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# IMMEDIATE, EARLY (6 WEEKS) AND DELAYED LOADING (3 MONTHS) OF SINGLE, PARTIAL AND FULL FIXED IMPLANT-SUPPORTED PROSTHESES: THREE-YEAR POST-LOADING DATA FROM A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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**PURPOSE.** To compare the clinical outcomes of single, partial and complete fixed implant-supported prostheses immediately loaded (within 48 hours), early loaded at 6 weeks, and conventionally loaded at 3 months (delayed loading).

**MATERIALS AND METHODS.** Fifty-four patients (18 requiring single implants, 18 partial fixed prostheses, and 18 total fixed cross-arch prostheses) were randomised in equal numbers in two private practices to immediate loading (18 patients), early loading (18 patients), and conventional loading (18 patients) according to a parallel group design with three arms. To be immediately or early loaded, implants had to be inserted with a torque superior to 40 Ncm. Implants were initially loaded with provisional prostheses, replaced after 4 months by definitive ones. Outcome measures were prosthesis and implant failures, complications and peri-implant marginal bone levels.

**RESULTS.** Two conventionally loaded patients rehabilitated with cross-arch fixed total prostheses dropped-out before 3-year post-loading follow-up. No implant failed. One early-loaded partial prosthesis had to be remade (P = 1.0). Three complications occurred in the immediately loaded group, two in the early-loaded and one in the conventionally loaded group with no statistically significant differences across groups (P = 0.861). Peri-implant marginal bone loss was -0.04 ± 0.85 mm at immediately loaded implants, -0.01 ± 0.55 mm at early-loaded implants and 0.33 ± 0.36 mm at conventional loaded implants with no statistically significant differences between the three loading strategies (P=0.191).

**CONCLUSIONS.** All loading strategies were highly successful, and no differences were observed in terms of implant survival and complications when implants were loaded immediately, early or conventionally.

**CONFLICT OF INTEREST STATEMENT.** This trial was partially funded by MegaGen (Gyeongbuk, South Korea), the manufacturer of the implants evaluated in this investigation; however, data belonged to the authors and the manufacturer by means interfered with the conduct of the trial or the publication of its results.

## INTRODUCTION

Osseointegrated dental implants are traditionally placed following a two-stage protocol[1], in which implants are left to heal unloaded for 3 to 4 months in mandibles and 6 to 8 months in upper jaws. Successful osseointegrated dental implants are anchored directly to bone. However, in the presence of movement, a soft-tissue scar tissue may encapsulate the implant, causing its failure[2]. It has been recommended to keep the implants load-free during the bone healing process to minimize the risk of soft-tissue encapsulation[1].


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This traditional approach requires longer treatment periods, and, according to the procedures used, a second surgical intervention may be needed to uncover submerged implants to allow abutment fitting. However, initial attempts to load implants earlier than the traditional protocols were associated with increased failure rates[1]. Removable prostheses are often used during the implant healing period, but many patients find these temporary prostheses uncomfortable. It would therefore be beneficial for patients if the healing period could be shortened without jeopardizing implant success.

In 1990, the first longitudinal study suggesting that implants could be loaded immediately or early in mandibles of selected patients was published[3]. Nowadays, implants are commonly loaded immediately and early, particularly in fully edentulous mandibles with good bone quality. A Cochrane systematic review suggested that there was no convincing evidence of a clinically significant difference in prosthesis failure, implant failure, or bone loss associated with different loading times of implants[4]. However, the review also stressed that the quality of the evidence was scored as being very low, and that there is some evidence of reporting bias, so clinicians should treat these findings with caution[4]. Indeed, immediately[5,6] and early[7] loaded implants have occasionally been associated with clinically significant increased failure rates; it is therefore important to evaluate whether predictable results can also be obtained when loading dental implants immediately or early in different clinical situations (i.e., missing single tooth, partial and full edentulism).

The aim of this randomised controlled trial (RCT) of parallel group design with three arms was to compare the effectiveness of immediate loading, within 48 hours (test group 1), *versus* early loading (test group 2), at 6 weeks, *versus* delayed (or conventional) loading, at 3 months (control group). Immediate loading was defined as seating a provisional prosthesis within 48 h of implant placement. Early loading was defined as seating a provisional prosthesis 6 weeks after implant placement, and delayed loading as seating a provisional prosthesis 3 months after implant placement.

Groups were also balanced for type of edentulism; three subgroups of identical numbers of patients requiring the replacement of a single tooth, partial edentulism and full edentulism, respectively, were included. The null hypothesis was that there would be no difference in clinical outcomes between the three procedures, against the alternative hypothesis of a difference.

