CLINICAL ORAL IMPLANTS RESEARCH

Marco Degidi
Diego Nardi
Adriano Piattelli

A comparison between immediate loading and immediate restoration in cases of partial posterior mandibular edentulism: a 3-year randomized clinical trial

Authors' affiliations:
Marco Degidi, Diego Nardi, Private Practice Bologna, Italy
Adriano Piattelli, Dental School, University of Chieti-Pescara, Chieti, Italy

Corresponding author:
Prof. Adriano Piattelli
Dental School, University of Chieti-Pescara,
Via F. Sciucchi 63
66100 Chieti
Italy
Tel.: +39 0871 3554076
Fax: 011 39 0871 3554076
e-mail: apiattelli@unich.it

Key words: clinical research, clinical trials, prosthodontics, soft tissue–implant interactions

Abstract

Objective: The aim of this study was to compare the survival rate, the bone loss and soft-tissue healing patterns of immediately loaded and immediately restored implants in cases of partial posterior mandibular edentulism.

Material and methods: Fifty patients with partial posterior mandibular edentulism were randomly selected for two treatments: 25 were included in the immediate loading group (test) and 25 in the immediate restoration group (control). All implants were placed in healed sites with a torque of >25 N cm. The temporary prosthesis of the immediate restoration group was placed so as to avoid occlusal contact in centric and lateral excursions. Both groups received fully occluding final restorations 6 months after surgery. Mean marginal bone loss was assessed at 6-, 12-, 24- and 36-month follow-up examinations by a blinded examiner.

Results: A total of 100 implants were placed in the period between February 2004 and October 2006, of which 42 (42%) were for men and 58 (58%) for women. Five and 7 weeks after surgery, mobility of one implant was assessed in one (4%) patient in the test group and one (4%) patient in the control group, respectively. At the 36-month follow-up, the accumulated mean marginal bone loss was 0.987 mm (SD = 0.375) for the immediate restoration group ($n = 48$) and 0.947 mm (SD = 0.323) for the immediate loading group ($n = 48$). There was no statistically significant difference ($P > 0.05$) for the tested outcome measures between the two procedures.

Conclusions: This study was unable to detect any statistically significant difference in the survival rate, bone loss and soft tissue healing patterns between the immediately loaded and the immediately restored implants in cases of partial posterior mandibular edentulism. The immediate temporary rehabilitation of the partially edentulous posterior mandible is a predictable procedure using both procedures.

Date:
Accepted 5 December 2009

To cite this article:
Degidi M, Nardi D, Piattelli A. A comparison between immediate loading and immediate restoration in cases of partial posterior mandibular edentulism: a 3-year randomized clinical trial.
Clin. Oral Impl. Res. **21**, 2010; 682–687.
doi: 10.1111/j.1600-0501.2009.01910.x

The rehabilitation of the partially edentulous posterior mandible with immediately loaded, standard diameter implants, in cases when there is a suitable bone volume and quality, has been proposed by many authors (Glauser et al. 2001, 2005, 2007; Cannizzaro & Leone 2003; Testori et al. 2003; Degidi et al. 2006; Achilli et al. 2007; Schincaglia et al. 2007; Galli et al. 2008; Ganeles et al. 2008). Severe chewing forces and bruxism are considered to be significant factors that may compromise the effectiveness of this treatment option (Glauser et al. 2001), as parafunctional activity in the posterior regions of the mouth has been reported as an etiological factor closely

related to implant failure (Balshi 1996; Piattelli et al. 1998; Jaffin et al. 2007). In order to reduce the early risks of mechanical overload, some authors have proposed to modify the immediate temporary restoration to avoid occlusal contact in centric and lateral excursions (Misch 1998; Testori et al. 2003; Achilli et al. 2007; Degidi et al. 2009a). The thus-modified restoration is still involved in the chewing process, but the mechanical loading stress is reduced. Using non-occluding temporary restorations supported by immediately restored implants, a recent study (Galli et al. 2008) concluded that there were no statistically or clinically significant differences between immediate and early loading of dental implants with regard to peri-implant bone and soft tissue levels. Using two to four immediate temporary tooth restorations that were out of occlusal contact, Ganeles et al. (2008) demonstrated a safe and predictable outcome, with survival rates comparable with those for conventional or delayed loading, even with poor-quality bone.

