

# Periodontal regeneration *versus* extraction and prosthetic replacement of teeth severely compromised by attachment loss to the apex: 5-year results of an ongoing randomized clinical trial

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Cortellini P, Stalpers G, Mollo A, Tonetti MS: Periodontal regeneration versus extraction and prosthetic replacement of teeth severely compromised by attachment loss to the apex: 5-year results of an ongoing randomized clinical trial. *J Clin Periodontol* 2011; 38: 915–924. doi: 10.1111/j.1600-051X.2011.01768.x

## Abstract

**Aims:** Aim of this randomized, long-term clinical trial was to compare clinical- and patient-based outcomes following periodontal regeneration or extraction and replacement of hopeless teeth with chronic perio-endo lesions and/or attachment loss to or beyond the apex.

**Methods:** Fifty patients presenting with generalized severe periodontitis and at least one hopeless tooth to be extracted for periodontal reasons were entered in this study. The *test treatment* consisted in the application of a regenerative strategy to 25 hopeless teeth. The *control treatment* consisted in the extraction of the 25 hopeless teeth and their replacement with conventional or implant-supported fixed partial dentures.

**Results:** In the *control group*, 14 teeth were replaced with implant-supported restorations, eight with tooth-supported bridges, two with Maryland bridges, while one was not replaced. All fixed partial dentures survived the 5-year follow-up period and 83% were free from biological complications. In the *test group*, 23 of the 25 regenerated teeth showed important clinical improvements: the two teeth with unsatisfactory outcomes were extracted at 1 year. The 23 successfully regenerated teeth (92%) were in good health and function at 5-year examination visit and 84% did not develop biological complications during the recall period. All patients consistently reported comfort in function at the experimental test and control units. In the test group, average clinical attachment level gains were  $7.7 \pm 2.8$  mm, radiographic bone gain  $8.5 \pm 3.1$  mm, probing pocket depth (PPD) reduction  $8.8 \pm 3$  mm. Residual PPDs were  $4 \pm 1.7$  mm. Most of the regenerated teeth showed a decrease in tooth mobility.

**Conclusions:** Regenerative therapy can be applied at hopeless teeth and has the potential to change their prognosis; it is a suitable alternative to extraction of severely compromised teeth with intra-bony defects to or beyond the root apex.

Key words: clinical trial; hopeless tooth; long-term; periodontal regeneration; periodontal surgery; tooth extraction

Accepted for publication 20 June 2011

## Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.

This study has been self-supported by the authors, and the European Research Group on Periodontology, ERGOPERIO.

The persistence of deep pockets following active periodontal therapy has been associated with increased probability of tooth loss in patients attending supportive periodontal care programs (Matuliene et al. 2008).

Teeth with deep pockets associated with deep intra-bony defects have long been considered a clinical challenge. Most authors have classified such teeth as having either a questionable or a hopeless prognosis: the complex interplay of reduced residual periodontal attachment, deep pocketing, functional demands and frequently the resulting tooth hypermobility have been the key elements for such opinions (Lang & Tonetti 1996, McGuire & Nunn 1996a,b, Kwok & Caton 2007). The difference between assigning a questionable (i.e. the tooth needs advanced treatment to change tooth prognosis) or a hopeless (i.e. the tooth needs to be extracted as soon as possible) prognosis has profound and frequently far-reaching consequences in treatment planning.

McGuire and Nunn (1996a,b) proposed a classification in which a tooth was defined 'hopeless' when there was inadequate attachment to maintain the tooth in health, comfort, and function. Kwok and Caton (2007) proposed to base the prognostication system on the stability of the periodontal supporting apparatus and on the evaluation of evidence-based modification factors, like plaque and infection control, smoking habit, and systemic conditions. According to these authors a tooth declared 'hopeless' should be extracted. In clinical practice, more conservative definitions of a tooth requiring extraction are sometimes used, like attachment loss to the apex, especially when the periodontium has been destroyed on multiple root surfaces.

Indeed early on in modern periodontology it was shown that teeth with severe loss of periodontal support can be retained and kept healthy within a strict program of periodontal therapy and supportive periodontal care (Lindhe & Nyman 1984, Pretzl et al. 2009a, Huynh-Ba et al. 2009, Chambrone et al. 2010, Leininger et al. 2010, Bäumer et al. 2011, Ng et al. 2011).

A growing amount of evidence indicates that periodontal regeneration can result in long-term retention of teeth presenting with deep pockets associated with intra-bony defects (Cortellini & Tonetti 2004, Sculean et al. 2008, Pretzl et al. 2009b, Nygaard-Østby et al. 2010). In this context, the ability to

predictably obtain clinically significant attachment level gains and shallow, maintainable pockets are key elements for the clinical decision to treat intra-bony defects with periodontal regeneration (for a review, see Murphy & Gunsolley 2003, Needleman et al. 2006, Esposito et al. 2009). At present, however, it is unclear what is the limit, if any, of severity of an intra-bony defect that renders the tooth no longer amenable to regenerative treatment. The limit(s) of periodontal regeneration in intra-bony defects has clear implications on tooth prognosis and on the decision of which teeth should be extracted.

Aim of this randomized, long-term clinical trial was to compare clinical- and patient-based outcomes following periodontal regeneration or extraction of teeth with chronic perio-endo lesions and/or attachment loss to or beyond the apex. In the conduct of this trial we also sought to explore the limits of periodontal regeneration in changing the prognosis of hopeless teeth.

## Material and Methods

### Experimental population and study design

This was a parallel group, randomized, controlled clinical trial designed to compare the outcomes of periodontal regeneration or extraction of teeth clinically defined as having hopeless prognosis as a consequence of the presence of a chronic perio-endo lesion and/or attachment loss to the apex. The test arm was also designed to explore the potential of periodontal regenerative therapy in changing the prognosis of hopeless teeth. Patient recruitment was performed in a periodontal practice in a period of 5 years between June 1998 and June 2003. Patients presenting with generalized severe periodontitis and at least one tooth to be extracted for periodontal reasons – chronic perio-endo lesion and/or attachment loss to the apex – were considered eligible for this study. The test treatment consisted in the application of a periodontal regenerative strategy to modify the prognosis of the hopeless tooth. The control treatment consisted in the extraction of the hopeless tooth and its replacement with tooth- or implant-supported fixed partial restorations, as indicated. Each patient contributed with one experimental tooth.