This report presents data at 3-year post-loading. At the protocol stage, it was planned to follow-up these patients to the third year of function. The present article is reported in line with the CONSORT statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/). Previous publications presented the 4-month[8] and the 1-year[9] post-loading data. More specifically, the 4-month publication[8] presented the data from three centres with a total of 81 patients; however, one of the three centres failed to submit any data regarding the 1-year follow-up[9], and after repeated requests, it was decided to exclude this centre. The full data from the excluded centre has been described in the previous publication[8]. Finally, due to some minor mistakes in the imputation of the baseline radiographic data presented in the 1-year publication[9], there are minor differences in the radiographic data presented in this publication update.

## MATERIALS AND METHODS

### Study design

This was a multicentre randomised controlled trial (RCT) of parallel group design with three arms, balanced randomisation and blind assessment. After implant placement, patients with single, partial or full edentulism were randomised in equal numbers into three groups according to a parallel group design: immediately loading (within 48 hours), early loading at 6 weeks, and conventional loading at 3 months (delayed loading).

Patients were recruited and treated in two private dental clinics located in Larissa, Greece, and Rome, Italy, both having extensive experience with immediate loading procedures. Originally five centres agreed to participate in the study, but two centres withdrew before initiating the study without treating any patient, and the third centre only provided data up to 4-month post-loading[8]. One experienced dentist at each centre performed all the procedures.

## Inclusion and exclusion criteria

Any partially or fully edentulous patient requiring at least one implant supported prosthesis was eligible for inclusion in this trial, provided that they were 18 years of age or older and able to understand and sign an informed consent form. Only patients allowing placement of one or more implants with minimal dimensions of 7.0 x 3.5 mm were included. A maximum of six implants were to be placed in an edentulous jaw. All patients received thorough explanation and signed an informed written consent form prior to being enrolled in the trial to document that they understood the scope of the study (including procedures, follow-up assessments, and any potential risks involved). Patients were allowed opportunities to ask questions pertaining to this investigation, and were fully apprised of treatment alternatives. The study was open to qualifying patients without regard to sex or race. For patients requiring more than one prosthesis, operators were free to choose the one to be included in the study at the screening appointment. Only one prosthesis per patient was included in the study. Pre-operative radiographs (periapical, panoramic, cone-beam CT scans or other radiographical examinations, at the discretion of the operators) and clinical examination were used to determine bone volumes and anatomical landmarks.

Patients were not accepted onto the study if any of the following exclusion criteria was applicable:

- General contraindications to implant surgery;
- Irradiation to head and/or neck with greater than 70 grays;
- Immunosuppression or immunocompromised;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;
- Substance misuse;
- Psychiatric problems and/or unrealistic expectations;
- Poor oral hygiene and motivation;
- Untreated periodontitis;
- Acute infection/inflammation in the area intended for implant placement;
- Need for bone augmentation at implant insertion site, with the exception of filling bone-to-implant gaps at immediate post-extraction implants;
- Lack of opposite occluding dentition or prosthesis in the area intended for implant placement;
- Severe bruxism or clenching;
- Participation in other investigations, if precluding proper adherence to the present protocol;
- Inability to commit to a 3-year follow-up;
- Referrals for implant placement alone, i.e., if the patient could not be followed-up at the treatment centre.

Patients were categorised into three groups according to their declarations: i) non-smokers, ii) moderate smokers (up to 10 cigarettes per day), and iii) heavy smokers (more than 10 cigarettes per day). Patients were also categorised into two groups: i) whether the opposing jaw had natural dentition/fixed prostheses or ii) removable prosthesis/dentures.

## Clinical procedures

All patients received prophylactic antibiotic therapy, 2 g amoxicillin, at the dental practice one hour before implant placement. Patients allergic to penicillin were given 600 mg clindamycin 1 hour before implant placement. All patients rinsed with 0.2% chlorhexidine mouthwash for 1 minute prior to any intervention. Local anaesthesia was obtained using articaine with 1:100,000 adrenaline. Intravenous sedation was also a possibility.

If a tooth was to be extracted, intrasulcular incisions were performed and extended mesially and distally without any vertical incision. Para-crestal or mid-crestal incisions were performed, and full-thickness crestal flaps were raised with a minimal extension to minimise patient discomfort. Teeth extractions were performed as atraumatically as possible, using periotomes and small levers, to preserve the buccal alveolar bone. Extraction sockets were carefully cleaned of any granulation tissue.

