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Surgical regenerative treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane: a four-year clinical follow-up report

Frank Schwarz, Narja Sahm, Katrin Bieling and Jürgen Becker

Department of Oral Surgery, Westdeutsche Kieferklinik Heinrich Heine University, Düsseldorf, Germany

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Abstract

Objectives: The present case series aimed at investigating the 4-year clinical outcomes following surgical regenerative therapy of peri-implantitis lesions using either a nanocrystalline hydroxyapatite (NHA) or a natural bone mineral in combination with a collagen membrane (NBM+CM).

Materials and Methods: Twenty patients suffering from moderate peri-implantitis ($n = 20$ intrabony defects) were randomly treated with (1) access flap surgery (AFS) and the application of NHA ($n = 9$), or with AFS and the application of NBM+CM ($n = 11$). Clinical and radiographic (R) parameters were recorded at baseline (R) and after 36 and 48 (R) months of non-submerged healing.

Results: One patient from the NBM+CM group was discontinued from the study due to severe pus formation at 36 months. Compared with NHA, the application of NBM+CM resulted in higher mean PD reductions (NBM+CM: 2.5 ± 0.9 mm *versus* NHA: 1.1 ± 0.3 mm) and clinical attachment-level gains (NBM+CM: 2.0 ± 1.0 mm *versus* NHA: 0.6 ± 0.5 mm) at 48 months. A radiographic bone fill was observed for five sites in the NHA group, and eight sites in the NBM+CM group.

Conclusion: While the application of NBM+CM resulted in clinical improvements over a period of 4 years, the long-term outcome obtained with NHA without barrier membrane must be considered as poor.

Key words: bone graft; collagen membrane; nanocrystalline hydroxyapatite; peri-implantitis; surgical regenerative therapy

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Conflict of interest and source of funding statement

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The recent consensus report of the sixth European Workshop on Periodontology defined peri-implantitis as an infectious disease affecting the peri-implant mucosa as well as the supporting alveolar bone (Lindhe & Meyle 2008). Clinically, these lesions are characterized by a positive bleeding on probing (BOP), which is commonly associated with suppuration, a probing pocket depth (PD) of >4 mm, and signs of a radiographic bone loss.

Even though the replacement of missing teeth by endosseous titanium implants has become an evidence-based treatment procedure showing excellent success rates of 99% after 5 years in function (Bornstein et al. 2005), a few cross-sectional and longitudinal studies (⩾5 years) also indicated that the prevalence of peri-implantitis varies between 28% and ⩾56% on the patient, and 12% and 43% on the implant level (Zitzmann &

Berglundh 2008). Nowadays, there is substantial evidence supporting the view that a poor oral hygiene, a history of periodontitis and cigarette smoking must be considered as risk indicators for peri-implant diseases. In addition, limited evidence has pointed to an association with poorly controlled diabetes mellitus or alcohol consumption. In recent years, non-surgical and surgical treatment of peri-implantitis lesions has become a topic of growing interest and was evaluated in both experimental and clinical studies (Claffey et al. 2008, Renvert et al. 2008b). Even though non-surgical therapy including mechanical debridement with an adjunct of local antibiotics or laser application has been reported to be effective in resolving progression of peri-implantitis lesions, these beneficial clinical outcomes were limited to a period of 6–12 months (Schwarz et al. 2005, 2006a, 2006d, Renvert et al. 2006, 2008a). A re-infection of the former defect area was most probably due to the inability of a non-surgical surface debridement procedure to completely remove bacterial deposits from structured titanium implant surfaces, thus lacking a new bone-to-implant contact on the histological level (Schwarz et al. 2006c). In addition, the specific configuration of both naturally occurring human- and ligatur-induced peri-implantitis defects in animals was commonly characterized by a combined circumferential intrabony (humans: 55.3%; dogs: 86.6%) and supracrestal (humans: 79%; dogs: 53.3%) defect component (Schwarz et al. 2007). Accordingly, the surgical elimination of pathological peri-implant pockets in combination with an implantoplasty may reduce the risk for a re-infection at supracrestally exposed titanium implants (Romeo et al. 2005, 2007). In addition, the elevation of a mucoperiosteal flap may provide better access to the intrabony defect component, thus allowing to combine a thorough implant surface decontamination with regenerative procedures such as bone grafts/substitutes and/or the principle of guided bone regeneration (Claffey et al. 2008). So far, only very few controlled clinical studies have reported on the outcome of surgical regenerative treatment of peri-implantitis defects (Schwarz et al. 2006b, Roos-Jansåker et al. 2007). Even though the short-term clinical and radiographic results of this procedure, including different types of bone graft substitutes, with or without the application of resorbable barrier membranes, were reported to be beneficial over a period of 6–12 months, the long-term effects of these approaches remained unknown. Therefore, in a previous study (Schwarz et al. 2008) reported on 2-year results obtained following treatment of intrabony peri-implantitis lesions using either a nanocrystalline hydroxyapatite (NHA) or a natural bone mineral (NBM) in combination with a native collagen membrane (CM). Even though both treatment procedures have also shown efficacy over a period of 24 months, two patients from the NHA group had to be discontinued from the study due to severe pus formation at 12 months. Based on these findings, it was hypothesized that the clinical outcome of healing in the NHA group was primarily related to an obstruction of the former defect area, thus increasing the risk for a re-infection over time.