All subjects received comprehensive periodontal and dental treatment, including oral hygiene instruction and motiva-

tion, scaling and root planing, periodontal surgery, endodontic treatment when needed, splinting of hypermobile teeth, and temporary reconstructions. All patients were enrolled in a supportive periodontal care program. Pocket depth, attachment level, and radiographic bone level were recorded yearly around experimental test teeth treated with regeneration and around natural abutment teeth or implants in the control group.

### Study outcomes

The primary outcome of the study was tooth retention according to pre-specified criteria: patient comfort, masticatory function, and clinical measurements contributing to the assessment of tooth prognosis according to McGuire and Nunn (1996a,b) and Kwok and Caton (2007). Secondary outcomes included: (i) the assessment of biological complications at the experimentally treated teeth or at the abutments of tooth- or implant-supported bridges, (ii) patient outcomes, and (iii) health economics measures. Outcomes were evaluated at 1 and 5 years. The study flow chart is outlined in Fig. 1.

### Inclusion and exclusion criteria

Patients in good general health and satisfying the following inclusion criteria were considered eligible for this study:

1. *Good general health*: Patients with uncontrolled or poorly controlled diabetes, unstable or life threatening conditions, or requiring antibiotic prophylaxis were excluded.
2. *Smoking status*: Only patients smoking <20 cigarettes/day were included.
3. *Good oral hygiene*: Full-mouth plaque score  $\leq 25\%$ .
4. *Low levels of residual infection*: Full-mouth bleeding score  $\leq 25\%$ .
5. *Compliance*: Only patients with optimal compliance, as assessed during the cause-related phase of therapy, were selected.
6. Presence of severe generalized periodontal disease (attachment loss  $\geq 6$  mm at  $\geq 30\%$  of sites).
7. Presence of at least one tooth to be extracted for periodontal reasons, defined as fulfilling all the following criteria:
  - Radiographic bone loss to the apex or beyond the apex on at least one inter-dental aspect.

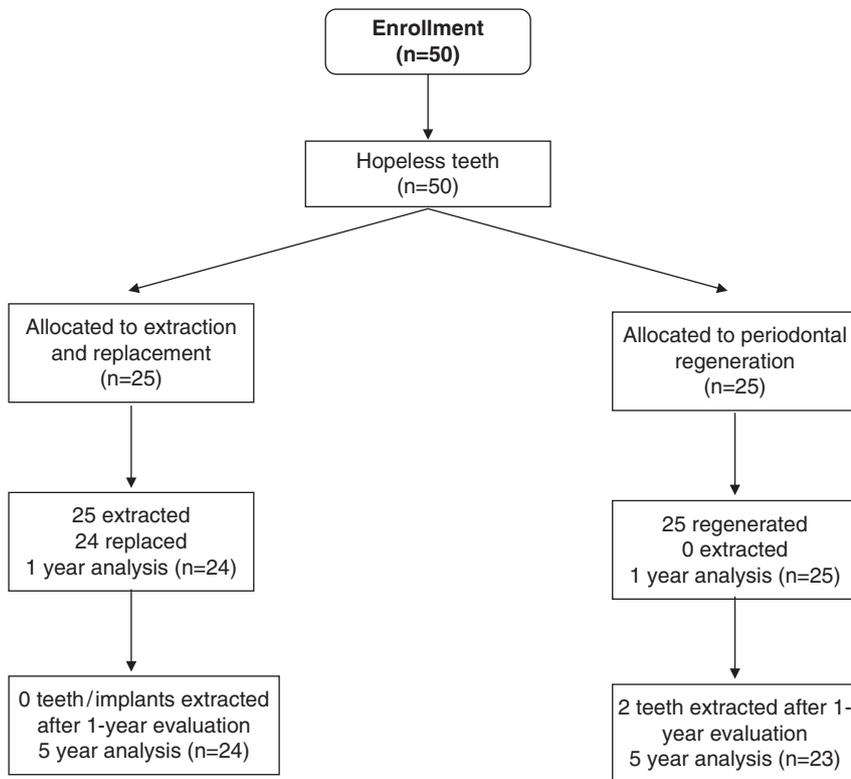


Fig. 1. Consort flowchart of the study.

- Presence of a severe attachment loss (> 10 mm) at the same inter-proximal site/s and at least at one of either the buccal or lingual aspect.
  - Inter-dental bone destruction with the anatomical characteristic of an intra-bony defect, thereby presenting with a clearly detectable bone crest at the neighbouring tooth/teeth.
  - Lack of function because of hypermobility, and/or lack of chewing strength, and/or pain, and/or recurrent periodontal infection/abscesses.
8. *Endodontic status*: Both vital and non-vital teeth were included. The vitality of each tooth was tested with electrical pulp-testing and criotest. Non-vital teeth were endodontically treated and teeth with improper root canal therapy were retreated (Cortellini & Tonetti 2001). The radiological and clinical evaluation was performed after a period of at least 3 months following the completion of the endodontic approach.

#### Patient entry (informed consent, patient registration, randomization)

Informed consent was obtained from all the subjects entered into the study. The study was approved by the ethics com-

mittee of the Accademia Toscana di Ricerca Odontostomatologica (ATRO). The study was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects. For patient protection, possible side effects of surgical therapy were handled according to the current standards of care in private practice. After verification of the entry criteria, 50 subjects gave informed consent and were entered into the study. Randomization was performed with a computer-generated randomization table using a random permuted block approach to ensure balanced allocation to both treatments. Allocation was concealed with opaque envelopes until immediately before treatment.

#### Clinical measures

The following clinical parameters were evaluated at baseline within 2 weeks before the experimental treatment (at least 3 months after the endodontic treatment, when performed, and after completion of non-surgical periodontal therapy), and at 1- and 5-year examination visits.

1. *Full-mouth plaque scores (FMPS)*: It was recorded as the percentage of total surfaces (four aspects per tooth), which revealed the presence of pla-

que (O'Leary et al. 1972). FMPS were then calculated.

