operated at 70 kW/7.5 mA and were developed in an automatic developer under standardized conditions. The radiographs, set on a cephalometric unit in a darkroom, were captured, converted to digital images with a camera, and saved as .tiff images. Then, each image was processed with specific software (Scion Image Beta 4.03 for Windows XP, Scion LTD, Frederick, MD) and displayed on a high-resolution monitor. A computer-assisted calibration was made on the mesial and distal side of each implant, measuring the known distance between the 2 threads. The following reference points were assessed on each image: implant-abutment junction, threads, and the most coronal bone-to-implant contact on both the mesial and distal sides. This allowed to make linear measurements of the remaining peri-implant bone (expressed in millimeters), measured from the mesial and distal marginal bone levels and the implant-abutment junction at different time points (from T0 to T7) and then averaged for each implant. The linear measurements were made by a trackball driven cursor on a 10 times magnified digitized image of the implant on the monitor. The measurements were performed by 2 blinded examiners who did not take part either in the planning or in the execution of the study.[26]

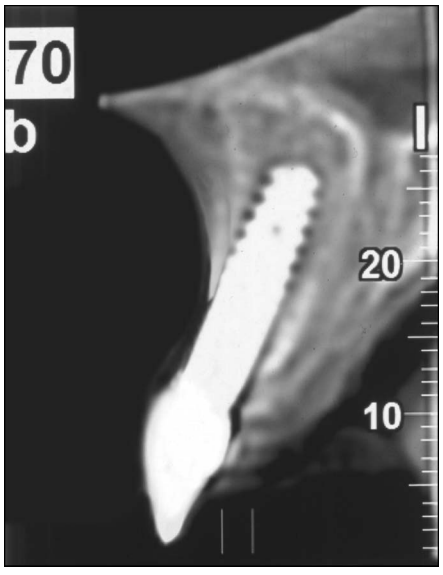

Fig. 3. Part of cone beam CT showing the facial bone remodeling around the implant after 12 years of follow-up.

Table 3. PD of All Implants Measured at Baseline (T0), After 6 Months (T1), After 18 Months (T2), 4 Years After Surgery (T3), and Every 2 Years up to 12 Years of Follow-Up (T4, T5, T6, T7)

	T0	T1	T2	T3	T4	T5	T6	T7
Mean	2.54	2.70	2.97	3.12	2.83	2.91	4.18	4.23
SD	0.34	0.35	0.47	0.35	0.33	0.35	0.15	0.32
Dunn's multiple comparison test								
T0		ns	*	*	ns	**	*	*
T1			***	**	ns	ns	*	*
T2				ns	ns	ns	**	**
T3					ns	ns	ns	***
T4						ns	*	*
T5							*	*
T6								ns

Values are presented as mean ± SD.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.
ns, not significant ($P > 0.05$).

Statistical Analyses

PDs and peri-implant bone remodeling values over time were evaluated by means of Friedman test and Kruskal–Wallis test, respectively; differences among different time points were assessed by Dunn' multiple comparisons test. All the data are presented as mean ± SD; statistically significant differences were accepted as $P < 0.05$.

RESULTS

Fifteen days after implant placement, 2 patients presented pain and inflammation in the area of surgery and antibiotic therapy was administered (Augmentin 1gr; Smithkline Beecham, New York, NY) every 12 hours for 5 days; no additional complications were recorded.

After 1 month, 3 additional subjects presented an initial peri-implantitis. The patients underwent a second stage surgery at the implant site to reopen the flap and remove the reactive tissue; an antibiotic therapy (Augmentin 1gr; Smithkline Beecham, New York, NY) every 12 hours for 5 days was prescribed and 10 days after

Table 4. Mean mGi e mPI Evaluated According to Mombelli et al[24] on the Mesiofacial, Facial, Distofacial, Palatal Aspect for Each Implant at Baseline (T0), After 6 Months (T1), After 18 Months (T2), 4 Years After Surgery (T3), and Every 2 Years up to the 12-Year Follow-Up (T4, T5, T6, T7)

