Regenerative Treatment of Peri-Implantitis Using Bone Substitutes and Membrane: A Systematic Review

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ABSTRACT

Purpose: This systematic review aimed to assess the available literature for regenerative treatment of peri-implantitis using bone graft substitutes and membranes.

Methods: A search in electronic databases was conducted to assess all types of clinical studies treating bone defects derived from peri-implantitis using guided bone regeneration (GBR) techniques.

Results: During the first screening, 399 titles were identified. Finally, 17 articles reporting on 173 implants were included. The articles mainly focused on radiographic bone fill of the defect. Qualitative measures of "bone fill" were reported: 10.4% of the implants showed complete "bone fill," whereas 85.5% revealed incomplete defect closure. No bone fill was shown in 4.0%. Little information (in 53.2%) was provided regarding the probing depth before or after treatment. Data concerning the inflammatory status of soft tissues were also scarce and only reported in three studies. A large heterogeneity concerning disinfection protocols and regenerative materials used was found. The high percentage of low-quality studies rendered a meta-analysis impossible.

Conclusion: Complete fill of the bony defect using GBR seems not to be a predictable outcome. The mucosal health status is left unconsidered in most studies. Well-controlled trials are needed to determine predictable treatment protocols for the successful regenerative treatment of peri-implantitis using GBR technique.

KEY WORDS: bone loss, guided tissue regeneration, peri-implantitis, probing depth, review

During the last decades, the use of dental implants has become a routine procedure in dentistry to replace one or more missing teeth. Using implant survival as the indicator of successful clinical outcome, a majority of clinical studies have shown very positive results for dental implants.[1] However, limited focus has been put on peri-implant mucosal health thus far. Recent studies reported a rate of 8.6 to 9.7% of chronic inflammation of soft and hard tissues neighboring implants after 5 years.[2,3] Lately, a comprehensive investigation concluded that the peri-implant inflammation is a common clinical finding about 10 years after implantation.[4] The pathological conditions termed mucositis and "peri-implantitis" are considered the major complication in dental implantology.[3] Clinical manifestations like gingival bleeding, swelling, and at a later state, bone loss highly resemble periodontal inflammation. Plenty of research has been conducted, proving that both diseases have a bacterial etiology with a similar spectrum of pathogens.[5–7] In analogy to periodontitis and gingivitis, peri-implantitis can be distinguished from mucositis by the clinical finding of attachment loss to supporting tissues, that is, to the supporting bone. Thus, increased peri-implant probing depth (PPD) and radiographic bone loss around the implant's neck are considered the most reliable parameters proving peri-implantitis.[8,9] Additionally, bleeding

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on periodontal probing (BoP), although an indicator for mucositis and not peri-implantitis, is a relevant parameter for the risk assessment of peri-implantitis.[10]

A broad variety of different treatment modalities have been proposed for the treatment of peri-implantitis, and there is still a lack of evidence concerning their indication and outcome.[11] At the turn of the millenium, a systematic treatment scheme called "Cumulative Interceptive Supportive Therapy" (CIST)[9] was formulated. Based on clinical and radiographical findings, a peri-implant lesion was categorized into a maintenance classification system, which consistently leads to a specific treatment recommendation. In the CIST protocol, regenerative surgery using guided tissue regeneration (GTR) techniques is recommended to fill bony defects caused by peri-implantitis. Because of the fact that in peri-implantitis treatment, regeneration is limited to bony tissue; the term "guided bone regeneration" (GBR) has obtained acceptance in the literature.[12]

There have been numerous case reports, case series, and clinical trials published reporting on GBR techniques in peri-implantitis treatment, in which a combination of both membrane and bone graft substitutes was used. However, there is limited evidence on success and reliability of that treatment protocol. The aim of the present review was to systematically evaluate the outcome of GBR using a bone graft substitute in combination with a membrane to treat bone defects derived from peri-implantitis on the basis of the parameters PPD, BoP, and marginal bone loss (BL).

MATERIALS AND METHODS

Search Method

Using the US National Library of Medicine (Medline), EMBASE, and OVID, a literature search was performed on articles published up to January 2008. The following synonyms and groups were included: (periimplant*) or (peri-implant*), (membrane) or (gtr) or (gbr), and (clinical).

A manual search covered the reference lists of the included articles, as well as of review articles concerning the topic. Furthermore, the "related aticles" option on the NCBI Web site was used as data source.

Screening and Selection

In the first step, titles and abstracts of the electronic search were independently screened by two reviewers (P.S. and P.R.S.), and assessed for possible inclusion in the review.

- Randomized controlled trial (RCT) studies comparing interventions using membrane and bone graft substitutes to control groups treated without GBR techniques;
- Non-randomized clinical trials, and case reports and series;
- Only cases treating bone defects derived from marginal peri-implantitis were considered. Studies dealing with peri-apical peri-implantitis were not included because of its different etiology and therapeutic approaches.

With respect to a valid comparability of the treatment modalities, only publications reporting on a treatment protocol including application of both membrane (resorbable and nonresorbable) and bone substitutes were included.

In the second step, the full texts of all possibly relevant studies, including manually retrieved articles, were then evaluated separately and independently by the same reviewers. Disagreement between the reviewers was resolved by discussion.

From the included articles, the data for the assessment parameters probing depth around implants (PPD), BoP, and bone level (BL) were extracted if given. The difference of these values before and after treatment, and their weighted means were calculated if possible. For publications providing only means and standard deviations for a collective of peri-implantitis cases, differences of the means were calculated. In some cases, more detailed data from the authors of the more comprehensive studies were requested.