Therefore, the aim of this case series was to evaluate the 4-year results obtained following treatment of moderate intrabony peri-implantitis defects using either NHA or NBM+CM.

Materials and Methods

Study population

At baseline, the patient population consisted of eight men and 14 women (mean age 54.4 ± 12.5 years) exhibiting a total of $n = 22$ implants. The 6-month and 2-year clinical results have been described in detail previously (Schwarz et al. 2006b, 2008). After 12 months, two patients from the NHA group ($n = 2$ implants) had to be discontinued from the study due to severe pus formation, which was defined as a stop criterion in the study protocol (Schwarz et al. 2008).

Accordingly, the present follow-up of this parallel-design study reports on a total of 20 partially edentulous patients suffering from moderate peri-implantitis (Mombelli & Lang 1994). These patients attended the Department of Oral Surgery, Heinrich Heine University, Düsseldorf, Germany, for surgical regenerative treatment procedures. Each patient was given a detailed description of the procedure and was required to sign an informed consent before participation. The study was in accordance with the Helsinki Declaration of 1975, as revised in 2000, and all participants signed informed consent forms. The study protocol including the extended follow-up observation period was approved by the ethics committee of the Heinrich Heine University.

Patient selection

Before the start of the experimental part of the study, all patients received a single course of non-surgical instrumentation of respective titanium implants using plastic curettes (Straumann, Waldenburg, Switzerland) combined with an antisepctic pocket irrigation using 0.2% chlorhexidine digluconate solution (Corsodyl®, GlaxoSmithKline Consumer Healthcare, Bühl, Germany) (CHX) and subgingival application of CHX gel 0.2% (Corsodyl® Gel, GlaxoSmithKline Consumer Healthcare).

For patient selection, the following inclusion criteria were defined: (1) presence of at least one screw-type implant exhibiting an intrabony defect with a probing depth (PD) of >6 mm and an intrabony component of >3 mm as detected on radiographs (in case of multiple implants, the most advanced defect was selected as the primary target site), (2) no implant mobility, (3) single tooth and bridgework restorations without overhangings or margins, (4) no evidence of occlusal overload, (5) presence of keratinized peri-implant mucosa to facilitate a repositioning of the mucoperiosteal flap at the augmented areas, (6) no signs of acute periodontitis, (7) a good level of oral hygiene [plaque index (PI) <1] (Löe 1967), (8) no systemic diseases that could influence the outcome of the therapy [i.e. diabetes (HbA1c <7), osteoporosis, bisphosphonate medication] and (9) light smoking status in smokers (<10 cigarettes per day). Hollow cylinder implants were excluded from the study. The distribution, mean age and position of different implant systems in both groups are presented in Tables 1 and 2.

Clinical measurements

The following clinical measurements were performed immediately before surgery (baseline), at 3 and 4 years after treatment using a periodontal probe (PCP 12, Hu-Friedy, Leimen, Germany) (K. B.): (1) PI (Löe 1967), (2) bleeding on probing (BOP), evaluated as present if bleeding was evident within 30 s after probing, or absent, if no bleeding was noticed within 30 s after probing, (3) PD measured from the mucosal margin to the bottom of the probeable pocket, (4) gingival recession (GR) measured from the implant neck (IN) to the mucosal margin, and (5) clinical attachment level (CAL), measured from IN to the bottom of the

probeable pocket. The primary outcome variable was CAL. All measurements were made at six aspects per implant: mesiovestibular (mv), midvestibular (v), distovestibular (dv), mesiooral (mo), midoral (o), and distooral (do) by one blinded and previously calibrated investigator (K. B.).