AnyRidge Xpeed (MegaGen Implant, Gyeongbuk, South Korea) threaded titanium implants with internal connection were used. Operators were free to choose implant lengths (7.0, 8.5, 10.0, 11.5, 13.0 and 15.0 mm) and diameters (3.5, 4.0, 4.5, 5.0, 6.0 and 7.0 mm) according to clinical indications and their preference.

After initial drilling of the implant site, a 2 mm-diameter pilot drill was used to prepare the implant site and to subjectively discriminate bone quality into hard, medium or soft. Implant sites were prepared according to bone quality: in hard bone the sequence of drills suggested by the manufacturer was used. In medium bone quality, sites were underprepared using as the last drill one diameter smaller than the one suggested. In the case of soft bone, sites were underprepared using as the last drill two diameters smaller than suggested.

Implants were inserted in the osteotomy site with the motor set with a torque of 40 Newton/cm and, once the motor stopped, manually with a dedicated ratchet until seated at the level of the alveolar bone crest. In the event that an implant was inserted with a torque of less than 40 Ncm, operators were free to decide whether to prepare an alternative implant site, to replace it with a larger diameter or longer implant in order to attempt to obtain the required insertion torque, or to load it conventionally after 3 months of healing.

Post-extractive implants were placed slightly palatally, 1 to 2 mm below the most coronal bone of the surrounding crest. In case of a bone-to-implant gap, the treatment centres adopted different strategies: the Greek centre used no biomaterial or membrane while the Italian centre used granules of anorganic bovine bone (Bio-Oss 0.25–1 mm, Geistlich Pharma, Wolhusen, Switzerland) to fill the bone-to-implant gaps and, if needed, the exposed grafted areas were covered with resorbable collagen membranes (Bio-Gide, Geistlich Pharma).

After having completed the implant placement procedure, the sequentially numbered envelope corresponding to the patient in question was opened to inform the operator when to load the implant, i.e., immediately, early (after 6 weeks), or conventionally (after three months). According to the random allocation, impression copings or cover screws were placed. Implants were submerged, and interrupted sutures were placed. Baseline periapical radiographs of the study implants were taken with the paralleling technique and, if the peri-implant marginal bone levels were not clearly discernible or the implant image was too distorted, a second periapical radiograph was to be taken. Impressions at implant level with the pick-up impression copings were made for those implants to be immediately loaded.

The following post-surgical instructions were given:

- Cold and soft diet for 1 week;
- No removable prosthesis compressing the surgical wound to be used for 1 week;
- Ibuprofen 400 mg (or paracetamol 1 g for patients allergic to NSAIDs) to be taken 2 to 4 times a day during meals, only if needed;
- Chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks.

Provisional screw-retained acrylic resin prostheses (which could also be reinforced according to the clinical situation) were fabricated and delivered within 2 days from implant placement for the immediately loaded group. If necessary, abutments were cut and modified on implant analogues. In the early loaded group, implants were exposed at 6 weeks and in the conventionally loaded group implants were exposed at 3 months, and all were subjected to identical prosthetic procedures.
Upon loading with provisional prostheses, periapical radiographs of the early and conventionally loaded implants were taken with the paralleling technique. Patients were seen after 3 days to check the occlusion, and after 10 days for a second check-up of the occlusion, oral hygiene instructions, and suture removal.
Provisional prostheses were replaced after 4 months by definitive screw-retained or cemented metal-ceramic prostheses. All implants were manually tested for mobility by tightening the abutment screws with the removed crowns using the dedicated manual ratchet at 35 Ncm.
Patients were to be recalled at least every 6 months for oral hygiene maintenance and prosthetic controls.

## Outcome measures

Primary outcome measures were the following.

- Prosthesis failure: whether it was not possible to place the prosthesis due to implant failure or implant loss, or replacement of the definitive prosthesis for any reason.
- Implant failure: defined as implant mobility and/or any infection dictating implant removal or any mechanical failure rendering the implant unusable, such as implant fracture, or deformation of the implant-abutment connection. The stability of each implant was measured manually by tightening the abutment screw at definitive prosthesis delivery, and at 1 and 3 years after loading, using a manual wrench with 35 Ncm force. The stability of single implants at the 1- and 3-year check-ups was ascertained by attempting to rock the crown with the handles of two metal instruments. Rotating implants were considered failures.

Secondary outcome measure were the following.