RESULTS

Initially, 399 titles and abstracts from the electronic search were screened and assessed for possible inclusion in the review. Out of these, titles that obviously did not meet the inclusion criteria were excluded in the first step, and 62 studies remained for further analysis. Four additional articles were included by manual search, and two by the "related links function." These 68 studies were then separately and independently evaluated by the reviewers. In this step, 51 articles were further excluded. The main reasons for exclusion were: animal studies (12),[13–24] review articles (10),[6,8,25–32] missing peri-implantitis situation or peri-implantitis treatment

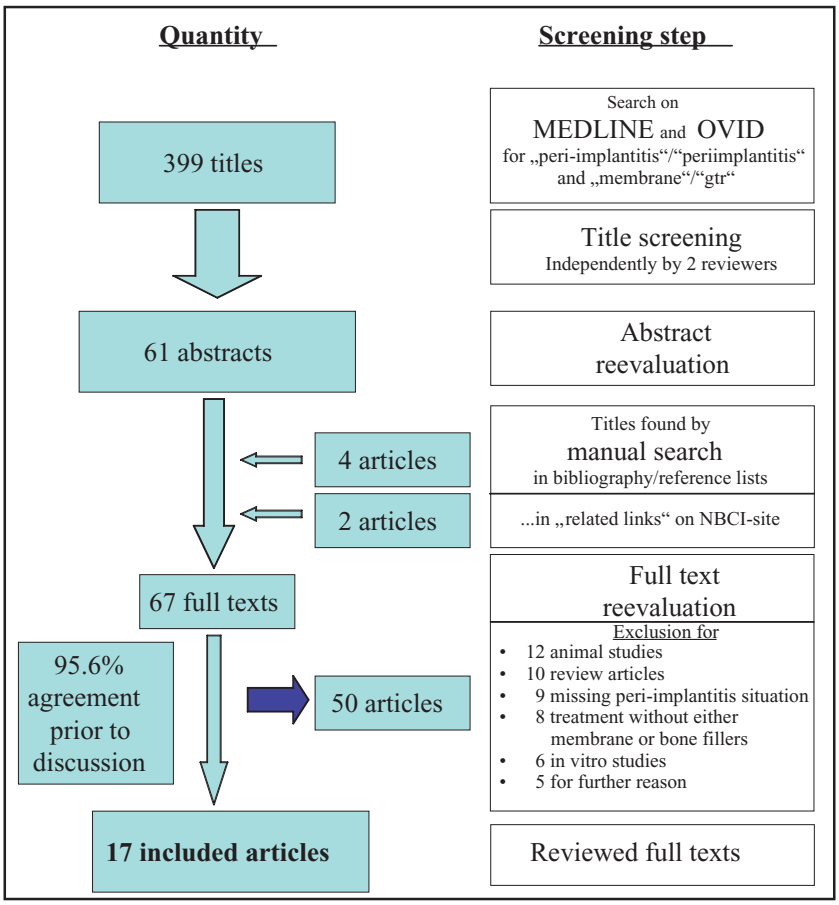

Figure 1 Flowchart of the screening procedure and included/excluded articles.

(9),[31,33–40] treatment with only membrane or only bone graft substitute or none of both (8),[41–48] in vitro studies (6),[49–54] or for further reason (5)[4,55–58] (Figure 1).

Disagreement between the reviewers in 4.4% of the cases was consequently resolved by discussion.

From finally remaining 17 original articles, including 173 treated implant cases, the data for the assessment parameters BoP, PPD, and BL were extracted if given.

Description of the Studies

No RCT studies comparing peri-implantitis treatment by using membrane and bone graft substitutes to a non-GBR treatment were found.

Finally, 17 clinical studies were included: three controlled clinical trials, two cohort studies, eight case series, and four single case presentations (Table 1).

Different types of membranes (diverse synthetic membrane products, resorbable bovine or porcine collagene) were used in combination with different bone substitutes (DFDBA,[59–66] DFDBA in combination with PepGen and PRP,[66] autogenous bone,[60,66–71] hydroxyl apatite,[63] bovine xenografts,[72,73] and algae-derived calcium carbonate[74,75]). Furthermore, a broad variety of different implant types were treated (Table 2).

Treatment strategies varied between the studies in terms of the pre- or postsurgical use of antibiotics, and the kind of disinfection protocol used for implant surface decontamination. In most of the studies, plastic or carbon curettes were used for mechanical debridement. Single studies used an ultrasonic scaler, rotating instruments, air powder, or soft laser treatment. As a supportive maintenance program, different strategies concerning appointment frequency and treatment were executed (see Table 2). The reevaluation periods in the various publications varied from 5 to 36 months.

Periodontal Probing Depth

Seven studies comprising 92 (53.2%) of the total 173 included implants provided information concerning the values of the PPD before and after the treatment or PPD reduction. All articles except one assessing more than three cases reported on mean values and standard

TABLE 1 Data Extraction of the Included Studies Reporting on Differences in Bleeding on Probing (ΔBoP), Periodontal Probing Depth (ΔPPD), and Depth of the Bony Defect (ΔBL)

Author(s) (year of publication)	*n*	Study design	ΔBOP (%)	ΔPPD (mm)	ΔBL
Artzi et al. (1998)[59]	2	cs	n.d.	n.d.	100%
	4				+
Bell and Cavazos (1994)[60]	1	scp	n.d.	n.d.	+
Deporter and Todescan (2001)[61]	1	scp	n.d.	n.d.	40%
El Chaar and Jalbout (2002)[62]	2	cs	n.d.	n.d.	+
Haas et al. (2000)[67]	24	ct	n.d.	n.d.	2.00 ± 1.90
Khoury and Buchmann (2001)[68]	20	cct	n.d.	2.6 ± 1.6	2.8 ± 3.1
	9			5.4 ± 3.0	1.9 ± 3.2
Kraut and Judy (1991)[63]	4	cs	n.d.	n.d.	100%
Mellonig and Triplett (1993)[64]	10	cs	n.d.	n.d.	100%
	2				+
Mellonig et al. (1995)[65]	1	cs	n.d.	8	9.0 mm
	1			8	>6 mm
	1			5–7	+
Petrungaro (2002)[66]	1	scp	n.d.	n.d.	100%
Romanos and Nentwig (2006)[72]	27	cs	n.d.	n.d.	+
Roos-Jansåker et al. (2007a)	16	ct	68.7	4.2 ± 1.5	2.3 ± 1.2
Roos-Jansåker et al. (2007b)	29	cct	57.7	2.86 ± 2.0	1.52 ± 1.16 (7× no bone fill)
Schwarz et al. (2008)[73]	11	cct	36	1.5 ± 0.6	+
Suh et al. (2003)[69]	1	cs	n.d.	n.d.	100
	2				+
Tinti and Parma-Benfenati (2001)[70]	3	cs	(Reestablishment of healthy and firm mucosa)	3.5	2.7
von Arx et al. (1997)[71]	1	scp	(Reestablishment of healthy and firm mucosa)	(Reestablishment of healthy and firm mucosa)	5.0

n, number of implants; scp, single case presentation; cs, case series; ct, clinical trial; cct, controlled clinical trial; +, no further specified bone win; n.d., no data provided.