Pre- and post-operative radiographs at 4 years were taken using the long cone paralleling technique and evaluated by one blinded investigator (N. S.).

Configuration assessment of peri-implant bone defects

During open flap surgery, the supraalveolar, circumferential and intrabony components of the defects were measured by one blinded and previously calibrated investigator.

1. Supraalveolar component – s(a) of the defect, measured as the maximum linear mesial or distal distance from the borderline between the bony and the transmucosal part (BTB) of the implant to the alveolar bone crest,
2. Circumferential component – s(c) of the defect, measured as the linear distance from the vestibular – s(c-v), mesial – s(c-m), distal – s(c-d) and oral – s(c-o) bone wall of the defect to the implant surface, and
3. Intrabony component of the defect, measured as the linear distance from the alveolar bone crest to the bottom of the defect (v, m, d, o).

The figures illustrating the clinical assessment of these defect components have been reported in detail previously (Schwarz et al. 2006b). The baseline defect characteristics in both groups are presented in Table 3.

Intra-examiner reproducibility

Five patients, each showing two implants with PDs $\geqslant 4$ mm on at least one aspect, were used to calibrate the examiner. The examiner evaluated the patients on two separate occasions, 48 h apart. Calibration was accepted if measurements at baseline and at 48 h were within a millimetre $>90\%$ of the time.

Randomization procedure

The randomization procedure has been described in detail previously (Schwarz et al. 2006b, 2008). Briefly, supra- and intrabony components were estimated before surgery on radiographs and by performing transgingival bone sounding. Subsequently, all defect sites were randomly assigned to the following treatment procedures according to a computer-generated protocol (RandList®, DatInf GmbH, Tübingen, Germany): (1) access flap surgery (AFS) and the application of NHA or (2) AFS and the application of NBM+CM.

The randomization process resulted in comparable mean values of all investigated clinical parameters at baseline in both groups. Furthermore, the number of smokers was equally distributed between both groups (i.e. two in the NHA and two in the NBM+CM group).

Table 1. Distribution and mean age (years ± SD) of different implant systems in both groups at baseline

Group	BRA	CAM	ITI	KSI	MTX	TSV	ZL	Age
NHA ($n = 9$)	0	1	1*	1	4	1	1	3.4 ± 1.2
NBM+CM ($n = 11$)	1	1	2†	1	3	2	1	4.0 ± 0.9

BRA, Brånemark System®, (cylindrical screw, machined surface), Nobel Biocare, Göteborg, Sweden.
CAM, Camlog Screw Line®, (cylindrical screw, sand blasted and acid etched surface), Camlog, Wimsheim, Germany.
ITI, ITI®, Straumann, (cylindrical screw), Waldenburg, Switzerland.
*sand blasted large grit and acid etched surface.
†Titanium plasma flamed surface.
KSI, KSI Bauer Schraube®, (conical screw, machined surface), KSI GmbH, Bad Nauheim, Germany.
MTX, Spline Twist (MTX)®, (cylindrical screw, grit blasted surface), Zimmer Dental, Freiburg, Germany.
TSV, Tapered Screw Vent®, (tapered screw, grit blasted surface), Zimmer Dental, Freiburg, Germany.
ZL, ZL-Duraplant (Ticer)®, (cylindrical screw, anodic oxidized surfaces), ZL Microdent, Breckerfeld, Germany.
NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

Table 2. Position of implants in both groups at baseline

Group	Upper jaw		Lower jaw	
	anterior	posterior	anterior	posterior
NHA ($n = 9$)	1	3	0	5
NBM+CM ($n = 11$)	1	5	0	5

NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

Table 3. Baseline defect characteristics in mm (mean ± SD)

Treatment	s(a)	s(c)	i	Semi-circular	Circular
NHA ($n = 9$)	1.3 ± 0.5	2.3 ± 0.4	4.3 ± 0.5	1	8
NBM+CM ($n = 11$)	1.5 ± 0.5	2.4 ± 0.7	4.3 ± 0.6	3	8

NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

Treatments

All operative procedures have been described in detail previously (Schwarz et al. 2006b, 2008). Briefly, under local anaesthesia, full-thickness, mucoperiosteal flaps were raised vestibularly and orally by means of intracrevicular incisions. Subsequently, all granulation tissue was completely removed from the defect area and the implant surfaces were thoroughly debrided using plastic curettes (Straumann® Dental Implant System, Straumann AG, Basel, Switzerland). Following cleaning, the exposed implant and bony surfaces were rinsed with sterile physiologic saline.