	Score	T0 (%)	T1 (%)	T2 (%)	T3 (%)	T4 (%)	T5 (%)	T6 (%)	T7 (%)
mGi	0	100	44.5	42.3	42.1	22	8.3		
	1		55.5	50	54	74	83.4	91.3	100
	2			7.7	3.9	4	8.3	8.7	
	3								
mPi	0	100	70.4	53.9	38.4	16	4.2		
	1		29.6	38.4	57.7	84	87.5	91.3	100
	2			7.7	3.9		8.3	8.7	
	3								

Table 5. Marginal Bone Loss (mm) Around the Studied Implants After 6 Months (T1), 18 Months (T2), 4 Years (T3), and Every 2 Years up to the 12-Year Follow-Up (T4, T5, T6, T7). Values are Presented as Mean ± SD

	T1	T2	T3	T4	T5	T6	T7
Mean	1.86	2.13	2.23	2.34	2.55	2.66	2.82
SD	0.09	0.43	0.33	0.28	0.44	0.39	0.24
Dunn's multiple comparison test							
T0	ns	*	*	*	*	*	*
T1		ns	**	*	*	*	*
T2			ns	ns	**	*	*
T3				ns	ns	**	*
T4					ns	ns	**
T5						ns	ns
T6							ns

*$P < 0.001$.
**$P < 0.05$.
ns, not significant ($P > 0.05$).

sutures were removed. One month after the surgery and the antibiotic therapy, the peri-implant tissue did not show signs of infection.

Implant success and survival rates at each follow-up recall, according to the ICOI Pisa Consensus Conference Criteria, are shown in Table 2. After 12 years, 22 patients (81.48%), for a total of 22 implants (81.48%), were available for the final data analysis (Fig. 2, A–H). The implants achieved a 100% cumulative survival rate at the end of the study period (Fig. 3).

Clinical parameters assessment consisted of measurement of PD, mGI, mPI on 4 aspects of each implant at baseline and at every follow-up visit. Mean PDs values slightly increased over time, and however, were always less than 4.5 mm. Significant statistical differences were observed between T6 and T0, T1, T2, T4, T5 and between T7 and T0, T1, T2, T3, T4, T5 (Table 3).

Mean mGI and mPI outcomes are presented in Table 4. After 10 years of follow-up (T6), none of the implants scored 0 regarding the assessment of mGI and mPI and; 2 years later (T7), 100% of implants scored 1. Overall, only a mild degree of inflammation of the periodontal tissue was recorded after such a long study period.

The radiographic evaluation of the implants revealed a physiological marginal bone remodeling during the 12-year follow-up. Peri-implant bone loss was observed to increase over time, indeed, a significant statistical difference was reported between the baseline (T0) and all the evaluated time points, except for T1 (Table 5).

DISCUSSION

After tooth avulsion, the loss of blood supply to the buccal cortical plate produces local alterations to the biology of the bone resulting in a gradual resorption that may cause a reduction of tissue stability and aesthetic value of the implant rehabilitation over time. In this way, the surgical site elected for the insertion of immediate dental implant needs an accurate evaluation of the soft and hard tissues conditions in relation to the function and the harmony of the smile aesthetics.[27–29]

The different techniques of peri-implant crestal bone tissue preservation are useful to obtain a lower vertical and horizontal remodeling of the ridge after extraction.[30,31] Indeed, according to a systematic review of Tan et al,[32] the horizontal remodeling is between 29% and 63% and the vertical one ranges from 11% to 22% after 6 months from extraction. Cardaropoli et al[33] published a study about socket preservation allowing to partially maintain the original volume of crestal bone tissue in postextractive sockets (1.04 mm horizontal remodeling and 0.46 mm vertical remodeling). The thickness of the buccal plate seemed to affect the amount of horizontal and vertical resorption of postextractive sockets.[33,34] In the present study, the patients have not been evaluated by the thickness of the buccal plate, and probably this is the reason why in this experimentation the volume of crestal bone tissue remodeling is greater than that one of the authors mentioned above.[33,34] Probably, in the present study, the longevity of the implants 12 years after the placement is also justified by the insertion of a mixture of autologous bone, anorganic bovine bone and PRP in the gap between the bone andthe implant, and the implant surface characteristics.[35] Indeed, the coating used for the present implants was applied on the TPS surface by electrodeposition; this is an alternative process developed to overcome the drawback of currently commercially available plasma sprayed CaP-coatings, which showed brittleness and insufficient strength. The plasma-spray technique uses very high temperatures, which may alter the chemical structure of the hydroxyapatite (HA), and may not permit uniform coating of complex surface geometries, whilst electrochemical deposition of CaP is one of the most promising technique, as stated by He et al.[36–37] It enables to control the morphology of HA crystals by regulating the concentration of electrolytes prepared for deposition, it uses aqueous solutions at low temperatures, which cannot affect the structure of the implant, the homogeneity of the CaP coating and which can be applied to complex shapes.[38] CaP coatings have been shown to increase the bioactivity and success rate of dental implants, allowing the formation of strong chemical bonding with the bone, increasing the mechanical interlocking and the percentage of bone contact for CaP-surfaced implants when compared with non-coated titanium implants.[21]