deviations or confidence intervals. Only one of the studies reported on individual values for every treated implant.[67] In the studies, both parametric and nonparametric statistical tests were used indicating the same skewness of the data. Consequently, values for the single implant often remain unknown and uncalculable, impeding any attempt of interstudy comparison or even meta-analysis. The authors' request for more detailed information in case of insufficient data did not yield any useful additional information. In studies where values for PPD were given, no outliers could be identified. Consequently, mean values instead of medians were calculated and used for comparison. Two studies reported on "healthy and firm mucosa"[70,71] after treatment, but were not included in the calculation of means. The weighted mean reduction of PPD for all implants was 3.29 mm (Table 3). In most cases, there were no data given for PPD after surgery, although in some cases it was possible to calculate it by subtracting probing depth reduction from the probing depth measured before treatment. This value served for estimating a mean value of the residual pocket depth of 3.23 mm posttreatment. Search for clinical attachment level data provided no additional information.

BoP

Of the 17 included articles, five studies reported on pretreatment BOP values, but only three of these also reported on posttreatment data. It has to be noted that most study designs included an immediate conservative

TABLE 2 Characteristics of the Included Studies

Author (Year)	Number/type of implants	Treatment protocol*	Bone substitute/membrane	Systemical antibiotic therapy	Reevaluation period (month)	Supportive maintenance program
Artzi et al. (1998)[59]	2/int, omn 4/nd (hx)	Ultrasound instrumentation	(DFDBA + agb + tcycl)/lamellar bone sheet (DFDBA + agb + tcycl)/ePTFE	—	9	nd
Bell and Cavazos (1994)[60]	1/nd	Citric acid + tcycl	DFDBA/ePTFE	—	9	<6 months
Deporter and Todescan (2001)[61]	1/edp	Citric acid	(DFDBA + tcycl)/$CaSO_4$	amx 2 g 1 h pre 0.5 g/day for 7 days post	12 rx 24 clin	nd
El Chaar and Jalbout (2002)[62]	2/bv (hx)	Rotating instrumentation + citric acid	DFDBA/resorbable bovine membrane	amx 0.5 g/day for 10 days	6	7 days postop
Haas et al. (2000)[67]	24/imz	Toluidine blue + soft laser (906 nm)	Agb/ePTFE	Augmentine for 5 days	9.5	nd
Khoury and Buchmann (2001)[68]	20/imz f2 9/imz f2	0.2% CHX + citric acid + H_2O_2 rinsing	agb/ePTFE agb/resorbable porcine collagene	div. 4w pre for 7 days, post for 7 days	36	Implant cleaning 1 + 2 weeks and 3–6 months postop
Kraut and Judy (1991)[63]	4/nd (hx)	Hypertonic saline	DFDBA + HA/ePTFE	650 mg/day clindamycin for 7 days	10	nd
Mellonig and Triplett (1993)[64]	59/brm (tt)	—	DFDBA/ePTFE	Broadband antibiotics in case of membrane exposure for 14–21 days	nd	nd
Mellonig et al. (1995)[65]	3/(tpc hc)	tcycl	DFDBA/ePTFE	Doxycycline 0.1 g/day for 14 days	8/12	nd
Petrungaro (2002)[66]	1/nd	Citric acid + EDTA	(DBDFA + PRP + PepGen)/ resorbable bovine collagene	10 days pre mnz 1 g/day + amx 11 g/day for 4 days	5	nd
Romanos and Nentwig (2006)[72]	27/nd		Bdx/resorbable porcine collagene	Nd	24	nd
Roos-Jansaker et al. (2007a)	16/brm	H_2O_2 rinsing	$CaCO_3$/resorbable synthetic polymer	amx 3 × 375 mg clindamycin 600 mg + 800 mg mnz for 10 days	12	Implant cleaning every 3 months
Roos-Jansaker et al. (2007b)	29/brm	H_2O_2 rinsing	$CaCO_3$/resorbable synthetic polymer	amx 3 × 375 mg/clindamycin 600 mg + 800 mg mnz for 10 days	12	Implant cleaning every 3 months
Schwarz et al. (2008)[73]	11/brm, clo, sla (2), tps, ksi, mtx (3), tsv, zld	Sterile physiological saline	bdx/resorbable porcine collagene	nd	24	Every second week during 2 months postop, then monthly
Suh et al. (2003)[69]	1/iti(ss) 2/iti(hc)	Mechanical smoothing	agb/ePTFE	amx 1.5 g for 7 days	6	nd
Tinti and Parma-Benfenati (2001)[70]	3/brm	Air powder $NaCO_3$ tcycl-solution	agb + DFDBA/ePTFE	amx 2 g 2 h pre, 1 g/day amx for 7 days	21	Monthly
von Arx et al. (1997)[71]	1/iti(fb)	Chx 0.5%	agb/resorbable polylactide	amx/clv 1,875 g/day for 7 days	6	—

*Additional to instrumental debridement, full thickness flap, and degranulation. tcycl, tetracyclin solution; CHX, chlorhexidine; DFDBA, demineralized freeze-dried bone allograft; agb, autogenous bone; ePTFE, expanded polytetrafluorethylene; HA, hydroxylapatite; βTCP, -β-tricalcium phophate; bdx, bovine-derived xenograft; amx, amoxycilline; mnz, metronidazole; clv, clavulanate; nd, no data.
Implant types: (fb), full body; (hc), hollow cylinder; (hx), hydroxyl coated; (ss), solid screw; (tpc), titanium plasma coated; (tt), threated type; brm, Branemark; bv, Biovent; clo, Camlock; edp, Endpore; f2, Frialit 2; imz, imz; int, integral; iti, ITI Straumann (not further specified); ksi, Bauer-screw; mtx, spline twist Sulzer; omn, Omniloc; sla, ITI SLA-surface; tsv, Zimmer; zld, ZL-Duraplant.