NHA was delivered as a ready-to-use paste in a syringe, containing about 65% water and nanoscopic apatite particles (35%) in an aqueous dispersion (Ostim®, Heraeus, Hanau, Germany), was applied to the intrabony defect component in direct contact to the adjacent alveolar bone, without interposition of a blood clot. Defects were slightly overfilled,

as NHA has a viscous, fluid-like consistence and tends to leak from the defect. Because of its physicochemical properties, NHA is intended for use without the additional application of a barrier membrane.

Similarly, NBM (BioOss® spongiosa granules, particle size 0.25–1 mm, Geistlich, Wolhusen, Switzerland) was applied in a way as to homogeneously fill the intrabony defect component. Before its application, the graft material was moistened in sterile saline for 5 min. Following grafting, a bioresorbable type I/III CM of porcine origin (BioGide®, Geistlich Biomaterials, Wolhusen, Switzerland) was trimmed and adapted over the entire defect so as to cover 2–3 mm of the surrounding alveolar bone and to ensure stability of the graft material. Neither sutures nor pins were used for membrane fixation or stabilization. Finally, the mucoperiosteal flaps were repositioned coronally and fixed with vertical or horizontal mattress sutures to ensure a non-submerged healing procedure. All treatments were performed by the same experienced surgeon (F. S.).

Post-operative care and long-term maintenance

Post-operative care consisted of rinsing with a 0.2% chlorhexidine digluconate solution (Corsodyl®, GlaxoSmithKline Consumer Healthcare) twice a day for 2 weeks. The sutures were removed 10 days after the surgery. Recall appointments were scheduled every second week during the first 2 months after surgery and monthly during the short-term observation period of 6 months. During the rest of the observation period of 48 months, the patients were recalled every 6 months. A supragingival professional implant/tooth cleaning and reinforcement of oral hygiene were performed at 1, 3, 6, 12, 18, 24, 30, 36, 42, and 48 months after treatment (K. B. and N. S.).

Results

At 36 months following treatment, one patient (smoker of <10 cigarettes per day) of the NBM+CM group had to be discontinued from the study due to severe pus formation. Subsequently, this patient received further peri-implantitis treatment procedures including non-surgical (i.e. Er:YAG laser decontamination) and surgical regenerative protocols (i.e. NBM+CM). At re-entry, the former defect area was observed to be completely filled by a loose granulation tissue, exhibiting minute amounts of embedded residual NBM particles. The histo-pathological analysis of tissue biopsies revealed a mixed chronic inflammatory cell infiltrate without any sings of a dysplasia. The radiograph exhibited an increased intrabony peri-implant translucency (Fig. 1).

Thus, in the following, only the data of the 19 available patients are presented. In these cases, the follow-up healing period was generally considered as uneventful. Basically, all patients reported a high degree of satisfaction with the provided treatment, which was related to the possibility of maintaining the implants. However, some patients of both groups reported on an increased bleeding tendency upon domestic implant cleaning.

The mean PI and BOP as assessed in both groups at baseline and after 36 and 48 months are summarized in Tables 4–6.