- Any complication or adverse event, which were to be recorded and reported.
- Peri-implant marginal bone levels changes, as evaluated on periapical radiographs taken using the paralleling technique at implant placement, at initial loading, and 1 and 3 years after loading. Non digital radiographs were scanned into TIFF format with 600-dpi resolution, and stored on a personal computer. Peri-implant marginal bone levels were measured using OsiriX (Pixmeo Sarl, Bernex, Switzerland) software. The software was calibrated for each single image using the known implant diameter. Measurements of the mesial and distal bone crest level adjacent to each implant were made to the nearest 0.01 mm and averaged at implant level, then at patient level and, finally, at group level. The measurements were taken parallel to the implant axis. Reference points for the linear measurements were the coronal margin of the implant collar and the most coronal point of bone-to-implant contact.

Implant stability was assessed by local blinded outcome assessors, and complications were assessed by the treating dentists (who were therefore not blinded). Peri-implant bone levels were measured by experienced blinded centralised assessors (Dr. Trullenque-Eriksson up to 1 year after loading and thereafter by Dr. Sbricoli).

### Sample size and statistical procedures

The sample size was calculated on the primary outcome measure as the proportion of patients experiencing an implant failure. A two-group continuity-corrected chi-square test with a 0.050 two-sided significance level has 90% power to detect the difference between a Group 1 proportion of 0.100 and a Group 2 proportion of 0.200 (*odds ratio* of 2.250) when the sample size in each group is 286. However, our recruitment capacity could not match the required sample size, and it was therefore decided to include 45 patients per group. Originally, five centres agreed to participate in the study, each agreeing to recruit 27 patients (nine patients in each group) for a total of 45 patients per group. Unfortunately, due to three centres withdrawing from the study, only 18 patients per group actually completed the 3-year follow-up.

Five computer-generated restricted random lists were created with three groups of equal numbers of patients. Only one of the investigators (Dr. Esposito), not involved in the selection and treatment of patients, was aware of the random sequence and had access to the randomisation list, stored on a password-protected laptop. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially only after all implants were placed, and treatment allocation was therefore concealed from the investigators in charge of enrolling and treating the patients.

All data analysis was carried out according to a pre-established analysis plan. The patient was the statistical unit of the analyses. A dentist (Dr. Buti) with expertise in dental biostatistics analysed the data, without knowing the group allocation, according to intention-to-treat analysis. Fisher's exact (and Freeman-Halton extension of the Fisher exact test for more than two group comparisons) probability test was used to compare dichotomous variables, the Kruskal-Wallis test for continuous outcomes (bone levels) between the three groups, and the Mann-Whitney U test for continuous outcomes (bone levels) between the two centres; when the Kruskal Wallis test was significant, pairwise comparisons were carried out using the Dunn-Bonferroni approach. Comparisons between each time point and baseline measurements were made using the Wilcoxon signed rank test, to detect any changes in marginal peri-implant bone levels in each study group. All statistical comparisons were conducted at a 0.05 level of significance.

## RESULTS

Sixty-six patients were originally screened for eligibility, but 12 patients from the Italian centre were not enrolled on the trial because they did not want to have their implants loaded at a randomly decided time. Fifty-four patients were consecutively enrolled in the trial and randomised: 18 to the immediate-, 18 to the early- and 18 to the conventional-loading groups. As per protocol, each centre recruited nine patients in need of a single implant-supported crown, nine patients in need of a partial fixed prosthesis, and nine patients requiring a cross-arch prosthesis, and randomly allocated them in equal numbers to the three different loading protocols. All patients were treated according to the allocated interventions. Two drop-outs occurred up to 3-year after loading, both from the Rome centre, and both fitted with conventionally loaded cross-arch fixed prostheses; one elderly lady received only two mandibular implants instead of the four planned ones was last seen at the 4-month follow-up, being unwilling to attend further follow-ups, and who died after the 1-year follow-up. Another elderly lady was last seen at 1-year follow-up and then became severely ill and was unable to attend further visits. Neither patient reported any problems. As described in the previous 1-year report, another patient with a conventionally loaded maxillary cross-arch prosthesis emigrated to Australia after the 4-month post-loading follow-up, did not attend the 1-year follow-up, and was therefore considered a drop-out. However, the patient then returned to his home country and completed the 3-year follow-up. Data from all remaining patients was evaluated in the statistical analyses.

A torque of 40 Ncm was not achieved in four implants in two fully edentulous patients from the

Rome centre: three implants were to be loaded immediately and one early. The operator therefore loaded the implants that achieved at least 40 Ncm torque according to the random scheme and loaded the other implants after 4 months, at delivery of the definitive prostheses. Deviations from the operative protocol are listed below.