TABLE 3 Studies Reporting Periodontal Probing Depth (PPD) Reductions

Author(s) (year of publication)	Number of implants	Mean ΔPPD (mm)
Khoury and Buchmann (2001)[68]	9	5.4
	20	2.6
Mellonig et al. (1995)[65]	1	8
	1	8
	1	6
Roos-Jansåker et al. (2007a)	16	4.2
Roos-Jansåker et al. (2007b)	29	2.86
Schwarz et al. (2008)[73]	11	1.5
Tinti and Parma-Benfenati (2001)[70]	3	3.5
Sum	91	299.7
Mean		3.29

treatment like rinsing of the peri-implant pockets prior to surgical treatment, so BOP values at baseline might differ from those immediately before intervention. Two studies suggested absence of BoP after intervention when "healthy and firm mucosa" was found[70,71] (Figure 2).

Bone Fill

In all of the 17 included articles, quantitative or qualitative data on the bone level around implant sites were given: seven studies (comprising 104 implants) reported a quantitative analysis of bone level values (see Table 1). In three studies, mean values and standard deviations of bone level reduction were given.[68,74,75] One study reported the values for every single implant.[67]

Eighteen (10.4%) out of 173 implants investigated showed a complete fill of the intrabony defect. In 148 implant cases (85.5%), a gain of bone level was reported: 98 implants (56.6%) showed incomplete bone fill, and 50 implants (28.9%) showed "bone win" which was not further specified. Finally, seven implants (4.0%) failed to gain any new bone or showed bone loss, or the implant had to be removed (Table 4).

A weighted mean value of bone win of 2.2 mm was calculated after GBR treatment (Table 5). The residual mean bone defect depth at the time of reevaluation was 2.6 mm.

Twelve studies reported qualitative or semiquantitative information like "partial" or not further specified "bone fill" without providing any quantitative data (see Table 4).

DISCUSSION

This review aimed to assess the outcome of peri-implantitis treatment using membranes and bone graft substitutes. Unfortunately, there were no RCT studies comparing the results of peri-implantitis treatment with GBR techniques using both membrane and bone graft substitute, to an adequate control group (i.e., scaling or non-regenerative surgery). Consequently, studies of a lower level of evidence, like case presentations and

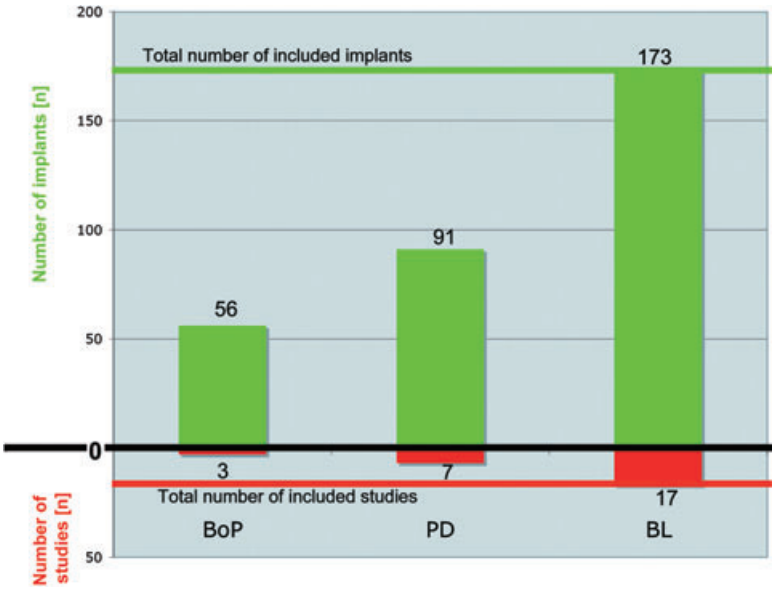

Figure 2 Data distribution for different reported parameters bleeding on probing, peri-implant probing depth, and bone loss.

TABLE 4 Number of Implants with Different Levels of Bone Fill

	Complete bone fill	Partial bone fill	Bone fill (not further specified)	No bone fill/bone loss/failure	Total
Number of implants	18	98 (166)	50	7	**173**
%	10.4	56.6 (96.0)	28.9	4.0	**100**

proportions of patient cohorts from RCT studies with a different aim, were included in order to benefit from the available data in literature and to investigate possible differences in the quality of data presentation. The risk of including confounding factors was estimated low, as with GBR techniques the plausibility of intervention–outcome affinity is high. Therefore, it was decided to enclose these noncontrolled studies in the analysis.

Furthermore, there was a lack of studies with numerous implants: The majority of the studies presented data of single cases or small case series. Only six studies included more than seven implants. These studies assessed clinical parameters like BoP and PPD more often. However, incomplete data presentation in these studies hampered comparability and rendered a meta-analysis impossible.

This study focused on GBR techniques using both bone graft substitute and membrane; this treatment modality represents the major part of published GBR cases. Hence, studies using solely one of both materials were excluded in order not to further jeopardize the validity of comparison.

There are a multitude of different implant systems with varying fixture design and different surfaces combined with a diversity of bone graft substitutes and barrier membranes. Therefore, comparison among the different peri-implant surgery cases is also problematic.

Observation periods in the included studies ranged from 5 months to 3 years, and reexamination intervals varied greatly. Thus, a comparison after the same period for all studies was impossible. Moreover, short observation times strongly limit the clinical relevance of the treatment outcome. Long-term follow-up examinations are required for a more valid assessment.

Not surprisingly, all studies investigated radiographic bone morphology. However, less attention was paid to crucial clinical parameters like BoP and PPD. These parameters were rarely reported. This conflicts with the recommendations of the American Academy of Periodontology and the European Workshop on Periodontology which explicitly call for the data collection of BoP and PPD in the examination of peri-implantitis cases.[76,77] This finding indicates a shortcoming in soft tissue evaluation and is in accordance with a lately published review on peri-implantitis therapy.[78]

Still, the etiology of marginal bone defects around implants is a topic of debate: reasons for marginal peri-implant bone loss like adverse occlusal loading effects from hyper-contacts,[79,80] unfavorable healing,[81] and the effect of position and adaption of the microgap[82] are common topics of the discussion about peri-implant bone loss. However, studies in periodontology prove a pivotal role of the soft tissues in the inflammation process.