Although the effectiveness of PRP associated with bone substitute materials is still largely debated in the scientific literature,[39] a recent human clinical study demonstrated the significant role of growth factors in terms of enhanced bone quality in grafted extraction sockets.[40] Kurikchy et al[41] showed that, in

the early stage of healing, the addition of PRP to anorganic bovine bone increased bone formation in an animal model and provided a faster bone healing than the biomaterial alone. The use of PRP may contribute to the peri-implant tissue stability that resulted in the present work, although its effect alone or in addition to autologous bone and xenografts should be further investigated in a larger sample size.

Moreover, in the present study, the constant maintenance of the crestal bone volume for a long period (12 years) is also due to the graft of keratinized gingival tissue in the area of the gap. This provides a thick barrier of keratinized soft tissue, which may help not only to get aesthetic results but also to protect the implant over the long term.[42–44] In 1990, Block et al found that the keratinized soft tissues surrounding natural teeth have an optimal state of health compared with those with poorly keratinized soft tissue.[45] Several authors showed that the lack of keratinized tissues around implants lead to an increased resorption of the peri-implant bone tissue, attachment loss, significant plaque accumulation, and gingival bleeding.[42,46–48] In the last few years, many authors studied the techniques to increase the amount of soft tissue around implants, in particular when these are placed in areas where keratinized gingiva is not present.[49–55] Some systematic recently published reviews analyzed different materials and techniques to increase peri-implant soft tissues. These reviews concluded that the connective tissue grafts are effective to increase keratinized tissue around implants.[56,57] Also in our study, despite the reduced number of implants used, we found a good preservation of the residual bone tissue in postextraction implant sites treated with keratinized epithelial connective tissue grafts. The soft tissue around implants may result after its placement in a border tissue composed of keratinized masticatory mucosa or nonkeratinized mucosa. A reduced height of the bone ridge is often associated with a lack of keratinized gingiva.[58,59] The role of the keratinized mucosa around an implant is still debated and controversial, but several authors have described that it plays a role enhancing the aesthetic contour and harmony of the restorations with a decreased risk of marginal recessions. Indeed, the masticatory mucosa plays an important part as a barrier against the bacterial and plaque aggression, and in the long term, health maintenance of the soft-tissue stability supported implant crowns.[43] It would be interesting to examine this topic with a longitudinal study using a larger number of patients.

Conclusions

Although our study had a long follow-up (12-year follow-up compared with other studies with shorter follow-up),[51–54] the low number of treated cases does not allow us to propose this experimental protocol to all cases of bone defects, but it certainly represents an option that should be further investigated on a greater number of clinical cases and using implants with different surface characteristics for a better understanding of its indications and potential.

Disclosure

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

Approval

The study was approved by the Ethical Committee of Sapienza University of Rome (approval number: 3691).

Roles/Contributions by Authors

V. Perrotti: Data analysis and interpretation, artwork preparation, drafting, and revision of the manuscript. I. Vozza: Protocol design, patient recruitment, and data collection. M. Tumedei: Interpretation of the data and writing of the manuscript. G. Pompa: Protocol design and clinical sessions. F. Iaculli: Data analyses and interpretation, revision of the manuscript, and its submission. A. Quaranta: clinical sessions, and critical revision of the manuscript.

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