Basically, both groups revealed low mean PI values throughout the study

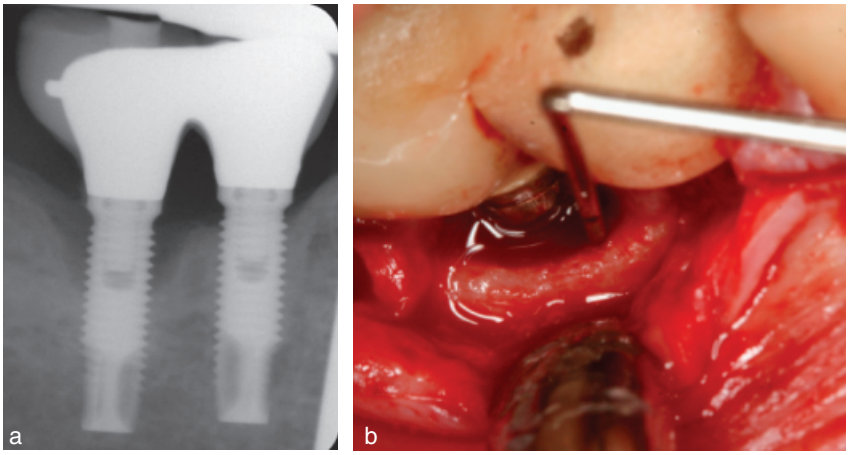

Fig. 1. (a) Intra-oral radiograph of a natural bone mineral in combination with a collagen membrane treated implant which had to be discontinued from the study due to severe pus formation at 36 months. An increased peri-implant translucency was limited to the intrabony aspect of the implant and approached about 50% of its length (for corresponding baseline and 6-month figures, see Schwarz et al. 2006a – Figs 3a and b). (b) Defect situation following granulation tissue removal. Note that the buccal aspect of the supporting alveolar bone was still intact, which in turn appears to be contradictory to the corresponding radiograph.

Table 4. Clinical parameters (mean ± SD) at baseline and 36 months for the NHA ($n = 9$ patients) and NBM+CM ($n = 10$ patients) groups

	Baseline	36 months	Difference
Plaque index			
NHA	0.6 ± 0.5	1.0 ± 0.4	0.4 ± 0.7
NBM+CM	0.8 ± 0.4	0.8 ± 0.5	0.0 ± 0.5
Bleeding on probing (%)			
NHA	80	46	34
NBM+CM	79	28	51
Probing depth (mm)			
NHA	6.9 ± 0.6	5.6 ± 0.4	1.3 ± 0.4
NBM+CM	7.1 ± 0.7	4.6 ± 0.8	2.5 ± 0.9
Gingival recession (mm)			
NHA	0.4 ± 0.2	0.9 ± 0.4	0.5 ± 0.4
NBM+CM	0.4 ± 0.3	0.9 ± 0.2	0.5 ± 0.3
Clinical attachment level (mm)			
NHA	7.3 ± 0.8	6.5 ± 0.8	0.8 ± 0.7
NBM+CM	7.5 ± 0.9	5.5 ± 0.7	2.1 ± 1.0

NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

Table 5. Clinical parameters (mean ± SD) at baseline and 48 months for the NHA ($n = 9$ patients) and NBM+CM ($n = 10$ patients) groups

	Baseline	48 months	Difference
Plaque index			
NHA	0.6 ± 0.5	1.1 ± 0.3	0.5 ± 0.5
NBM+CM	0.8 ± 0.4	1.0 ± 0.6	0.2 ± 0.6
Bleeding on probing (%)			
NHA	80	48	32
NBM+CM	79	28	51
Probing depth (mm)			
NHA	6.9 ± 0.6	5.8 ± 0.7	1.1 ± 0.3
NBM+CM	7.1 ± 0.7	4.6 ± 0.9	2.5 ± 0.9
Gingival recession (mm)			
NHA	0.4 ± 0.2	0.9 ± 0.4	0.4 ± 0.5
NBM+CM	0.4 ± 0.3	0.9 ± 0.2	0.5 ± 0.4
Clinical attachment level (mm)			
NHA	7.3 ± 0.8	6.7 ± 1.0	0.6 ± 0.5
NBM+CM	7.5 ± 0.9	5.5 ± 0.9	2.0 ± 1.0

NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

Table 6. Clinical parameters (mean ± SD) at 36 and 48 for the NHA ($n = 9$ patients) and NBM+CM ($n = 10$ patients) groups

	36 Months	48 Months	Difference
Plaque index			
NHA	1.0 ± 0.4	1.1 ± 0.3	0.1 ± 0.4
NBM+CM	0.8 ± 0.5	1.0 ± 0.6	0.2 ± 0.3
Bleeding on probing (%)			
NHA	46	48	2
NBM+CM	28	28	0
Probing depth (mm)			
NHA	5.6 ± 0.4	5.8 ± 0.7	0.2 ± 0.5
NBM+CM	4.6 ± 0.8	4.6 ± 0.9	0.0 ± 0.3
Gingival recession			
NHA	0.9 ± 0.4	0.9 ± 0.4	0.0 ± 0.0
NBM+CM	0.9 ± 0.2	0.9 ± 0.2	0.0 ± 0.0
Clinical attachment level (mm)			
NHA	6.5 ± 0.8	6.7 ± 1.0	0.2 ± 0.5
NBM+CM	5.5 ± 0.7	5.5 ± 0.9	0.0 ± 0.4

NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

period. However, a slight increase was noted in both groups at either 36 or 48 months, respectively. In comparison with the respective baseline values, this difference appeared to be more pronounced for the NHA group at the 36-month examination (Table 4).