The authors concluded a mean probing depth reduction of 3.29 mm and a residual probing depth of 3.23 mm. It is thereby estimated that a peri-implant probe penetrates approximately 3 mm in a healthy situation,[83,84] and according to the CIST protocol no further invasive intervention is indicated. Therefore, these results seem to suggest peri-implant health. However, it must be considered that the calculated PPD mean value was derived from a broad range of PPD values varying from study to study and even from case to case.

TABLE 5 Result of Bone Fill Reported in the Included Studies

Author(s) (year of publication)	Number of implants	Mean ΔBL (mm)
Haas et al. (2000)[67]	24	2
Khoury and Buchmann (2001)[68]	9	1.9
	20	2.8
Mellonig et al. (1995)[65]	1	9.0
	1	6.0
Roos-Jansåker et al. (2007a)	16	2.3
Roos-Jansåker et al. (2007b)	29	1.52
Tinti and Parma-Benfenati (2001)[70]	3	2.0
Von Arx et al. (1997)[71]	1	5.0
Sum/Mean	104	2.2

There is clear evidence that peri-implantitis processes start as a peri-mucosal inflammation from the most external contact of implant and tissues (i.e., from the mucosal seal around the implant neck).[7,29,85] Analog to the transition from gingivitis to periodontitis, the drawdown of attachment level is the crucial symptom to distinguish peri-mucositis from peri-implantitis. As early as in the 1980s, it was shown that the PPD differs from the histological pocket depth in periodontal sites.[86] In inflamed periodontal situations, probes tend to penetrate deeper into the tissues because of the decreased tenseness of the soft tissues. The same effect, although more pronounced, has been shown for peri-implant situations.[87,88] This finding underlines that PPD assessment is an even more sensitive instrument for the detection of attachment loss in potentially inflamed situations. The inaccuracies of deeper probe penetration should not restrain practitioners from using this diagnostic tool: as inflammation fades in the course of treatment, the difference between clinical and histological pocket depth will decrease and in the same way the accuracy of the parameter PPD will increase. Contrary to sporadically expressed assumptions, there is no evidence that careful peri-implant probing could damage the implant surface or create persistent injury to the tissues.[9,89]

Noteworthy, only 3 of 17 studies reported on BoP measurements. With regard to BoP assessment, it has been shown in periodontal sites that absence of bleeding after probing is a reliable predictor for periodontal stability.[89–91] Consequently, BoP assessment is most reasonable for both peri-implantitis screening and evaluation of a peri-implantitis treatment.

With regard to bone fill, most of the studies provided only qualitative or semiquantitative data for the amount of fill of the intrabony defect. For better comparability, improved parameters for the defect size characterization would be helpful. For this purpose, reliable and quick methods have been published.[92,93] In this review, 10.4% of the included implant collective showed a complete and 85.5% at least a partial defect fill. This amounts to 96% of all analyzed cases where a bone fill of whatsoever extent was achieved by GBR technique. In this respect, GBR treatment can be assumed to lead to rather safe success. The interpolated 2.6 mm of residual bone defect after surgery should be interpreted with caution: both the reference level (i.e., implant benchmarks or neighboring bone level) and the calculation might lead to inadequate conclusions. Anyhow, it should be kept in mind that there is no evidence for the need of either complete or incomplete defect fill.

The assessment of the crestal bone level on conventional radiographs has been proven to be a highly specific testing method.[94] Thus, an initial peri-implant defect is not easily detected on the radiograph: Studies show that on conventional radiographs, the sensitivity for identification of smaller defects, as expected for the onset peri-implant defect, is low.[94,95] Considerable improvements with CT and DVT technique have recently been reported.[96]

Of course, the radiographs provide no information about the nature of bone and interface. It is indeterminable in an augmented site with an apparently dense bone formation at the implant's neck, whether osseointegration on a histological level has actually occured.[94] Putting the main focus on radiographic bone fill relies on a phenomenon of doubtful nature; there is still no evidence showing what kind of structure actually fills the bone defect. Furthermore, there is disagreement in research about the amount of remaining bone substitute and regenerated genuine bone, which can be expected depending on resorption time of the various bone graft materials.[94,97–99] Autogenous bone, defined as the gold standard in bone augmentation, shows a volume loss of approximately 40% during healing time. On the other hand, synthetic bone graft substitutes show a high stability in volume, but remain nearly or completely unresorbed even several years after surgery.[100] In clinical practice, this implies that visual bone fill on the x-ray per se is not sufficient to claim a successful biological outcome after peri-implantitis treatment,[101] especially in the long term.

CONCLUSION

Complete fill of bony defects caused by peri-implantitis using a GBR protocol with membrane and bone graft substitutes does not seem to be a predictable outcome, although a partial defect fill can be expected.

Published peri-implantitis literature lacks comprehensive studies with a high number of cases that would enable a sound statistical analysis. The mucosal health status as a reliable indicator for peri-implant inflammation, reflected by the parameters BoP and PPD, is not reported in the majority of the studies.

RCT studies comparing GBR treatment to noninvasive debridement in peri-implantitis cases are needed in order to provide evidence for an additional benefit of

the use of bone graft substitutes and membranes. In these studies, assessment of quantitative values for bone loss, PPD, and BoP would be desirable.