A study group, however, reported a successful outcome for the immediate rehabilitation of the partial edentulous mandible using temporary restorations placed under a fully occlusal load (Glauser et al. 2001, 2005, 2007). One study (Cannizzaro & Leone 2003) also reported that immediate fully occlusal loading of partial restoration supported by micro-textured implants in partially edentulous patients demonstrated excellent clinical results, with no adverse periodontal consequences after 24 months of function in highly motivated patients with excellent oral hygiene.

A recent systematic review analyzed the correlation between the indications for immediate loading of implants and implant success (Nkenke & Fenner 2006). The authors assessed that several different approaches to immediate loading could lead to survival rates in controlled studies comparable with those of conventionally loaded implants, but also that it was not possible to draw conclusions on the relevance of immediate functional loading and immediate non-functional loading under certain conditions.

Another systematic review of marginal soft tissue at implants subjected to immediate loading or immediate restoration (Glauser et al. 2006) concluded that once immediately loaded or restored, implants integrated successfully showed a soft tissue reaction comparable with those of the conventionally loaded implants and that no evidence suggested that peri-implant mucosal complications could be directly attributed to immediate loading or restoration protocols.

The aim of this randomized clinical trial was to compare the survival rate, bone loss and soft tissue healing patterns of immediately loaded and immediately restored implants in cases of partial posterior mandibular edentulism, in order to verify the hypothesis that the full occlusal load would compromise or jeopardize the osseointegration process.

Material and methods

The present randomized clinical trial included patients aged 18 years or more with partial posterior mandibular edentulism. The condition of the opposing dentition was not considered to be a discriminating factor. This study was designed and conducted in full accordance with the World Medical Association Declaration of Helsinki, as revised in 2002. All patients signed a specific written informed consent form. Each of them received a fixed temporary restoration that was attached to two 3.4- or 3.8-mm-diameter parallel screw, grit-blasted and acid-etched implants with an internal hexagonal connection (XiVe Plus, DENTSPLY-Friadent, Mannheim, Germany) positioned in a partially edentulous posterior mandible. Patients were not included in the study if they met any of the following exclusion criteria: (1) active infection in the sites intended for implant placement; (2) systemic disease that could compromise osseointegration; (3) treatment with radiation therapy in the craniofacial region within the previous 12 months; (4) if they smoked >10 cigarettes per day; (5) pregnancy or lactation; (6) presence of bruxism signs or symptoms, as worn occlusal facets or myalgia; and (7) unsuitable quantity of bone in the surgery site or need for bone augmentation procedures before implant placement. All implants were placed in healed sites by one experienced surgeon (M.D.) in a private dental office in Bologna, Italy.

During the implant placement procedure, the insertion torque and the implant stability quotient (ISQ) were registered by a surgical unit (FRIOS Unit E, W&H Dentalwerk GmbH, Buermoos, Austria) and a digital measurement probe (Osstell AB, Gamlestadsvägen 3B, Göteborg, Sweden). Patients were excluded from the study if any of the implants lacked good primary stability by meeting one of the following exclusion criteria: (1) insertion torque <25 N cm and (2) an ISQ of <60.

Sample size was based on a comparison of the number of single mandibular implants placed to support a multiple-implant partial restoration that was likely to fail using the immediate loading and the immediate restoration approach. Average implant failure percentages were retrieved from the most recent literature and analyzed using a computer software program (Quick Calc, GraphPad Software Inc., Avenida de la Playa, La Jolla, CA, USA) with the following results: an average 1.5% of control subjects – immediate restoration – (Achilli et al. 2007; Galli et al. 2008; Ganeles et al. 2008; Degidi et al. 2009a, 2009b) and 3.7% of experimental subjects – immediate loading – (Glauser et al. 2001, 2005, 2007; Cannizzaro & Leone 2003) had an implant failure, with an absolute risk increase of 2.2%. This resulted in a sample size of 46 subjects, meaning that about one in every 46 single immediate implants in each group was expected to fail. This number was increased to 50 implants to compensate for possible drop-outs. Cases were randomized following a locked list created with a non-repeatable computerized random number generator (Quick Calc, GraphPad Software Inc.). As a minimum of 50 implants were necessary to obtain a reliable result, we assigned 25 patient subjects with two implants per person to each of the two groups. The random number generator is seeded with the time of day and displays a different number/letter combination each time. Each subject is first assigned to a group non-randomly. Then the assignment of each subject is swapped with the group assignment of a randomly chosen subject. This process is automatically repeated twice.