- Larissa centre: all patients from the conventionally loaded group were directly rehabilitated with definitive prostheses without using any interim provisional restorations:
  - One partially edentulous patient from the early loading group had implants that were not submerged;
  - One partially edentulous patient from the conventionally loaded group did not have radiographs taken at the 3-year follow-up; radiographic evaluation was performed on a panoramic radiograph taken at the 4-year follow-up;
  - One fully edentulous patient from the early-loaded group had an panoramic radiograph instead of periapical radiographs taken at the 3-year follow-up which was judged to be unreadable;
  - One fully edentulous patient from the conventionally loaded group had periapical radiographs taken at the 4$^{th}$ year of follow-up instead of the 3$^{rd}$ year.
- Rome centre, immediate-loading group:
  - One single implant was grafted using a tissue graft from the palate at implant insertion to augment soft tissue thickness;
  - One fully edentulous maxilla received seven instead of six implants;
  - Two fully edentulous patients had tooth 27 still present but never in occlusion; one patient had two new provisional prostheses made, and the another one a new provisional prosthesis made but not as a consequence of complications;
  - Two fully edentulous patients who had post-extraction sites filled with anorganic bovine bone were also subjected to simultaneous horizontal augmentation with the same bone substitute, and had the grafts covered with resorbable collagen membrane.
- Rome centre, early-loading group:
  - One fully edentulous patient who had post-extraction sites filled with anorganic bovine bone was also augmented horizontally with the same bone substitute and had the graft covered with A-PRF (platelet-rich-fibrin) membrane;
  - One partially edentulous patients had both implants that were not submerged;
  - One fully edentulous patient still had teeth 18 and 27 present but never in occlusion;
  - One fully edentulous patient had the provisional prosthesis made twice;
  - The 3-year periapical radiograph of a single implant was taken at 2.5 years.
- Rome centre, conventional-loading group:
  - One fully edentulous maxilla received eight implants instead of six implants;
  - One fully edentulous maxilla received seven implants instead of six implants, and the provisional prosthesis was replaced 1 year after loading by another provisional, rather than definitive, prosthesis, as per the patient's request;
  - One fully edentulous mandible received only two of four planned implants. The patient, during surgery, had a hypotensive episode with oxygen saturation dropping to 86 (severe hypoxic condition), which led to the anaesthetist advising that the procedure be stopped. The patient was fitted with an overdenture;
  - Three patients were subjected to augmentation procedures: one crestal sinus lift at a single implant using anorganic bovine bone (Bio-Oss); one horizontal augmentation with Bio-Oss and resorbable collagen membrane (Bio-Gide) in a partially edentulous patient, and one split-crest procedure using Bio-Oss in another partially edentulous patient;
  - One partially edentulous patient received the definitive instead of the provisional prosthesis first;

- Only panoramic radiographs (seven out of nine patients) or no radiographs (two out of nine patients), were taken for fully edentulous patients at implant placement instead of periapical radiographs, and only panoramic radiographs (three out of six patients) or no radiographs (two out of six patients), were taken for fully edentulous patients at initial loading instead of periapical radiographs.

Patients were recruited and treated from September 2012 to July 2015. The follow-up focused on the time between implant placement and 3 years after loading. The main baseline patient characteristics are presented in **TABLE 1**. Baseline patient characteristics were similar, with the following exceptions: in the immediate loading group there were fewer removable prostheses in the opposing jaw, more implants in maxilla, fewer implants in molar sites, more implants inserted in sites after less than 3 months of healing, and more implants in augmented sites; in the conventional loading group there were more implants in bone of soft quality, and more implants placed with a torque of less than 40 Ncm.

- Prosthesis failures: one partial prosthesis from the early-loaded group had to be remade after just the first year of loading because of multiple fractures of the porcelain layer (P = 1.0).