REFERENCES

1. Merickse-Stern R, Aerni D, Geering AH, Buser D. Long-term evaluation of non-submerged hollow cylinder implants. Clinical and radiographic results. Clin Oral Implants Res 2001; 12:252–259.
2. Pjetursson BE, Tan K, Lang NP, Bragger U, Egger M, Zwahlen M. A systematic review of the survival and complication rates of fixed partial dentures (FPDs) after an observation period of at least 5 years. Clin Oral Implants Res 2004; 15:667–676.
3. Jung RE, Pjetursson BE, Glauser R, Zembic A, Zwahlen M, Lang NP. A systematic review of the 5-year survival and complication rates of implant-supported single crowns. Clin Oral Implants Res 2008; 19:119–130.
4. Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. J Clin Periodontol 2006; 33:296–301.
5. Mombelli A. Microbiology of the dental implant. Adv Dent Res 1993; 7:202–206.
6. Meffert RM. Periodontitis vs. peri-implantitis: the same disease? The same treatment? Crit Rev Oral Biol Med 1996; 7:278–291.
7. Pontoriero R, Tonelli MP, Carnevale G, Mombelli A, Nyman SR, Lang NP. Experimentally induced peri-implant mucositis. A clinical study in humans. Clin Oral Implants Res 1994; 5:254–259.
8. Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. Periodontol 2000 1998; 17:63–76.
9. Lang NP, Wilson TG, Corbet EF. Biological complications with dental implants: their prevention, diagnosis and treatment. Clin Oral Implants Res 2000; 11(Suppl 1):146–155.
10. Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease? J Clin Periodontol 1986; 13:590–596.
11. Kotsovilis S, Karoussis IK, Trianti M, Fourmousis I. Therapy of peri-implantitis: a systematic review. J Clin Periodontol 2008; 35:621–629.
12. Wilson TGJ, Buser D. Advances in the use of guided tissue regeneration for localized ridge augmentation in combination with dental implants. Tex Dent J 1994; 111:7–10.
13. Fiorellini JP, Kim DM, Nakajima Y, Weber HP. Osseointegration of titanium implants following guided bone regeneration using expanded polytetrafluoroethylene membrane and various bone fillers. Int J Periodontics Restorative Dent 2007; 27:287–294.
14. Nociti FHJ, Machado MA, Stefani CM, Sallum EA. Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs: a histometric investigation. Int J Oral Maxillofac Implants 2001; 16:646–652.
15. Nociti FHJ, Machado MA, Stefani CM, Sallum EA, Sallum AW. Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs. Part I. A clinical investigation. Clin Oral Implants Res 2001; 12:115–120.
16. Persson LG, Ericsson I, Berglundh T, Lindhe J. Guided bone regeneration in the treatment of periimplantitis. Clin Oral Implants Res 1996; 7:366–372.
17. Schou S, Holmstrup P, Jorgensen T, et al. Anorganic porous bovine-derived bone mineral (Bio-Oss) and ePTFE membrane in the treatment of peri-implantitis in cynomolgus monkeys. Clin Oral Implants Res 2003; 14:535–547.
18. Schou S, Holmstrup P, Jorgensen T, et al. Implant surface preparation in the surgical treatment of experimental peri-implantitis with autogenous bone graft and ePTFE membrane in cynomolgus monkeys. Clin Oral Implants Res 2003; 14:412–422.
19. Schou S, Holmstrup P, Jorgensen T, Stoltze K, Hjorting-Hansen E, Wenzel A. Autogenous bone graft and ePTFE membrane in the treatment of peri-implantitis. I. Clinical and radiographic observations in cynomolgus monkeys. Clin Oral Implants Res 2003; 14:391–403.
20. Schou S, Holmstrup P, Skovgaard LT, Stoltze K, Hjorting-Hansen E, Gundersen HJ. Autogenous bone graft and ePTFE membrane in the treatment of peri-implantitis. II. Stereologic and histologic observations in cynomolgus monkeys. Clin Oral Implants Res 2003; 14:404–411.
21. Singh G, O'Neal RB, Brennan WA, Strong SL, Horner JA, Van Dyke TE. Surgical treatment of induced peri-implantitis in the micro pig: clinical and histological analysis. J Periodontol 1993; 64:984–989.
22. Warrer K, Buser D, Lang NP, Karring T. Plaque-induced peri-implantitis in the presence or absence of keratinized mucosa. An experimental study in monkeys. Clin Oral Implants Res 1995; 6:131–138.
23. Wetzel AC, Vlassis J, Caffesse RG, Hammerle CH, Lang NP. Attempts to obtain re-osseointegration following experimental peri-implantitis in dogs. Clin Oral Implants Res 1999; 10:111–119.
24. Zou DR, Zhu H, Qu XH. [Re-osseointegration of peri-implantitis bone defects: an experimental study in dogs]. Shanghai Kou Qiang Yi Xue 2006; 15:614–618.
25. Baron M, Haas R, Dortbudak O, Watzek G. Experimentally induced peri-implantitis: a review of different treatment methods described in the literature. Int J Oral Maxillofac Implants 2000; 15:533–544.
26. Bower RC. Peri-implantitis. Ann R Australas Coll Dent Surg 1996; 13:48–57.
27. Forna N, Burlui V, Luca IC, Indrei A. Peri-implantitis. Rev Med Chir Soc Med Nat Iasi 1998; 102:74–79.