Preoperative analysis of anatomical features was performed with panoramic radiography. Impressions were made of the maxilla and mandible, and laboratory casts were made. The shade and mold of

the prosthetic teeth were selected and appropriate wear-resistant commercial denture teeth (Vita Physiodens, Vita Zahnfabrik, H. Rauter GmbH & Co. KG, Bad Säckingen, Germany) were chosen. Two or three teeth were arranged on a cast mounted on a semi-adjustable articulator and joined with an auto-polymerizing acrylic resin to create the temporary restoration.

Anti-microbial prophylaxis was performed with the use of 500 mg β-lactam antibiotic (Amoxicillin, Pfizer Manufacturing, Puurs, Belgium) twice daily for 5 days, starting 1 h before surgery. Local anesthesia (2% articaine/adrenaline 1:100,000) was administered at the time of surgery. Surgery began with a mid-crestal incision, a full-thickness flap was elevated and the crestal ridge was exposed. Two implants were placed using a surgical template with the smooth crestal collar positioned 0.5 mm above the alveolar crest. If both implants fulfilled the inclusion criteria, the abutments were splinted using the intra-oral welding technique (Degidi et al. 2009a), the temporary acrylic restoration was relined in position with a small quantity of auto-polymerizing acrylic resin and the correct vertical dimension was checked. The restoration was then removed from the oral cavity, completely filled with heat-processed acrylic, trimmed, polished and reinserted. The restoration was connected to the abutments by tightening the titanium retaining screws with 20 N cm of torque. Screw holes were closed with a light-cured composite resin. The soft tissue was positioned around the abutments and sutured into place. A consecutive number was then assigned to the case, and the randomization list was checked to verify in which group the case number was allocated.

Twenty-five patients underwent the immediate restoration procedure. The temporary restoration was carefully modified to avoid occlusal contact in centric and lateral excursions.

Twenty-five patients underwent the immediate loading procedure. The temporary restoration was not modified, leaving the prosthesis under a full occlusal load.

Instructions for oral hygiene were given, and patients were instructed to have a soft diet for 8 weeks. Sutures were removed 14 days after surgery (Figs 1 and 2). Twenty weeks after implant insertion, the provisional restoration was removed, implant mobility was checked, pocket probing depth was assessed and final impressions were recorded using polyether impression material (Impregum, 3M-Espe, St. Paul, MN, USA). The final fully occluding restoration was delivered approximately 6 months after implant insertion.

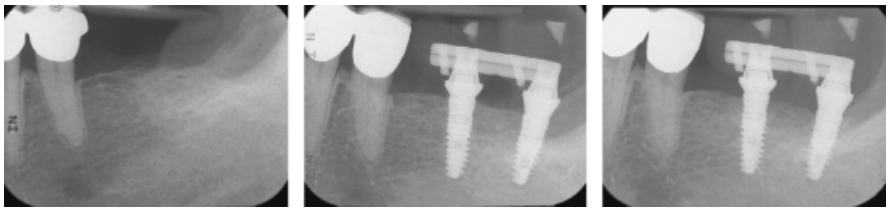

Fig. 1. Test case, periapical radiograph before surgery, after surgery and 6 months after surgery.

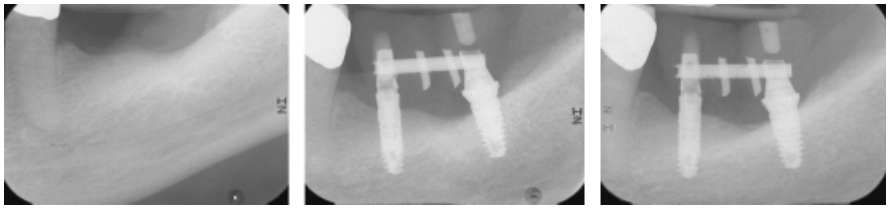

Fig. 2. Control case, periapical radiograph before surgery, after surgery and 6 months after surgery.

The following observations were made:

- Implant survival is defined as the presence of the implant at the time of follow-up examinations.
- Changes in marginal peri-implant bone level, defined as the modification of the distance between the implant–abutment junction and the highest coronal point of the supporting bone, were assessed using periapical radiographs taken with a customized positioning jig. Each periapical X-ray was digitized with a scanner (Epson Expression 1680 Pro, Epson Italia, Cinisello Balsamo, Milano, Italy) and coded with a computerized random list generator (Quick Calc, GraphPad Software Inc.). Each coded image was then analyzed with measurement software (Meazure® 2.0 build 158, C Thing Software, Sunnyvale, CA, USA) using platform height and implant length as double cross references (Jaffin et al. 2007).
- Level of marginal gingiva was assessed 20 weeks after implant insertion, with mesial, buccal and distal probing depth measurements taken using a pressure of 0.15 N, frequency of bleeding on probing.
- Biological or technical complications, adverse events.