**TABLE 1** PATIENT AND INTERVENTION CHARACTERISTICS

| | Immediate (n = 18) | Early (n = 18) | Delayed (n = 18) |
|---|---|---|---|
| Females | 13 (72.2%) | 8 (44.4%) | 11 (61.1%) |
| Mean age at implant insertion (range) | 57.67 (22 to 77) | 57.22 (24 to 73) | 57.72 (35 to 70) |
| Smoking up to 10 cigarettes/day | 4 (22.2%) | 4 (22.2%) | 5 (27.8%) |
| Smoking more than 10 cigarettes/day | 5 (27.8%) | 6 (33.3%) | 3 (16.7%) |
| Natural dentition/fixed prosthesis in opposing jaw | 18 (100%) | 17 (94.4%) | 16 (88.9%) |
| Removable prosthesis/denture in opposing jaw | 0 | 1 (5.6%) | 2 (11.1%) |
| Number of implants placed | 61 | 56 | 55 |
| Implants in mandibles | 24 (39.3%) | 35 (62.5%) | 30 (54.5%) |
| Implants in maxillae | 37 (60.7%) | 21 (37.5%) | 25 (45.5%) |
| Implants in incisor sites | 19 (31.1%) | 12 (21.4%) | 13 (23.6%) |
| Implants in canine sites | 6 (9.8%) | 4 (7.1%) | 3 (5.5%) |
| Implants in premolar sites | 25 (41%) | 24 (42.9%) | 19 (34.5%) |
| Implants in molar sites | 11 (18%) | 16 (28.6%) | 20 (36.4%) |
| Implants in immediate extraction sockets | 17 (27.9%) | 10 (17.9%) | 13 (23.6%) |
| Implants inserted in sites after less than 3 months of healing | 6 (9.8%) | 0 | 0 |
| Implants inserted in sites after more than 3 months of healing | 38 (62.3%) | 46 (82.1%) | 42 (76.4%) |
| Implants in sites augmented at implant placement | 21 (34.4%) | 9 (16.1%) | 6 (10.9%) |
| Mean implant length (mm) | 10.69 ± 1.44 | 10.70 ± 1.28 | 10.46 ± 1.50 |
| Mean implant diameter (mm) | 4.13 ± 0.57 | 4.22 ± 0.67 | 4.47 ± 0.60 |
| Implants in hard quality bone | 18 (29.5%) | 23 (41.1%) | 12 (21.8%) |
| Implants in medium quality bone | 38 (62.3%) | 28 (50%) | 22 (40%) |
| Implants in soft quality bone | 5 (8.2%) | 5 (8.9%) | 21 (38.2%) |
| Implants inserted with less than 40 Ncm torque | 4 (6.6%) | 5 (8.9%) | 12 (21.8%) |

- Implant failures**:** no implant failures were reported for any patients up to 3 years after loading.
- Complications**:** in total, six patients were affected by complications during the 3 years after loading: three from the immediately loaded group, two from the early-loaded group and one from the conventionally loaded group, but there were no statistically significant differences between groups (P = 0.861).

  In the immediate-loading group, there was one metal framework misfit in a cross-arch maxillary prosthesis, which was resolved by cutting and resoldering the framework. A porcelain fracture at the collar of the prosthesis at implant 23 was observed at the 3-year follow-up of another patient with a cross-arch prosthesis; this was repaired in the lab. A single implant in position 46 was found to be affected by peri-implantitis at the follow-up 3 years after loading. About 4 mm of peri-implant bone was lost. This was treated using Er:YAG laser and guided bone regeneration with inorganic bovine cortical graft (Step Biomaterials, Dimokritos, Greece) covered with a non-resorbable high-density PTFE membrane (Cytoplast, Osteogenics Biomedical, Lubbock, TX, USA) and stabilised with pins, submerging the implant. After 4 months the membrane was removed, the outcome was satisfactory, and a free gingival graft was grafted.

  In the early-loaded group, the ceramic vestibular cusps of one maxillary partial fixed prosthesis fractured at position 16. The metal was not exposed, so the ceramic was polished. A second fracture of the lining in the same prosthesis occurred just after the first year of loading and a new prosthesis was made. In another patient, wearing a mandibular cross-arch fixed prosthesis, symmetrical vestibular fractures were observed in the porcelain at implants 35 and 45 at the 3-year follow-up, and were repaired in the lab.

  In the conventionally loaded group, the distal cusp of a maxillary partial fixed prostheses fractured on implant 16. The metal was not exposed, and the ceramic was polished.

**TABLE 2** MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS BETWEEN GROUPS AND TIME PERIODS UP TO 3 YEARS POST-LOADING

| | Implant placement | Loading | 1 year after loading | 3 year after loading | Within-group P-value |
|---|---|---|---|---|---|
| | N Mean±SD (95% CI) | N Mean±SD (95% CI) | N Mean±SD (95% CI) | N Mean±SD (95% CI) | |
| **Immediate** | 16 0.44 ± 0.58 (0.13; 0.75)[a] | 16 0.44 ± 0.58 (0.13; 0.75) | 17 0.54 ± 0.40 (0.33; 0.75) | 18 0.39 ± 0.48 (0.15; 0.62) | Baseline – loading N/A<br>Baseline – 1 year 0.204<br>Baseline – 3 years 1.0 |
| **Early** | 15 0.23 ± 0.43 (-0.01; 0.47) | 15 0.39 ± 0.37 (0.19; 0.60) | 18 0.36 ± 0.39 (0.17; 0.56) | 17 0.26 ± 0.35 (0.08; 0.44) | Baseline – loading 0.180<br>Baseline – 1 year 0.311<br>Baseline – 3 year 0.938 |
| **Conventional** | 14 0.04 ± 0.13 (-0.04; 0.11)[a] | 16 0.39 ± 0.35 (0.20; 0.58) | 14 0.27 ± 0.36 w(0.06; 0.47) | 16 0.34 ± 0.43 (0.11; 0.57) | Baseline – loading 0.002*<br>Baseline – 1 year 0.008*<br>Baseline – 3 year 0.004* |
| **Between-Group P-value** | 0.005* | 0.939 | 0.125 | 0.587 | |