28. Ling LJ. Current concept of guided tissue regeneration with non-absorbable membrane. J N Z Soc Periodontol 1998; 83:32–37.
29. Mombelli A. Microbiology and antimicrobial therapy of peri-implantitis. Periodontol 2000 2002; 28:177–189.
30. Roos-Jansaker AM, Renvert S, Egelberg J. Treatment of peri-implant infections: a literature review. J Clin Periodontol 2003; 30:467–485.
31. Schou S, Berglundh T, Lang NP. Surgical treatment of peri-implantitis. Int J Oral Maxillofac Implants 2004; 19:140–149.
32. Zablotsky M. The surgical management of osseous defects associated with endosteal hydroxyapatite-coated and titanium dental implants. Dent Clin North Am 1992; 36:117–149, discussion 149–50.
33. De Boever AL, De Boever JA. Guided bone regeneration around non-submerged implants in narrow alveolar ridges: a prospective long-term clinical study. Clin Oral Implants Res 2005; 16:549–556.
34. Deppe H, Greim H, Brill T, Wagenpfeil S. Titanium deposition after peri-implant care with the carbon dioxide laser. Int J Oral Maxillofac Implants 2002; 17:707–714.
35. Kozlovsky AMO, Nemcovsky CE, Artzi Z. [Differential diagnosis and treatment strategies for peri-implant diseases][Article in Hebrew]. Refuat Hapeh Vehashinayim 2003; 20:30–41.
36. Li TF. Sinus floor elevation: a revised osteotome technique and its biological concept. Compend Contin Educ Dent 2005; 26:619–620, 622, 624–6 passim; quiz 630, 669.
37. Monov G, Strbac GD, Baron M, Kandler B, Watzek G, Gruber R. Soluble RANKL in crevicular fluid of dental implants: a pilot study. Clin Implant Dent Relat Res 2006; 8:135–141.
38. Paolantonio M, Di Placido G, Tumini V, Di Stilio M, Contento A, Spoto G. Aspartate aminotransferase activity in crevicular fluid from dental implants. J Periodontol 2000; 71:1151–1157.
39. Porras R, Anderson GB, Caffesse R, Narendran S, Trejo PM. Clinical response to 2 different therapeutic regimens to treat peri-implant mucositis. J Periodontol 2002; 73:1118–1125.
40. Prosper L, Gherlone EF, Redaelli S, Quaranta M. Four-year follow-up of larger-diameter implants placed in fresh extraction sockets using a resorbable membrane or a resorbable alloplastic material. Int J Oral Maxillofac Implants 2003; 18:856–864.
41. Buchmann RKF, Hesse T, Müller RF, Lange DE. Antimikrobielle Therapie der periimplantären Erkrankung. Z Zahnärztl Implantol 1996; 12:152–157.
42. Dortbudak O, Haas R, Bernhart T, Mailath-Pokorny G. Lethal photosensitization for decontamination of implant surfaces in the treatment of peri-implantitis. Clin Oral Implants Res 2001; 12:104–108.
43. Hammerle CH, Fourmousis I, Winkler JR, Weigel C, Bragger U, Lang NP. Successful bone fill in late peri-implant defects using guided tissue regeneration. A short communication. J Periodontol 1995; 66:303–308.
44. Khoury F, Happe A. The palatal subepithelial connective tissue flap method for soft tissue management to cover maxillary defects: a clinical report. Int J Oral Maxillofac Implants 2000; 15:415–418.
45. Kim SJ. Bone regeneration around failing IMZ implants using submerged guide bone regeneration technique: Report of four cases with 1- to 2-year data. Clin Oral Implants Res 2000; 11:391.
46. Leonhardt A, Dahlen G, Renvert S. Five-year clinical, microbiological, and radiological outcome following treatment of peri-implantitis in man. J Periodontol 2003; 74:1415–1422.
47. Romeo E, Ghisolfi M, Murgolo N, Chiapasco M, Lops D, Vogel G. Therapy of peri-implantitis with resective surgery. A 3-year clinical trial on rough screw-shaped oral implants. Part I: clinical outcome. Clin Oral Implants Res 2005; 16:9–18.
48. Schuckert KH, Jopp S, Muller U. De novo grown bone on exposed implant surfaces using photodynamic therapy and recombinant human bone morphogenetic protein-2: case report. Implant Dent 2006; 15:361–365.
49. Giannelli M, Chellini F, Margheri M, Tonelli P, Tani A. Effect of chlorhexidine digluconate on different cell types: a molecular and ultrastructural investigation. Toxicol In Vitro 2008; 22:308–317.
50. Kivela-Rajamaki M, Maisi P, Srinivas R, et al. Levels and molecular forms of MMP-7 (matrilysin-1) and MMP-8 (collagenase-2) in diseased human peri-implant sulcular fluid. J Periodontal Res 2003; 38:583–590.
51. Kuula H, Salo T, Pirila E, et al. Human beta-defensin-1 and -2 and matrix metalloproteinase-25 and -26 expression in chronic and aggressive periodontitis and in peri-implantitis. Arch Oral Biol 2008; 53:175–186.
52. 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.
53. Renvert S, Roos-Jansaker AM, Lindahl C, Renvert H, Rutger Persson G. Infection at titanium implants with or without a clinical diagnosis of inflammation. Clin Oral Implants Res 2007; 18:509–516.
54. Talarico GM, Neiders ME, Comeau RL, Cohen RE. Phenotypic characterization of mononuclear cells from gingiva associated with periodontitis and peri-implantitis. J Oral Implantol 1997; 23:5–11.
55. Lu SY, Huang CC. Resolution of an active peri-implantitis in a chronic steroid user by bone augmentation with PepGen P-15 and a barrier membrane. J Oral Implantol 2007; 33:280–287.