The frequency of the follow-up was:

- T0: after surgery and fitting of the immediate temporary restoration;
- T1: fitting of the final restoration – 6 months after surgery;
- T2: final restoration follow-up – 1 year after surgery;
- T3: final restoration follow-up – 2 years after surgery; and
- T4: final restoration follow-up – 3 years after surgery.

Statistical analysis

Statistically significant mean marginal bone loss at each follow-up and probing depth difference 20 weeks after implant insertion were assessed using the two-sample *t*-test with a 95% confidence interval ($P<0.05$).

Results

A total of 100 implants were placed in the period between February 2004 and October 2006. The mean age of the patients at the time of surgery was 45.1 years (SD = 9.1; $n=50$). Twenty-nine (58.0%) and 21 (42.0%) restorations were, respectively, placed in an equal number of female and male patients. All the restorations were placed in the far posterior position and had no teeth distal to them. The average insertion torque and ISQ values are listed

in Table 1. At the 36-month follow-up, the accumulated mean marginal bone loss was 0.987 mm (SD = 0.375) for the immediate restoration group ($n = 48$) and 0.947 mm (SD = 0.323) for the immediate loading group ($n = 48$). No statistically significant mean marginal bone loss difference and pocket probing depth ($P < 0.05$) were found. The radiographic evaluations and the level of marginal gingiva are summarized in Tables 2 and 3.

Similar early biological complications were recorded in two patients (Table 4). Five and 7 weeks after surgery, respectively, one female patient (4%) in the test group and one male patient (4%) in the control group reported swelling, discomfort and pain in the surgical site. The restorations were carefully removed, and mobility of one implant was observed. The mobile implant was removed and the patient underwent an anti-microbial cycle, consisting of 500 mg β-lactam antibiotic (Amoxicillin, Pfizer Manufacturing) twice daily for 5 days.

Both cases were classified as implant failures and were excluded from the study. Three months after the implant removal, both patients underwent surgery again. A new implant was inserted into the healed site and immediately restored with a newly made temporary restoration. Six months after the second operation, both patients were provided with a final restoration.

***Table 1.* Average insertion torque and ISQ values**

	Test group	Control group
Torque (N cm)	30.5 (SD 9.1)	28.7 (SD 5.2)
ISQ (T0, surgery)	65.9 (SD 7.2) ($n = 50$)	66.1 (SD 8.6) ($n = 50$)
ISQ (T1, 6 months)	74.1 (SD 9.1) ($n = 48$)	78.1 (SD 9.3) ($n = 48$)

ISQ, implant stability quotient.

***Table 2.* Mean measurements of bone loss pattern**

Follow-up range	Mean (mm)	Standard deviation	Median
Immediate restoration, control group ($n = 48$)			
From T0 to T1	0.498	0.192	0.46
From T1 to T2	0.213	0.133	0.2
From T2 to T3	0.152	0.195	0.09
From T3 to T4	0.123	0.149	0.09
From T0 to T4	0.987	0.375	0.91
Immediate loading, test group ($n = 48$)			
From T0 to T1	0.5	0.2	0.47
From T1 to T2	0.188	0.119	0.17
From T2 to T3	0.113	0.097	0.11
From T3 to T4	0.145	0.158	0.11
From T0 to T4	0.947	0.323	0.89

Follow-up range	Control group mean (mm)	Test group mean (mm)	*P*-value
Significant differences between the means of the two groups: two-sample *t*-test *P*-values			
From T0 to T1	0.498	0.5	0.9608
From T1 to T2	0.213	0.188	0.3342
From T2 to T3	0.152	0.113	0.2178
From T3 to T4	0.123	0.145	0.4846
From T0 to T4	0.987	0.947	0.5768

***Table 3.* Mean measurements of pocket probing depth and bleeding on probing frequency**

Immediate restoration PPD (mm), control group			Immediate loading PPD (mm), test group		
Mean	Median	BOP	Mean	Median	BOP
1.612 (SD 0.312) ($n = 48$)	1.59	18.1%	1.601 (SD 0.204) ($n = 48$)	1.57	19.1%
Significant differences between the means of the two groups: two-sample *t*-test *P*-values					
Control group mean			Test group mean		*P*-value
1.612 mm			1.601 mm		0.8384

BOP, bleeding on probing; PPD, pocket probing depth.