**N/A: not applicable. Statistically significant difference, [a] subsets with statistically significant difference in pairwise comparisons. Regarding the missing cases: 14 patients at baseline and nine at loading only had panoramic rather than periapical radiographs; in one case the loading radiographs were missing; the quality of the radiographs taken was not sufficient to enable measurement of marginal bone levels in two cases at loading, in three cases at 1-year follow-up, and in one case at 3-year follow-up; periapical radiographs of one patient and one panoramic radiograph judged to be readable of another patient were taken at the 4th instead of the 3rd year of follow-up; there were two drop-outs at 3-year follow-up.*

- Marginal bone level changes **(TABLES 2 AND 3)**: at implant placement, there were statistically significant differences between the three groups: bone levels were 0.44 ± 0.58 mm (CI95% 0.13; 0.75) at immediately, 0.23 ± 0.43 mm (CI95% -0.01; 0.47) early, and 0.04 ± 0.13 mm (CI95% -0.04; 0.11) conventionally loaded implants (P [Kruskal Wallis test] = 0.005; **TABLE 2**); pairwise comparisons showed statistically significant differences between the immediate and conventionally loaded groups (P = 0.0039).
  At loading, there was no statistically significant difference in peri-implant bone levels between the three groups, which were: 0.44 ± 0.58 mm (CI95% 0.13; 0.75) at immediately, 0.39 ± 0.37 mm (CI95% 0.19; 0.60) at early, and 0.39 ± 0.35 mm (CI95% 0.20; 0.58) at conventionally loaded (P [Kruskal Wallis test] = 0.939; **TABLE 2**). Differences in bone loss were likewise not statistically significant: 0.17 ± 0.39 mm (CI95% -0.06; 0.39) at early, and 0.36 ± 0.30 mm (CI95% 0.18; 0.53) at conventionally loaded implants; P (Kruskal Wallis test) = 0.207 **(TABLE 3)**.
  Similarly, there was no statistically significant difference in peri-implant bone levels between the three groups one year after loading, which were: 0.54 ± 0.40 mm (CI95% 0.33; 0.75) at immediately, 0.36 ± 0.39 mm (CI95% 0.17; 0.56) at early, and 0.27 ± 0.36 mm (CI95% 0.06; 0.47) at conventionally loaded (P [Kruskal Wallis test] = 0.125; **TABLE 2**). As for bone loss, only the conventionally loaded group gradually lost a statistically significant amount of marginal peri-implant bone at one-year post-loading (P [Wilcoxon signed rank test] = 0.008), the bone loss figures being: 0.15 ± 0.40 mm (CI95% -0.08; 0.37) at immediately, 0.15 ± 0.62 mm (CI95% -0.19; 0.49) at early, and 0.25 ± 0.28 mm (CI95% 0.07; 0.43) at conventionally loaded implants; P (Kruskal Wallis test) = 0.525 **(TABLE 3)**.
  Three years after loading, once again there was no statistically significant difference between the three groups in terms of peri-implant bone levels, which were: 0.39 ± 0.48 mm (CI95% 0.15; 0.62) at immediately, 0.26 ± 0.35 mm (CI95% 0.08; 0.44) at early, and 0.34 ± 0.43 mm (CI95% 0.11; 0.57) at conventionally loaded (P [Kruskal Wallis test] = 0.587; **TABLE 2**). In this case too, only the conventionally loaded group gradually lost statistically significant amounts of marginal peri-implant bone (P [Wilcoxon signed rank test] = 0.004), as bone loss at three-year post-loading was: -0.04 ± 0.85 mm (CI95% -0.49; 0.42) at immediately, -0.01 ± 0.55 mm (CI95% -0.33; 0.31) at early, and 0.33 ± 0.36 mm (CI95% 0.12; 0.54) at conventionally loaded implants (P [Kruskal Wallis test] = 0.191; **TABLE 3**).

A comparison of the clinical outcomes achieved at the two centres is presented in **TABLE 4**. There was a statistically significant difference in marginal bone loss of 0.38 ± 0.19 mm between the two operators at 3 years after implant placement (P [Mann-Whitney U test] = 0.0049).