Even though the mean BOP values improved in both groups over time, the mean reduction was higher in the NBM+CM group at both 36 and 48 months (Tables 4 and 5). While the NHA-treated sites revealed a slight increase of 2% in the mean BOP scores at 48 months, these values remained unchanged in the NBM+CM group (Table 6).

The mean PD, GR, and CAL values in both groups at baseline and after 36 and 48 months are summarized in Tables 4–6.

In particular, at 48 months after therapy, the NHA group showed a reduction in the mean PD from 6.9 ± 0.6 at baseline to 5.8 ± 0.7 mm and a change in the mean CAL from 7.3 ± 0.8 at baseline to 6.7 ± 1.0 mm. In the NBM+CM group, the mean PD was reduced from 7.1 ± 0.7 at baseline to 4.6 ± 0.9 mm, and the mean CAL changed from 7.5 ± 0.9 at baseline to 5.5 ± 0.9 mm (Table 5).

Table 7. Frequency distribution of CAL gain after 48 months in the NHA ($n = 9$ patients) and NBM+CM ($n = 10$ patients) groups

CAL gain (mm)	NHA		NBM+CM	
	N°	%	N°	%
0	5	55.6	0	0
1	3	33.3	3	30
2	1	11.1	2	40
3	0	0	0	20
4	0	0	0	10

CAL, clinical attachment level; NHA, nanocrystalline hydroxyapatite; NBM+CM, natural bone mineral in combination with a collagen membrane.

On comparing the 48-month clinical parameters with the 36-month values, both groups revealed a slight increase in the mean PD and CAL values. In particular, the mean increase in PD was 0.2 ± 0.5 mm in the NHA and 0.0 ± 0.3 mm in the NBM+CM group, respectively. Similarly, the mean increase in CAL was 0.2 ± 0.5 mm in the NHA group and 0.0 ± 0.4 mm in the NBM+CM group, respectively (Table 6).

The frequency distribution of CAL gains after 48 months in both treatment groups is shown in Table 7. In particular, in the NHA group, 44.4% of the sites gained at least 1 mm (33.3%; $n = 3$ defects) or 2 mm (11.1%; $n = 1$ defect) of CAL. In contrast, 70% of the NBM+CM-treated sites revealed a CAL gain of at least 1 mm (30%; $n = 3$ defects) or 2 mm (40%; $n = 2$ defects) (Table 7).

At 48 months, radiographic observation revealed a decreased translucency in the former peri-implant defect area for a total of five sites in the NHA group, and for eight sites in the NBM+CM group (Fig. 2). Compared with the radiographs obtained at 6 months, the remaining sites in both groups (NHA: 4; NBM+CM: 2) exhibited an increasing intrabony translucency at both mesial and distal aspects of the implant (Fig. 3).

Discussion

The present follow-up observation aimed at investigating the 4-year clinical results following surgical regenerative treatment of moderate intrabony peri-implantitis defects using either NHA or NBM+CM. The short- and intermediate-term clinical