2. *Bleeding on probing from the bottom of the pocket*: It was assessed dichotomously (six aspects per tooth) at a force of 0.3 N with a manual pressure sensitive probe (Brodontic Probe, Prima, By-fleet, UK) equipped with a PCP-UNC 15 tip (Hu-Friedy, Chicago, IL, USA). Full-mouth bleeding scores (FMBS) were then calculated (Cortellini et al. 1993).
3. *Probing pocket depth (PPD) and recession of the gingival margin (REC)* were recorded to the nearest millimetre with a manual pressure sensitive probe by a trained investigator at the deepest location of the four tooth aspects (mesial, distal, buccal, lingual). In abutment teeth, the cervical margin of the crown was considered as the reference point for REC measurements when the CEJ was not detectable.
4. *Clinical attachment levels (CAL)* were calculated as the sum of PPD and REC.
5. *Tooth mobility* was evaluated according to a clinical score ranging from 0 to 3, where degree 0 represented physiologic mobility, degree 1 mobility slightly greater than normal, degree 2 mobility  $\leq 1$  mm of the tooth in horizontal direction, and degree 3 mobility of the tooth > 1 mm and in vertical direction as well (Miller 1943).
6. *Chewing function and patient comfort* were assessed at baseline, 1, and 5 years.

#### Radiographic measures

Periapical radiographs [Kodak ultra-speed film, size 0 DF-54 for anteriors and size 2 DF-58 for posteriors (Kodak, Rochester, NY, USA)] were taken with the parallel technique. The radiographs were digitized (Epson Expression 1680 Pro, 8-bit, 1200 dpi) and measured with an electronic ruler at a  $\times 10$  magnification (ImageJ, NIH, Bethesda, MD, USA) on a high definition monitor [Hewlett Packard LP 2065, served with a NVIDIA FX 3700 graphic board (Hewlett Packard, Palo Alto, CA, USA)] at a resolution of  $1600 \times 1200$  pixels. The following measures were taken at the mesial and distal sides:

1. *X-ray-CEJ-apex*: Distance between the radiographic projection of the

cemento-enamel junction and the apex of the root.

2. X-ray-CEJ-BD: Distance between the radiographic projection of the cemento-enamel junction and the bottom of the defect.
3. X-ray-CEJ-BC: Distance between the radiographic projection of the cemento-enamel junction and the approximal bone crest.
4. The radiographic intra-bony component depth was calculated as the difference between X-ray-CEJ-BD and X-ray-CEJ-BC.
5. X-ray-BD-apex was calculated as the difference between X-ray-CEJ-BD and X-ray-CEJ-apex.
6. The radiographic defect angle of each defect was measured, as described previously (Tonetti et al. 1993).

In abutment teeth the cervical margin of the crown was considered as the reference point for X-ray measurements whenever the CEJ was not detectable.

#### Clinical characterization of the intra-bony defects

Defect morphology was characterized intra-surgically (only in the test group) at the deepest location of the four tooth aspects (mesial, distal, buccal, lingual), as follows:

1. CEJ-apex: Distance between the cemento-enamel junction and the apex of the tooth.
2. CEJ-BD: Distance between the cemento-enamel junction and the bottom of the defect.
3. CEJ-BC: Distance between the cemento-enamel junction and the approximal bone crest.
4. The intra-bony component depth was calculated as the difference between CEJ-BD and CEJ-BC.

In abutment teeth the cervical margin of the crown was considered as the reference point for bone measurements whenever the CEJ was not detectable.

#### Evaluation of tooth prognosis

Tooth prognosis was evaluated at baseline and re-evaluated at 1- and 5-year examinations applying the score of McGuire and Nunn (1996a, b).

This score spans from "fair" to "poor" to "questionable" to "hopeless" prognosis.

A secondary evaluation was done applying the score proposed by Kwok and Caton (2007). Their score spans from "favourable" to "questionable" to "unfavourable" to "hopeless".

#### Surgical procedure

After the collection of the baseline measures the patients were randomly assigned either to the control or test treatment.

*The control group* was treated with the extraction of the experimental hopeless teeth. Replacement of the extracted teeth was then performed according to the clinical indications with tooth- or implant-supported elements. Soft tissue augmentation and/or bone regeneration were performed as needed.

*The test group* was treated with periodontal regeneration (Fig. 2a–l). Hypermobile teeth were splinted to the neighbouring teeth before surgery (Cortellini et al. 2001). Non-vital teeth were endodontically treated or re-treated, when needed, at least 3 months before surgery. Vital teeth presenting with a bony defect beyond the apex were endodontically treated before surgery. All sites were surgically accessed with papilla preservation flaps (Cortellini et al. 1995a, 1999a), defect debridement, and root planing. When the apex of the tooth was exposed, apex debridement was performed with the aid of sonic diamond scalers (Sonicflex-lux, Kavo Biberach, Germany). Periodontal regeneration was performed with one of the following approaches: non-resorbable (Goretex, WL Gore and Associates, Flagstaff, AZ, USA) or bio-resorbable (Guidor AB, Huddinge, Sweden) barrier membranes; enamel matrix derivative (EMD, Straumann AG, Basel, Switzerland); a combination of bio-resorbable membranes and a xenograft of bovine origin (BioGide and BioOss, Geistlich, Wolhusen, Switzerland); a combination of EMD and alloplastic biomaterials; a combination of bio-resorbable membranes and EMD. When EMD was used, EDTA (Straumann AG) was applied to the root surface according to the manufacturer's indications. The regenerative approach was selected as described previously (Cortellini & Tonetti 2005). Internal mattress sutures (5-0 and 6-0, Goretex, WL Gore and Associates) were positioned to close the wound on top of the regenerative material.

A protocol for the control of bacterial contamination consisting of doxycycline

(100 mg b.i.d. for 1 week), 0.12% chlorhexidine mouth rinsing three times per day, and weekly prophylaxis was prescribed (Tonetti et al. 1998). Patients were requested to avoid brushing, flossing, and chewing in the treated area for period of 3–8 weeks. Non-resorbable barriers were surgically removed after 6 weeks. At the end of this period patients resumed full oral hygiene. At the end of the "early healing phase", patients were placed on a 3-month recall system.

Appropriate periodontal therapy was delivered, whenever needed, during the recall system to treat periodontal/implant contamination.