Discussion

The results of our study showed that there was no significant difference between immediately loaded and immediately restored implants regarding survival rate and biological response of the peri-implant tissues complex in the medium term. Both soft tissue and bone healed in a very similar way, in keeping with the observations already published regarding the restoration of the partially edentulous posterior mandible with immediately loaded, standard-diameter implants. The increase of load, applied to the prosthesis caused by the presence of the normal occlusal contact, seems to be unable to jeopardize or alter the healing process of the implant. Some factors may have contributed to this outcome: the use of a resilient acrylic resin for the fabrication of the temporary restoration, the exclusion of parafunctional bruxist patents and the immediate splinting provided by the intra-oral welding technique.

The biological differences in peri-implant tissue responses between immediately loaded and immediately restored implants were already analyzed in animal models. Meyer et al. (2003, 2004) did not observe any difference between the ultrastructural morphology of the cells at the

***Table 4.* Adverse events**

Gender	Age at surgery (years)	Implant failed (mm)	Mandible site	Reason for failure	Time of failure
Male	53	3.4–13	First molar 3.6	Mobile implant – failed to integrate	7 weeks after surgery
Female	39	3.4–13	Second molar 3.7	Mobile implant – failed to integrate	5 weeks after surgery

interface in occlusally loaded implants and non-occlusally loaded implants in the early phases of the osseointegration. A dog study (Ghavanati et al. 2006) compared implants loaded after 2 days and after 1 week with unloaded control implants and did not find statistically significant differences in the bone-to-implant contact percentages of the three groups.

A recently published human case report (Degidi et al. 2009b) reported on the histological and histomorphometrical analysis of the bone–titanium interface in implants with and without occlusal contact. The implants were placed in a split-mouth configuration in the single first molar position in the mandible of the same patient, and they were retrieved after a healing period of 5 weeks. The authors reported that both implants were stable, surrounded by newly formed bone lamellae and no differences were found in the histological response of the two implants.

The population of this study was homogeneous, came from a similar socio-economic background and was highly motivated and well trained with regard to oral hygiene. The age of the patients ranged from 35 to 54 years, with a mean age of 45.1 years (SD = 9.1; $n = 50$), although the inclusion criteria accepted patients as young as 18 years. An age range of 19 years could be considered a bias due to the possible differences in tissue healing capabilities, but it was necessary to achieve the desired sample size. Age, gender, smoking and the condition of the opposing dentition were not considered in the generation of the random list. The analysis of the failed cases was unable to detect any element that could explain the implant failure.

The results of our study suggest that the presence of the full occlusal load in the partially edentulous posterior mandible does not compromise the osseointegration process of two immediately splinted implants and that the first months after surgery are the most critical for the success of an immediate rehabilitation; indeed, both failures recorded in our study were assessed in the very early phase of the healing period.

Conclusions

This study was unable to detect any statistically significant difference in the survival rate, bone loss and soft tissue healing patterns between the immediately loaded and the immediately restored implants in cases of partial posterior mandibular edentulism. The immediate temporary rehabilitation of the partially edentulous posterior mandible is a predictable procedure using both procedures. This study had a 3-year follow-up, and further clinical studies with a longer follow-up will be necessary to confirm our results.

Acknowledgements: The authors would like to thank Mr. Gianluca Sighinolfi, dental technician, private practice, Bologna, Italy, for his invaluable technical support. The authors have no commercial or financial relationship that may pose a conflict of interest or a potential conflict of interest.

References

Achilli, A., Tura, F. & Euwe, E. (2007) Immediate/early function with tapered implants supporting maxillary and mandibular posterior fixed partial dentures: preliminary results of a prospective multicenter study. *Journal of Prosthetic Dentistry* **97** (Suppl. 1): 52–58. Erratum in: Journal of Prosthetic Dentistry (2008) **99**: 167.

Balshi, T.J. (1996) An analysis and management of fractured implants: a clinical report. *The International Journal of Oral & Maxillofacial Implants* **11**: 660–666.

Cannizzaro, G. & Leone, M. (2003) Restoration of partially edentulous patients using dental implants with a microtextured surface: a prospective comparison of delayed and immediate fully occlusal loading. *The International Journal of Oral & Maxillofacial Implants* **18**: 512–522.

Degidi, M., Nardi, D. & Piattelli, A. (2009a) Immediate restoration of small-diameter implants in cases of partial posterior edentulism: a 4-year case series. *Journal of Periodontology* **80**: 1006–1012.