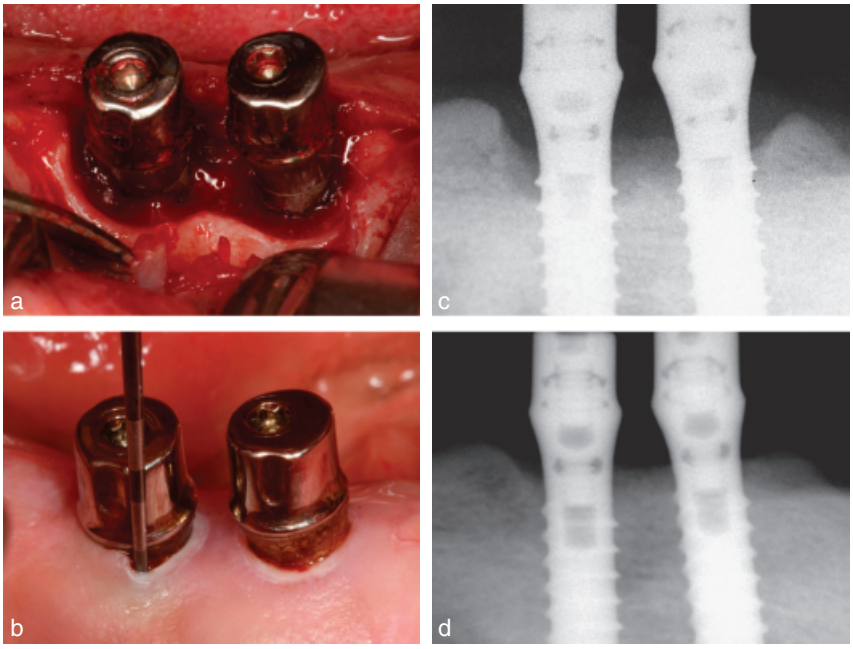

Fig. 2. (a) Two circular peri-implant bone defects at implants 044 and 045 at baseline (natural bone mineral in combination with a collagen membrane group). Implant 045 was included as the primary target site. (b) Clinical situation at 48 months indicating a probing depth reduction but also minimal bleeding on probing scores. (c) Corresponding intra-oral radiograph at baseline. (d) Corresponding intra-oral radiograph at 48 months indicating a complete radiographic bone fill in the former defect areas.

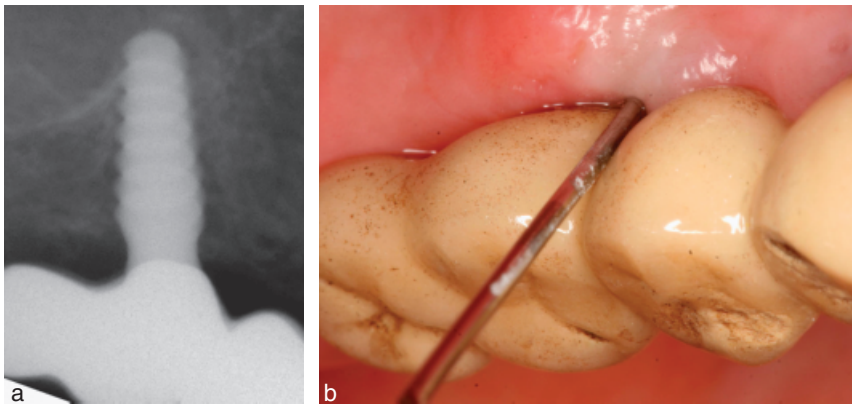

Fig. 3. (a) Intra-oral radiograph of an nanocrystalline hydroxyapatite-treated site at 48 months indicating an increased intrabony translucency at both mesial and distal aspects of the implant (for corresponding baseline and 6-month figures, see Schwarz et al. 2006a – Figs. 3c and d). (b) Corresponding clinical situation indicating increased probing depth but negative bleeding on probing values.

outcomes in both groups at 6 and 24 months have been reported previously (Schwarz et al. 2006b, 2008).

When evaluating the whole observation period of 48 months, it was observed that both treatment procedures resulted in clinical improvements as evidenced by PD reductions and CAL gains. In particular, the NHA group exhibited a mean PD reduction from 6.9 ± 0.6 mm at baseline to 4.9 ± 0.4, 5.4 ± 0.7, and 5.8 ± 0.7 mm at 6, 24, and 48 months, and a mean CAL gain from 7.3 ± 0.8 mm at baseline to 5.6 ± 0.8, 6.3 ± 0.9, and 6.7 ± 1.0 mm at 6, 24, and 48 months, respectively. Similarly, the NBM+CM group exhibited a mean PD reduction from 7.1 ± 0.7 mm at baseline to 4.5 ± 0.5, 4.6 ± 0.7, and 4.6 ± 0.9 mm at 6, 24, and 48 months, and a mean CAL gain from 7.5 ± 0.9 mm at baseline to 5.2 ± 0.6, 5.4 ± 0.6, and 5.5 ± 0.9 mm at 6, 24, and 48 months, respectively. Even though the mean PD reductions and CAL gains at 24 (Schwarz et al. 2008) and 48 months appeared to be the highest in the NBM+CM group, it must be emphasized that the present case series does not have the statistical power to rule out the possibility of a difference between both treatment groups (Gunsolley et al. 1998).