At 1 year, hypermobility was tested removing the resin splints or the temporary bridges. Definitive fixed bridges were applied attempting to maintain unmodified the position of the cervical preparation. The resin splint were re-applied or not re-applied in agreement with the patients after a period of evaluation of the de-splinted units for comfort and function. Similarly, the mobility evaluation was performed at 5 years with the exception of the abutment teeth included into fixed bridges.

#### Data analysis

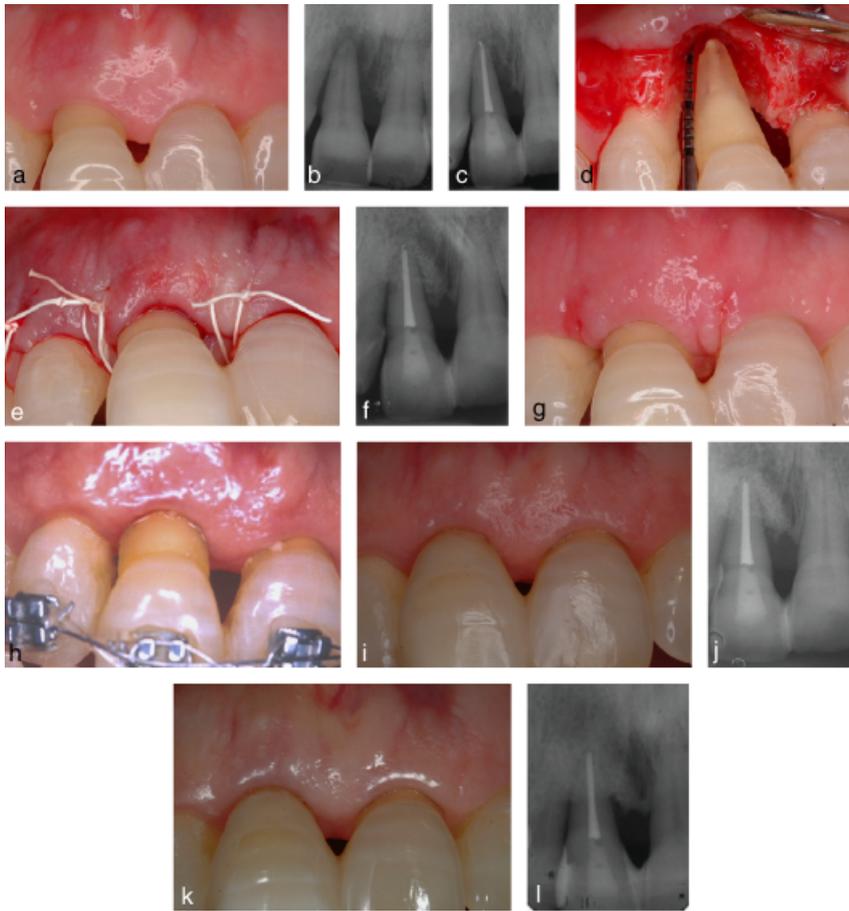
Primary outcome variable was tooth loss. Clinical attachment level gains (CAL gains), residual pocket depth, position of the gingival margin, and radiographic bone gain were the secondary outcome variables. The occurrence of negative events, i.e. CAL loss  $\geq 2$  mm, PPD increase  $\geq 2$  mm, and bone loss  $\geq 2$  mm, was recorded yearly in both the test and the control group (bridge abutment teeth or implant) during the 5-year follow-up.

Baseline clinical and radiographic data were expressed as means  $\pm$  standard deviation of the deepest inter-dental site of 50 teeth in 50 patients. Comparison between the test (25 patients) and the control (25 patients) group were made using the Student's *t*-test ( $\alpha = 0.05$ ). Comparisons between baseline and 1- and 5-year data in the test group only were made with the paired *t*-test ( $\alpha = 0.05$ ). No data points were missing.

#### Results

##### Baseline patient and experimental unit characteristics

The control group included 25 patients (10 females); three were smokers.



**Fig. 2.** (a) Baseline clinical image of an upper right central incisor splinted to the left incisor for severe hypermobility. The tooth was non-vital and presented with clinical attachment loss ranging 11–15 mm on the four tooth sides (patient 7: see Appendix S1). (b) Baseline radiographic image showing the presence of a deep intra-bony defect associated with periapical radiolucency. (c) Pre-surgical radiograph taken 4 months after completion of the endodontic treatment. Endo therapy did not substantially modify the bone density. (d) Intra-surgical image showing a 360° bone destruction beyond the apex. The mesial and distal intra-bony components are associated with a complete buccal bone dehiscence. (e) Complete closure of the modified papilla preservation flap after application of a bone substitute and a bioresorbable barrier. (f) Post-surgical radiograph showing the grafted bone substitute. (g). At 1 week the flap was completely closed. (h) After 10 months the tooth was orthodontically realigned and slightly intruded. (i) At 1 year, after completion of the orthodontic treatment, the experimental tooth was splinted and aesthetically improved with composite. (j) The 1-year radiograph shows the almost complete resolution of the intra-bony component. (k) The 5-year clinical image shows stability of the soft tissues. (l) The 5-year radiograph shows stability of the reconstructed supporting bone.

The test group included 25 patients (15 females); two were smokers. The patient characteristics for the control and the test groups are displayed in Table 1. Differences in terms of FMPS and FMBS were not statistically significant, while age reached borderline significance. In the control group the experimental teeth were 14 upper and one lower incisor, one upper and two lower cuspids, four upper bicuspid, and three lower molars. In the test group the experimental units were eight upper and three lower incisors, one upper and

four lower cuspids, five upper and one lower bicuspid, two upper and one lower molar.

Dental mobility scored zero in two experimental teeth of the test group and in one tooth of the control group; one control tooth had a degree 1; degree 2 was assigned to six test and to three control teeth; all the other teeth presented with degree 3 hypermobility (68% in the test group and 80% in the control one).

Baseline defect characteristics (referred to the deepest inter-dental

defect of each tooth) of the test and the control group are also reported in Table 1. Both groups presented with very deep pockets, large amounts of clinical attachment loss while radiographic bone destruction exceeded by  $1.1 \pm 1$  and  $1.7 \pm 1.4$  mm the total length of the root in the control and in the test group, respectively. Average percent radiographic bone loss, as referred to the root length, was  $112.8 \pm 11.2\%$  (range 100–153%) in the test group and  $107.7 \pm 7.1\%$  (range 100–125.2%) in the control group. Differences between test and control defects did not reach statistical significance in any of the clinical and radiological parameters.