56. Nuesry ESF, Bieling K, Becker J. Regenerative therapy of peri-implantitis intrabony defects. J Clin Periodontol 2006; 33:131–132.
57. Roos-Jansaker AM, Lindahl C, Renvert H, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part I: implant loss and associations to various factors. J Clin Periodontol 2006; 33:283–289.
58. Roos-Jansaker AM, Lindahl C, Renvert H, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part II: presence of peri-implant lesions. J Clin Periodontol 2006; 33:290–295.
59. Artzi Z, Tal H, Chweidan H. Bone regeneration for reintegration in peri-implant destruction. Compend Contin Educ Dent 1998; 19:17–20, 22–3, 26–8; quiz 30.
60. Bell FA, Cavazos EJ. Four-year experience with the placement, restoration and maintainance of dental implants by dental students. Int J Oral Maxillofac Implants 1994; 1994:725–731.
61. Deporter DA, Todescan RJ. A possible "rescue" procedure for dental implants with a textured surface geometry: a case report. J Periodontol 2001; 72:1420–1423.
62. El Chaar ES, Jalbout ZN. Regeneration of an osseous peri-implantitis lesion. Periodontal Clin Investig 2002; 24:5–10.
63. Kraut RAJ, Judy KWM. Implant preservation using guided tissue augmentation membrane and porous hydroxyapatite. Int J Oral Implantol 1991; 2:55–58.
64. Mellonig JT, Triplett RG. Guided tissue regeneration and endosseous dental implants. Int J Periodontics Restorative Dent 1993; 13:108–119.
65. Mellonig JT, Griffiths G, Mathys E, Spitznagel JJ. Treatment of the failing implant: case reports. Int J Periodontics Restorative Dent 1995; 15:384–395.
66. Petrungaro PS. Treatment of the infected implant site using platelet-rich plasma. Compend Contin Educ Dent 2002; 23:363–366, 368, 370 passim; quiz 378.
67. Haas R, Baron M, Dortbudak O, Watzek G. Lethal photosensitization, autogenous bone, and e-PTFE membrane for the treatment of peri-implantitis: preliminary results. Int J Oral Maxillofac Implants 2000; 15:374–382.
68. Khoury F, Buchmann R. Surgical therapy of peri-implant disease: a 3-year follow-up study of cases treated with 3 different techniques of bone regeneration. J Periodontol 2001; 72:1498–1508.
69. Suh JJ, Simon Z, Jeon YS, Choi BG, Kim CK. The use of implantoplasty and guided bone regeneration in the treatment of peri-implantitis: two case reports. Implant Dent 2003; 12:277–282.
70. Tinti C, Parma-Benfenati S. Treatment of peri-implant defects with the vertical ridge augmentation procedure: a patient report. Int J Oral Maxillofac Implants 2001; 16:572–577.
71. von Arx T, Kurt B, Hardt N. Treatment of severe peri-implant bone loss using autogenous bone and a resorbable membrane. Case report and literature review. Clin Oral Implants Res 1997; 8:517–526.
72. Romanos GE, Nentwig GH. Infrared laser-assisted peri-implantitis treatment. Clinical and radiological experiences in 27 cases. J Clin Periodontol 2006; 33(Suppl 7):131–132.
73. Schwarz F, Sculean A, Bieling K, Ferrari D, Rothamel D, Becker J. Two-year clinical results following treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane. J Clin Periodontol 2008; 35:80–87.
74. Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Submerged healing following surgical treatment of peri-implantitis: a case series. J Clin Periodontol 2007a; 34:723–727.
75. Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: a prospective cohort study. J Clin Periodontol 2007b; 34:625–632.
76. Cohen RE. Position paper: periodontal maintenance. J Periodontol 2003; 74:1395–1401.
77. Salvi GE, Bardet P, Lang NP. Clinical parameters in longitudinal implant studies. Consensus report of Session III. London: Quintessence Publishing Co Ltd., 1994.
78. Hultin M, Komiyama A, Klinge B. Supportive therapy and the longevity of dental implants: a systematic review of the literature. Clin Oral Implants Res 2007; 18(Suppl 3):50–62.
79. De Smet E, van Steenberghe D, Quirynen M, Naert I. The influence of plaque and/or excessive loading on marginal soft and hard tissue reactions around Brånemark implants: a review of literature and experience. Int J Periodontics Restorative Dent 2001; 21:381–393.
80. Halg GA, Schmid J, Hammerle CH. Bone level changes at implants supporting crowns or fixed partial dentures with or without cantilevers. Clin Oral Implants Res 2008; 19:983–990.
81. Oh TJ, Yoon J, Misch CE, Wang HL. The causes of early implant bone loss: myth or science? J Periodontol 2002; 73:322–333.
82. King GN, Hermann JS, Schoolfield JD, Buser D, Cochran DL. Influence of the size of the microgap on crestal bone levels in non-submerged dental implants: a radiographic study in the canine mandible. J Periodontol 2002; 73:1111–1117.
83. Apse P, Zarb GA, Schmitt A, Lewis DW. The longitudinal effectiveness of osseointegrated dental implants. The Toronto study: peri-implant mucosal response. Int J Periodontics Restorative Dent 1991; 11:94–111.
84. Nishimura K, Itoh T, Takaki K, Hosokawa R, Naito T, Yokota M. Periodontal parameters of osseointegrated dental implants. A 4-year controlled follow-up study. Clin Oral Implants Res 1997; 8:272–278.

85. Lindhe J, Berglundh T, Ericsson I, Liljenberg B, Marinello C. Experimental breakdown of peri-implant and periodontal tissues. A study in the beagle dog. Clin Oral Implants Res 1992; 3:9–16.
86. Listgarten MA. Periodontal probing: what does it mean? J Clin Periodontol 1980; 7:165–176.
87. Schou S, Holmstrup P, Stoltze K, Hjorting-Hansen E, Fiehn NE, Skovgaard LT. Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. A histologic comparison in cynomolgus monkeys (*Macaca fascicularis*). Clin Oral Implants Res 2002; 13:113–126.
88. Lang NP, Adler R, Joss A, Nyman S. Absence of bleeding on probing. An indicator of periodontal stability. J Clin Periodontol 1990; 17:714–721.
89. Etter TH, Hakanson I, Lang NP, Trejo PM, Caffesse RG. Healing after standardized clinical probing of the periimplant soft tissue seal: a histomorphometric study in dogs. Clin Oral Implants Res 2002; 13:571–580.
90. Joss A, Adler R, Lang NP. Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. J Clin Periodontol 1994; 21:402–408.
91. Liskmann S, Zilmer M, Vihalemm T, Salum O, Fischer K. Correlation of peri-implant health and myeloperoxidase levels: a cross-sectional clinical study. Clin Oral Implants Res 2004; 15:546–552.
92. Schei OWJ, Lovdal A, Arno A. Alveolar bone loss as related or oral hygiene and age. J Periodontol 1959; 30:7–16.
93. Bassiouny MA, Grant AA. The accuracy of the Schei ruler: a laboratory investigation. J Periodontol 1975; 46:748–752.
94. Sewerin IP, Gotfredsen K, Stoltze K. Accuracy of radiographic diagnosis of peri-implant radiolucencies – an in vitro experiment. Clin Oral Implants Res 1997; 8:299–304.
95. Lang NP, Hill RW. Radiographs in periodontics. J Clin Periodontol 1977; 4:16–28.
96. Mengel R, Kruse B, Flores-de-Jacoby L. Digital volume tomography in the diagnosis of peri-implant defects: an in vitro study on native pig mandibles. J Periodontol 2006; 77:1234–1241.
97. Browaeys H, Bouvry P, De Bruyn H. A literature review on biomaterials in sinus augmentation procedures. Clin Implant Dent Relat Res 2007; 9:166–177.
98. Pappalardo S, Puzzo S, Carlino V, Cappello V. Bone substitutes in oral surgery. Minerva Stomatol 2007; 56:541–557.
99. Karabuda C, Ozdemir O, Tosun T, Anil A, Olgac V. Histological and clinical evaluation of 3 different grafting materials for sinus lifting procedure based on 8 cases. J Periodontol 2001; 72:1436–1442.
100. Iezzi G, Degidi M, Scarano A, Petrone G, Piattelli A. Anorganic bone matrix retrieved 14 years after a sinus augmentation procedure: a histologic and histomorphometric evaluation. J Periodontol 2007; 78:2057–2061.
101. Salvi GE, Lang NP. Diagnostic parameters for monitoring peri-implant conditions. Int J Oral Maxillofac Implants 2004; 19:116–127.