When interpreting these results, however, it was also noted that after the short-term healing period of 6 months, both groups revealed a slight but consistent increase of the mean PD values as well as a decrease of the mean CAL values over time. The calculated difference in mean the PD scores between 6 and 48 months was 0.9 ± 0.5 mm in the NHA and 0.1 ± 0.8 mm in the NBM+CM group. Similarly, the difference in the mean CAL scores was 1.1 ± 0.8 mm in the NHA group and 0.3 ± 0.8 mm in the NBM+CM group (Schwarz et al. 2006b). There might be several reasons to explain the instability of the short-term clinical outcomes in both groups over time. First of all, it must be emphasized that the mean PI scores slightly increased between 6 and 48 months of healing, thus resulting in a mean difference of 0.6 ± 0.5 in the NHA and 0.4 ± 0.6 in the NBM+CM group (Schwarz et al. 2006b). This might probably be explained by a higher frequency of the recall appointments during the initial healing period of 6 months. Even though the mean PI scores at 48 months still indicated a good level of oral hygiene in both groups, it cannot be excluded that plaque accumulation might have caused an inflammation in the peri-implant soft and hard tissue, subsequently leading to a loss of CAL. This assumption might, at least in part, be supported by the increasing BOP scores, as observed in both groups over time. Previous data on regenerative periodontal treatment have also indicated that the stability of the clinical outcomes is dependent on stringent oral hygiene and compliance with a regular maintenance programme (Cortellini & Tonetti 2004). Similar results were also reported in a 3-year clinical follow-up observation of surgical regenerative therapy of peri-implantitis defects using autogenous bone (AB) as a particulate and block grafts with or without a GBR procedure (e.g. CM or ePTFE) (Khoury & Buchmann 2001). These data pointed to an initial reduction of the mean PD values and probing bone levels after 6 and 12 months of healing in all groups,

but also revealed a slight increase of these values at 36 months. In particular, the mean PD values in the AB+CM group decreased from 7.7 ± 0.5 mm at baseline to 6.4 ± 0.9, 4.4 ± 0.8, and 5.1 ± 1.2 mm at 6, 12, and 36 months, respectively. Unfortunately, the authors did not report on the mean PI scores over time (Khoury & Buchmann 2001). Finally, it must be queried whether surgical regenerative treatment of peri-implantitis using either NHA or NBM+CM was primarily related to an obstruction of the former defect area by the residual bone graft particles, rather than a new bone formation and subsequently re-osseointegration. A previous experimental animal study provides some evidence that the application of NBM+CM may support the process of re-osseointegration at ligature-induced peri-implantitis defects (Nociti et al. 2000). However, after a submerged healing period of 5 months (dog model, air powder flow, systemic administration of metronidazole for 3 weeks), the histomorphometric evaluation revealed no significant differences with respect to bone formation and re-osseointegration at sites receiving either surface debridement alone (49.5%/26.8%), CM alone (51%/26.6%), NBM alone (55.7%/28%), or a combination of NBM+CM (48%/25.6%) (Nociti et al. 2000). Within the limitations of an experimental animal study, these data suggest that the clinical application of NBM+CM might also have the potential to support a certain amount of new bone formation and subsequently re-osseointegration in the former defect area. This assumption might be supported by the radiographic bone gain as assessed on either a short-, an intermediate- (Schwarz et al. 2006b, 2008), or a long-term follow-up of the present study. In this context, however, it must be emphasized that these radiographs were not standardized and can in no case reflect the cellular reactions at the bone–implant interface.

For the time being, no experimental data are available reporting on the histological pattern of wound healing following NHA application in intrabony peri-implantitis defects.

Within the limits of the present case series, it was concluded that the application of NBM+CM resulted in clinical improvements over a period of 4 years. The long-term outcome obtained with NHA without barrier membrane, however, must be considered as poor.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Supporting information in accordance with the CONSORT Statement 2001 checklist used in reporting randomized trials.

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Address:
Frank Schwarz
Department of Oral Surgery
Westdeutsche Kieferklinik
Heinrich Heine University
D-40225 Düsseldorf, Germany
E-mail: frank.schwarz@med.uni-dueseldorf.de

Clinical Relevance

Scientific rationale for the study: The data on the long-term outcomes following surgical regenerative treatment of intrabony peri-implantitis lesions are limited.
Principal findings: The present results have indicated that at 36 and 48 months after surgery, the application of NBM+CM resulted in higher PD reductions and gains of CAL than an NHA. However, both therapies also revealed slight but consistently increasing BOP and PD values and thus CAL loss over time.
Practical implications: At 4 years after surgical regenerative treatment of intrabony peri-implantitis lesions, NBM+CM seemed to be more suitable to maintain the clinical improvements achieved than NHA.