An evaluation of tooth prognosis applying the score proposed by McGuire and Nunn (1996a, b) and by Kwok and Caton (2007) confirmed the assignment of a ‘hopeless prognosis’ to all the experimental teeth.

#### Control group: treatment approach

In the control group all experimental ‘hopeless’ teeth were extracted at baseline, according to the study design. One tooth (second lower molar) was not replaced for patient’s choice. Fourteen teeth were replaced with implant-supported restorations, eight were replaced with tooth-supported bridges, while two were replaced with Maryland bridges. Eight out of 14 implanted sites needed the application of bone regenerative procedures while three additional sites received bone regeneration and soft tissue augmentation. All the sites treated with tooth-supported bridges and with Maryland bridges were treated with soft tissue augmentation of the edentulous ridge. One site treated with tooth-supported restoration needed also bone augmentation to correct the very ample ridge deformity.

#### Test group: treatment approach

In the test group 22 out of 25 teeth were splinted before surgery; five were included into temporary fixed bridges, while the remaining 17 were splinted with composite resin to the neighbouring teeth. Three teeth, presenting with degree 2 (one tooth) and degree 0 mobility were not splinted (Appendix S1).

Seventeen of 25 teeth presented with signs of pulp vitality: five were associated with bony defects extending to the root apex and were left vital. Twelve were associated with defects extending beyond the root apex and were

endodontically treated before surgery. Of the eight non-vital teeth, the four with improper root-canal treatment were endodontically re-treated, three non-vital non-treated teeth were endodontically treated, while one presented with a satisfactory root canal therapy. All root canal treatments were performed at least 3 months before surgery (Appendix S1).

The employed regenerative strategies were distributed as follows: 10 cases were treated with EMD alone, four cases with barrier membranes (two non-resorbable titanium-reinforced barriers and two bio-resorbable), four cases with a combination of bio-resorbable barrier and filler, five cases with a combination of EMD and filler, and two cases with a combination of bio-resorbable barrier and EMD (Appendix S1).

#### Tooth loss and occurrence of negative events

Smoking history and systemic conditions of the test and control group did not change substantially through the 5-

year observation period with respect to baseline.

All patients complied with a 3 months recall system. In the control group, average FMPS and FMBS were  $16.6 \pm 5.3\%$  (range 8–25%) and  $8.7 \pm 5.1\%$  (range 2–20%), respectively, at 1 year, while they were  $13.5 \pm 3.8\%$  (range 8–23%) and  $7.6 \pm 3.4\%$  (range 3–15%) at 5 years. In the test group, FMPS and FMBS averaged  $14.2 \pm 7.2\%$  (range 3–30%) and  $5.4 \pm 3.8\%$  (range 0–15%), respectively, at 1 year, while they averaged  $14.7 \pm 5.5\%$  (range 5–27%) and  $6.6 \pm 3.7\%$  (range 1–13%) at 5 years. No statistically significant differences were observed between test and control at 1 and 5 years.

In the *test group*, at the 1 year re-evaluation 23 out of 25 teeth showed important improvements in terms of both clinical and radiographic parameters at the four sites/tooth (Table 2 and Appendix S1). Residual pockets deeper than 4 mm were observed only in six teeth. Patients 4, 5, 8, and 10

presented with one 5 mm pocket either at the mesial or distal aspect of the experimental tooth. Patient 21 and 22 presented with pockets of  $\geq 6$  mm at three aspects/tooth. A re-evaluation of the tooth prognosis according to McGuire and Nunn (1996a,b) resulted into a score of ‘‘poor prognosis’’ assigned to 11 teeth, ‘‘fair prognosis’’ assigned to 12 teeth, while two were declared hopeless. Applying the Kwok & Caton score 19 out of 25 were considered ‘‘favourable’’, four ‘‘questionable’’, and two ‘‘hopeless’’. The two hopeless teeth, from patients 21 and 22 (Appendix S1), were extracted after the 1-year assessment since they did not improve enough in terms of clinical condition, function, and comfort as compared with baseline. All the other teeth were clinically assessed by the team of clinicians involved in this clinical trial and reportedly judged by the patients as ‘‘good for function and comfort’’. No further regenerated teeth were lost in the time frame between 1 and 5 years (Fig. 3).

In the *control group*, 24 out of 25 extracted teeth were replaced as reported above. At 1-year re-evaluation, the abutment teeth of the eight tooth-supported bridges and the two Maryland bridges presented with PPD  $\leq 3$  mm. The 14 implants had a radiographic bone level covering the first implant thread and PDs  $\leq 4$  mm. None of the 24 replaced units were lost during the 5-year observation period. At 5-year re-evaluation, the 24 replaced units of the control group (100%) and the 23 survived experimental units (92%) of the test group were still in function and in good clinical condition, as also consistently reported by all the patients (Fig. 3).

During the follow-up period few negative events were recorded both in the control and in the test group (Fig. 4). In particular, in the *control group* 2 implants showed a radiographic bone loss  $\geq 2$  mm associated with a PPD

Table 1. Baseline patient and defect characteristics of the control and test group

	Control group (N = 25)	Test group (N = 25)	Significance (p)
Age	51.2 $\pm$ 8.7	46.3 $\pm$ 8.9	0.041
FMPS %	16.6 $\pm$ 5.3	16 $\pm$ 5.1	0.317
FMBS %	8.7 $\pm$ 5.1	9.2 $\pm$ 4.5	0.349
PPD (mm)	12 $\pm$ 1.9	12.7 $\pm$ 2.6	0.265
REC (mm)	2.8 $\pm$ 1.3	2 $\pm$ 1.7	0.094
CAL (mm)	14.8 $\pm$ 1.7	14.8 $\pm$ 2.2	1
X-ray CEJ-apex (mm)	15.1 $\pm$ 1.8	14.3 $\pm$ 2.3	0.265
X-ray CEJ-BD (mm)	16.2 $\pm$ 1.8	16 $\pm$ 2.3	0.764
X-ray Infra (mm)	9.4 $\pm$ 1.8	9.6 $\pm$ 2.8	0.886
X-ray BD-apex (mm)	1.1 $\pm$ 1	1.7 $\pm$ 1.4	0.075
X-ray defect angle ( $^{\circ}$ )	33 $\pm$ 5.6	35.5 $\pm$ 5.9	0.103

Averages and standard deviations calculated at the deepest inter-proximal site (either mesial or distal) of each experimental tooth. Differences between test and control have been tested with the Student's *t*-test.