Degidi, M., Perrotti, V. & Piattelli, A. (2006) Immediately loaded titanium implants with a porous anodized surface with at least 36 months of follow-up. *Clinical Implant Dentistry & Related Research* **8**: 169–177.

Degidi, M., Piattelli, A., Shibli, J.A., Perrotti, V. & Iezzi, G. (2009b) Early bone formation around immediately restored implants with and without occlusal contact: a human histologic and histomorphometric evaluation. A case report. *The International Journal of Oral & Maxillofacial Implants* **24**: 734–739.

Galli, F., Capelli, M., Zuffetti, F., Testori, T. & Esposito, M. (2008) Immediate non-occlusal vs. early loading of dental implants in partially edentulous patients: a multicentre randomized clinical trial. Peri-implant bone and soft-tissue levels. *Clinical Oral Implants Research* **19**: 546–552.

Ganeles, J., Zöllner, A., Jackowski, J., ten Bruggenkate, C., Beagle, J. & Guerra, F. (2008) Immediate and early loading of Straumann implants with a chemically modified surface (SLActive) in the posterior mandible and maxilla: 1-year results from a prospective multicenter study. *Clinical Oral Implants Research* **19**: 1119–1128.

Ghavanati, F., Shayeg, S.S. & Rahimi, H., et al. (2006) The effect of loading time of osseointegration and new bone formation around dental implants. A histologic and histomorphometric study in dogs. *Journal of Periodontology* **77**: 1701–1707.

Glauser, R., Rée, A., Lundgren, A., Gottlow, J., Hämmerle, C.H. & Schärer, P. (2001) Immediate occlusal loading of Brånemark implants applied in various jawbone regions: a prospective, 1-year clinical study. *Clinical Implant Dentistry & Related Research* **3**: 204–213.

Glauser, R., Ruhstaller, P. & Windisch, S., et al. (2005) Immediate occlusal loading of Brånemark System TiUnite implants placed predominantly in soft bone: 4-year results of a prospective clinical study. *Clinical Implant Dentistry & Related Research* **7** (Suppl. 1): 52–59.

Glauser, R., Zembic, A. & Hammerle, C.H.F. (2006) A systematic review of marginal soft tissue at implants subjected to immediate loading or immediate restoration. *Clinical Oral Implants Research* **17** (Suppl. 2): 82–92.

Glauser, R., Zembic, A., Ruhstaller, P. & Windisch, S. (2007) Five-year results of implants with an oxidized surface placed predominantly in soft quality bone and subjected to immediate occlusal loading. *Journal of Prosthetic Dentistry* **97** Suppl. 1): 59–68. Erratum in: *Journal of Prosthetic Dentistry* (2008) **99**: 167.

Jaffin, R.A., Kolesar, M., Kumar, A., Ishikawa, S. & Fiorellini, J. (2007) The radiographic bone loss pattern adjacent to immediately placed, immediately loaded implants. *The International*

Journal of Oral & Maxillofacial Implants **22**: 187–194.

Meyer, U., Joos, U. & Mythili, J., et al. (2004) Ultrastructural characterization of the implant/bone interface of immediately loaded dental implants. *Biomaterials* **25**: 1959–1967.

Meyer, U., Wiesmann, H.P., Fillies, T. & Joos, U. (2003) Early tissue reaction at the interface of immediately loaded dental implants. *International Journal of Oral & Maxillofacial Implants* **18**: 489–499.

Misch, C.E. (1998) Nonfunctional immediate teeth. *Dentistry Today* **17**: 88–91.

Nkenke, E. & Fenner, M. (2006) Indications for immediate loading of implants and implant success. *Clinical Oral Implants Research* **17** (Suppl. 2): 19–34.

Piattelli, A., Scarano, A., Piattelli, M., Vaia, E. & Matarasso, S. (1998) Hollow implants retrieved for fracture: a light and scanning electron microscope analysis of 4 cases. *Journal of Periodontology* **69**: 185–189.

Schincaglia, G.P., Marzola, R., Scapoli, C. & Scotti, R. (2007) Immediate loading of dental implants supporting fixed partial dentures in the posterior mandible: a randomized controlled split-mouth study-machined versus titanium oxide implant surface. *The International Journal of Oral & Maxillofacial Implants* **22**: 35–46.

Testori, T., Bianchi, F. & Del Fabbro, M., et al. (2003) Immediate non-occlusal loading vs. early loading in partially edentulous patients. *Practical Procedures Aesthetic Dentistry* **15**: 787–794.

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.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.