PPD, probing pocket depth; REC, gingival recession; CAL, clinical attachment level; X-ray CEJ-apex, distance between cemento-enamel junctions and tooth apex; X-ray CEJ-BD, distance between cemento-enamel junctions and bottom of the defect; X-ray infra, depth of the infrabony component; X-ray BD-apex, distance between the bottom of the defect and the root apex; X-ray defect angle, width of the infrabony component.

Table 2. Clinical and radiographic parameters of the test group at baseline, 1 year and 5 years

	Baseline (n = 25)	1-year (n = 25)	$\Delta$ Baseline 1 year	Significance	5-years (n = 23)	$\Delta$ 1 year 5 years	Significance
PPD (mm)	12.7 $\pm$ 2.6	4 $\pm$ 1.7	8.8 $\pm$ 3	$p < 0.001$	3.4 $\pm$ 0.8	0.1 $\pm$ 0.7	$p = 0.186$
REC (mm)	2 $\pm$ 1.7	3.1 $\pm$ 1.8	- 1.1 $\pm$ 1.8	$p = 0.006$	3.2 $\pm$ 1.8	- 0.1 $\pm$ 0.4	$p = 0.919$
CAL (mm)	14.8 $\pm$ 2.2	7.1 $\pm$ 2.4	7.7 $\pm$ 2.8	$p < 0.001$	6.6 $\pm$ 2.1	0 $\pm$ 0.5	$p = 0.476$
X-ray CEJ-BD (mm)	16 $\pm$ 2.3	7.5 $\pm$ 2.7	8.5 $\pm$ 3.1	$p < 0.001$	6.7 $\pm$ 1.3	0.1 $\pm$ 0.4	$p = 0.219$

Averages and standard deviations calculated at the deepest inter-proximal site (either mesial or distal) of each experimental tooth.

Differences between baseline and 1 year and between 1 year and 5 years have been tested with the Student's *t*-test.

$\Delta$ , difference; PPD, probing pocket depth; REC, gingival recession; CAL, clinical attachment level; X-ray CEJ-BD, distance between cemento-enamel junctions and bottom of the defect.

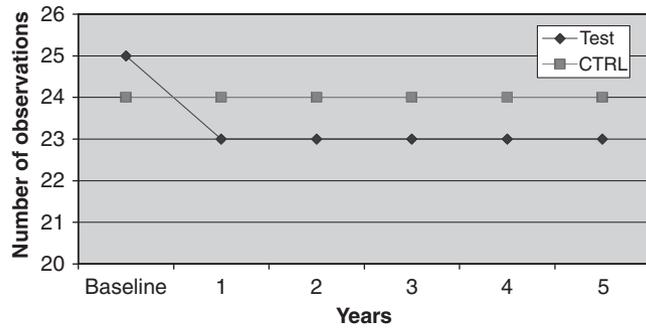


Fig. 3. Survival analysis. Comparison between hopeless test teeth treated with periodontal regeneration ( $N = 25$  at baseline) and replacement teeth at extraction sites of control hopeless teeth ( $N = 24$  at baseline): one extracted tooth of control group was not replaced for patients' choice). Survival at 5 years was 100% in the control group *versus* 92% in the test group.

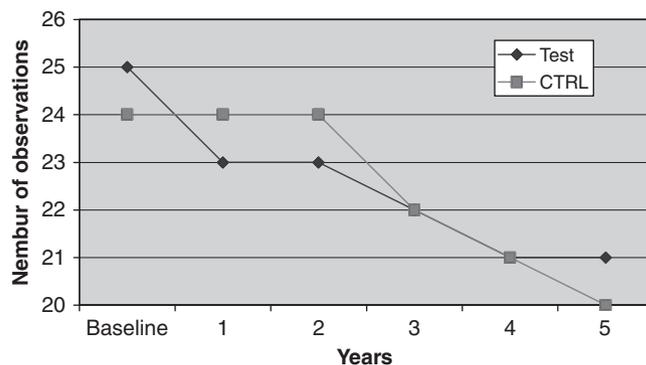


Fig. 4. Complication free units. Number of sites presenting without biological negative events from baseline to year 5 in the test ( $N = 25$ ) and in the control group ( $N = 24$ ). During the 5 years follow-up period 84% of test and 83% of control sites did not experience any negative event. "Negative events" were considered tooth loss, clinical attachment level (CAL) loss, bone loss or probing pocket depth (PPD) increase  $\geq 2$  mm.

increase (patient 4 at year 3 and patient 25 at year 5), while in patient 13 a PPD increase  $\geq 2$  mm was observed at year 3 (around teeth supporting a Maryland bridge) and in patient 6 a CAL loss  $\geq 2$  mm was observed at year 4 (around teeth supporting a bridge).

In the *test group*, a CAL loss of 2 mm was recorded in patient 3 after 3 years and a PPD increase  $\geq 2$  mm in patient 16 at 4 years.

The disease recurrences were treated with a non-surgical approach in all the cases. No further bone loss was observed at the implant sites, while in the natural teeth (both test and control) PPD reduction and CAL gain were recorded after treatment. All the other test and control elements showed clinical stability.

In the test group one vital tooth (patient 8) showed signs of pulp necrosis at year 4 and was root-canal treated. The resin splint broke in few patients (patients 1, 3, 8, 10) between 1 and 5 years and was repaired. In the control

group one Maryland bridge lost retention and was replaced at year 3. No other side effect or negative occurrences were reported between 1 and 5 years.

#### Control group: 5-year clinical conditions

At 5 years, in the control group, the abutment teeth of the eight tooth-supported bridges and the two Maryland bridges presented with shallow probing depth (PPD  $\leq 3$  mm) and stable clinical attachment level, with exception of patient 6 (CAL loss at year 4). The 14 implants had a radiographic bone level covering the first implant thread but implants in patients 4 and 25, due to the above described episodes of peri-implantitis.

#### Test group: 1 and 5 years clinical outcomes at regenerated sites

Individual patient data of the 25 experimental test units treated with periodontal regeneration is reported in Appendix S1.

Baseline radiographic and intra-surgical measures show that eight teeth presented with loss of periodontal support beyond or at the apex all around the tooth ( $360^\circ$ ), five teeth at three sides, seven teeth at two sides, and five teeth at one side. In 20 units out of 25 the bone destruction was beyond the tooth apex. The buccal bone plate was missing to or beyond the apex in 13 teeth, while in all the experimental units part of the lingual bony wall was present. In eight teeth the lingual plate formed no (two teeth) or shallow (six teeth) intra-bony component (1–2 mm); in the remaining 17 units the lingual intra-bony component ranged from 4 to 12 mm.

An important discrepancy between the CAL and the radiographic bone measures (9.7 mm) was observed at the mesial site of patient 1. At surgery, in this patient it was very clear the presence of some attached soft tissue at the coronal third of the mesial site of the experimental tooth: here the periodontal probe found its stop at baseline measurement. The bony defect, instead, extended from immediately below the attached soft tissue far beyond the apex of the tooth.

The 1-year clinical outcomes are reported in Table 2 and Appendix S1. Average CAL gain of  $7.7 \pm 2.8$  mm, radiographic bone gain of  $8.5 \pm 3.1$  mm, and pocket depth reduction of  $8.8 \pm 3$  mm were measured at the sites presenting with the baseline deepest interproximal defect of each experimental tooth (Table 2). Residual pocket depth at the deepest baseline interproximal defect side was  $4 \pm 1.7$  mm, on average.

All splinted teeth were de-splinted for an evaluation of the 1-year tooth mobility (Table 3). Most of the teeth showed a decrease in tooth mobility, with the exception of patients 21 and 22 that showed the same mobility as at baseline, and patients 14 and 17 that had no hypermobility at baseline. Eighteen teeth (72%) presented with degree 0 or 1, one with degree 3 and the remaining with degree 2. One tooth (patient 7, see Appendix S1) was orthodontically treated at 1 year for intrusion (Fig. 2h). Fixed definitive bridges were applied to four experimental teeth (patients 4, 5, 9, 11, see Appendix S1). A resin splint was reapplied to 10 teeth, while the remaining nine teeth remained non-splinted.

The 5-year clinical outcomes are reported in Table 2 and Appendix S1. There was no significant clinical and

Table 3. Tooth mobility and splinting of the test experimental teeth at baseline, 1 year and 5 years

Patient	Baseline		1 year		5 years		Outcome
	Mobility	Splint	Mobility	Splint	Mobility	Splint	
1	3	RS	2	RS	2	RS	Improved
2	3	RS	2	RS	2	RS	Improved
3	3	RS	1	RS	1	RS	Improved
4	3	FB	0	FB	–	FB	Resolved
5	3	FB	0	FB	–	FB	Resolved
6	3	RS	1	RS	1	RS	Improved
7	3	RS	2	RS	2	RS	Improved
8	3	RS	1	RS	1	RS	Improved
9	3	FB	0	FB	–	FB	Resolved
10	3	RS	2	RS	2	RS	Improved
11	2	FB	0	FB	–	FB	Resolved
12	3	RS	0	NS	0	NS	Resolved
13	2	RS	0	NS	0	NS	Resolved
14	0	NS	0	NS	0	NS	No change
15	3	RS	1	RS	1	RS	Improved
16	3	RS	2	RS	2	RS	Improved
17	0	NS	0	NS	0	NS	No change
18	3	RS	1	RS	1	RS	Improved
19	3	RS	1	NS	1	NS	Improved
20	2	NS	0	NS	0	NS	Improved
21	2	FB	2	–	–	–	Tooth extracted
22	3	RS	3	–	–	–	Tooth extracted
23	3	RS	1	NS	1	NS	Improved
24	2	RS	1	NS	1	NS	Improved
25	2	RS	0	NS	0	NS	Improved

Mobility of teeth included into definitive bridges could not be tested at 5 years. Teeth from patients 21 and 22 were extracted at 1 year. In terms of hypermobility, 15 teeth improved, six resolved, while two teeth had already degree 0 at baseline.

Mobility. Clinical score ranging from 0 to 3 (Miller 1943).

Splint. NS, no splint; RS, resin splint; FB, included into a fixed bridge.

statistical difference between the measures taken at 1 year and at 5 years at the deepest baseline defect site (Table 2) and at the four sites/tooth, with the exception of patients 3 and 16 (Appendix S1). The resin-splinted teeth were de-splinted for an evaluation of the 5-year tooth hypermobility (Table 3). There was no substantial difference with the records taken at 1 year, as well as for the non-splinted teeth. The teeth abutments of fixed bridges were not tested. A resin splint was reapplied to the 10 teeth previously splinted. The evaluation of tooth prognosis on the survived teeth (23 out of 25) resulted in scores overlapping the ones detected at 1 year with both methods.

## Discussion

This controlled clinical trial demonstrated that periodontal regenerative therapy can change the prognosis of clearly hopeless teeth due to the presence of deep intra-bony defects extending to or beyond the root apex.

Standard of care for these teeth calls for extraction in the context of the infection control phase of periodontal therapy: the presence of deep pockets and the minimal residual attachment are considered inadequate to maintain the tooth in health, comfort, and function (Mc Guire & Nunn 1996a, b, Bahrami et al. 2008, Pretzl et al. 2008). Control teeth were extracted and replaced with tooth- or implant-supported restorations. On the contrary, the test teeth were retained and treated with advanced periodontal regeneration: 23 out of 25 test teeth got an important clinical improvement, of such a magnitude that was able to change their prognosis at 1-year from a ‘‘hopeless’’ condition into a ‘‘maintainable’’ condition. The 23 improved teeth remained stable up to the 5-year evaluation. The two teeth that did not get a sufficient clinical improvement were declared ‘‘hopeless’’ and extracted at 1 year.

In terms of ability to retain the natural tooth, the test therapy showed a clear superiority over the control approach:

the tooth survival rate being 92% vs 0%. On the other side, the control treatment (tooth- or implant-supported prosthetic replacement of the extracted tooth) provided a 100% survival rate, while for the test the comparable figure was 92%.

The 5-year follow up period was uneventful for most of the test and control units. A similar amount of ‘‘complications’’ were encountered in both groups.

The clinical decision of retaining severely compromised teeth is based on complex considerations that allow the clinician to forecast the prognosis of the element under judgement. Most of the prognostication systems are based on tooth mortality (Hirschfeld & Wasserman 1978, Becker et al. 1984, McGuire & Nunn 1996a, b) and take into account mainly local factors. Lang and Tonetti (1996) proposed a system based on a continuous multilevel risk assessment. From this model, it is clear that the control of patient factors is on top of the general prognosis of the mouth, while local factors affect individual teeth. Further, the prognostication systems cannot be based on a single observation, but have to be continuously reconsidered, since the influencing factors could change over time. A similar approach has been recently proposed by Kwok & Caton (2007). From these evidences it is clear that retaining a tooth with a negative (‘‘hopeless’’) prognosis is potentially possible in a well-maintained patient. Furthermore, the retained hopeless teeth do not seem to negatively affect the remaining dentition (DeVore et al. 1988, Machtei et al. 1989, Wojcik et al. 1992, Machtei & Hirsch 2007). However, in spite of periodontal care a consistent number of these teeth are lost over time, and this negatively compares with the survival of most of the teeth with a baseline more favourable prognosis (Becker et al. 1984, McGuire & Nunn 1996a, b, Checchi et al. 2002, Bahrami et al. 2008, Eickholz et al. 2008, Huynh-Ba et al. 2009, Pretzl et al. 2009a, Chambrone et al. 2010, Leininger et al. 2010, Bäumer et al. 2011, Ng et al. 2011).

It is therefore clear that the possibility to change the prognosis of a tooth from ‘‘hopeless’’ into fair or favourable would greatly help clinicians and patients in the difficult job of maintaining teeth over time, and the possibility to gain periodontal support would help patients to improve their comfort and function.

Periodontal regeneration has been shown effective in the treatment of one-, two-, and three-wall intra-bony defects or combination thereof, from very deep to very shallow defects, from very wide to very narrow ones (for a review, see Murphy & Gunsolley 2003, Needleman et al. 2006, Esposito et al. 2009). We know today that most of the failures of regenerative therapy have an explanation in terms of negative patient factors, sub-optimal use of surgical approaches and materials, and insufficient clinical skill and experience of the surgeon (Tonetti et al. 1993, 1995, 1996a, 1998, 2002, 2004, Cortellini et al. 1995a, 1999a, 2001, Sanz et al. 2004). To overcome the cited problems, a clinical strategy has been proposed to optimize the clinical outcomes in the different defect anatomies (Cortellini & Tonetti 2000, 2005). Some of the published experimental populations report successful periodontal regeneration applied to teeth severely compromised (Cortellini et al. 1995a, b, Tonetti et al. 1996b, Cortellini & Tonetti 2001, Slotte et al. 2007).

The present study shifts the edge of the regenerative potential to an extreme limit of periodontal involvement, up to teeth that have lost the periodontium all around the root and beyond the root apex, to a point that it is difficult to set a limit to the regenerative potential of periodontally compromised teeth. In addition, the present study shows that hopeless teeth successfully treated with regeneration can be maintained over a period up to 5 years, in health and function.

It should be well underlined that the reported outcomes have been obtained in a carefully selected patient population, applying ‘‘the state of the art’’ of regenerative therapy by very experienced clinicians, within a high quality program of periodontal and dental therapy and a strict periodontal supportive care program. This is in agreement with the long-term studies following periodontal regeneration that report stability of the outcomes over time in patients who do not smoke and comply with a regular periodontal supportive care program (Cortellini et al. 1994, 1996, 1999b, Cortellini & Tonetti 2004, Sculean et al. 2008, Pretzl et al. 2009b, Nygaard-Østby et al. 2010).

These are all key issues for clinicians, since the clinical decision of retaining or not retaining a tooth with severe periodontal destruction is taken by the thera-

pist in the light of his/her educational background, the scientific evidence, the strategy for the treatment planning of the case, the personal skill and experience and a cost/benefit analysis in the short and long-term run. The outcomes of the present study, therefore, challenge an approach based on extraction and prosthetic replacement of compromised teeth (Kao 2008). Periodontal regeneration could help clinicians to retain teeth.

The following conclusions can be drawn from the present study:

1. Regenerative periodontal therapy resulted in favourable clinical healing even in hopeless teeth, presenting with bone loss at or beyond the root apex.
2. Regeneration led to retention of 92% hopeless teeth scheduled for extraction and improved their prognosis. Retained teeth had clinically-stable periodontal parameters, comfort and function for a 5-year period.
3. Both implant- and tooth-supported reconstructive therapies were successful in replacing the hopeless extracted teeth and maintaining comfort and function over 5-year.
4. Periodontal regeneration is a suitable alternative to tooth extraction in teeth compromised by extremely severe intra-bony defects.

#### Acknowledgements

This study was partly supported by the European Research Group on Periodontology (ERGOperio), Berne, Switzerland.

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## Supporting Information

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

**Appendix S1.** Individual patient data of the 25 test experimental units. The table reports baseline patient, treatment and defect characteristics (at 4 sites/tooth) and the differences between baseline and 1 year and between 1 year and 5 years in terms of CAL and radiographic bone level for the mesial and distal sides and CAL only for the buccal and lingual ones. Teeth # 21 and 22 have been extracted after the 1-year examination visit.

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## Clinical Relevance

**Scientific rationale for study:** This study tested a potential alternative to extraction of hopeless teeth and explored the limits of periodontal regeneration in changing the prognosis of hopeless teeth.

**Principal findings:** Application of regenerative therapies to hopeless teeth resulted into improved prognosis of 23 out of 25 experimental units. The 23 regenerated teeth showed clinical stability for a period of 5 years as well as the replaced units in the control patients.

**Practical implications:** Periodontal regeneration is a suitable alternative to extraction and replacement of severely compromised teeth with intra-bony defects extending to the root apex or beyond.

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