**TABLE 3** MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVEL CHANGES BETWEEN GROUPS AND TIME PERIODS UP TO 3-YEAR POST-LOADING

| | Difference placement – loading | Difference placement – 1 year | Difference placement – 3 year |
|---|---|---|---|
| | N Mean±SD (95% CI) | N Mean±SD (95% CI) | N Mean±SD (95% CI) |
| **Immediate** | - | 15 0.15 ± 0.40 (-0.08; 0.37) | 16 -0.04 ± 0.85 (-0.49; 0.42) |
| **Early** | 14 0.17 ± 0.39 (-0.06; 0.39) | 15 0.15 ± 0.62 (-0.19; 0.49) | 14 -0.01 ± 0.55 (-0.33; 0.31) |
| **Conventional** | 14 0.36 ± 0.30 (0.18; 0.53) | 12 0.25 ± 0.28 (0.07; 0.43) | 14 0.33 ± 0.36 (0.12; 0.54) |
| **P-value intergroup** | 0.207 | 0.525 | 0.191 |

**TABLE 4** COMPARISON OF THE CLINICAL OUTCOMES OF THE TWO OPERATORS AT 3-YEAR AFTER LOADING. EACH OPERATOR TREATED 27 PATIENTS

| | Dr. Siormpas | Dr. Pistilli | P-value |
|---|---|---|---|
| Drop-out | 0 | 2 | 0.491 |
| Patients with failed prostheses | 0 | 1 | 1.0 |
| Patients with failed implants | 0 | 0 | NE |
| Patients with complications | 1 | 5 | 0.192 |
| Marginal bone loss ± SD | N = 26<br>0.25 ± 0.70 | N = 18<br>-0.14 ± 0.48 | 0.0049* |

*SD: standard deviation; NE: not estimable; *statistically significant difference.*

## DISCUSSION

This trial was designed to evaluate whether immediate and early loading of dental implants could provide similar clinical outcomes as conventional (delayed) loading, since shorter treatment periods are highly appreciated and requested by many patients. No implant failure and very few complications were reported; therefore, all three procedures seem to work very well, and it would be up to clinicians and patients to choose which option they prefer.

Indeed, there have been many RCTs comparing immediate, early and conventional loading of dental implants[4,6,7,10-34], and our results are in line with most of the published RCTs and the conclusions of a Cochrane systematic review[4]. The only exception to this consensus are two trials[6,7] that reported higher failure rates of immediately loaded and early loaded implants, respectively.

The most relevant factor that may explain the good results obtained in this trial is the high insertion torque at implant placement. To qualify for immediate and early loading, implants had to be inserted with torque greater than 40 Ncm. To achieve this in medium and soft bone quality, implant sites were under-prepared with drills having a diameter one or two sizes smaller than the final implant diameter. This explanation is supported by the findings from two studies[5,35]; in one non-randomised controlled trial of split-mouth design, single implants were either immediately non-occlusally loaded or conventionally loaded. Those authors found a strong correlation between low implant insertion torque and implant failures in immediately loaded implants. In fact, out of ten single implants placed with an insertion torque of 20 Ncm, nine failed, whereas only one out of 10 implants inserted with a torque of at least 32 Ncm[5] failed. The other split-mouth RCT included 50 patients who received two single immediately loaded implants, one randomly inserted with a torque between 25 and 35 Ncm, and the other with a torque greater than 80 Ncm. Seven of the implants inserted with a torque between 25 and 35 Ncm failed *versus* none of the implants placed with insertion torque greater than 80 Ncm[35], a difference that was statistically significant. Those findings suggest that immediate and early loading of dental implants can be successful, if some clinical precautions are taken. Such precautions may include: under-preparation of the implant sites particularly in the presence of soft bone, use of implant designs favouring achievement of high insertion torques (35 Ncm or more)[35], and accurate control of loading. Some authors also advocate the use of specific implant surface modifications to reduce healing time[36], but no evidence has yet been produced to support this hypothesis[37]. Therefore, if a clinician is able to place implants with

good insertion torques (more than 40 Ncm), they could be loaded immediately or early. However, when choosing between immediate and early loading, it might be wiser to load implants immediately, since there are no additional advantages or benefits when loading early[4], and patients, most likely, prefer immediate loading.

Apparently bone levels improved at the 3-year follow-up when compared to the 1-year follow-up, but this "improvement" is unlikely to be real; it may be explained by the change in radiographic outcome assessors, with a new assessor being more "optimistic" or the previous assessor being more "pessimistic"; the lack of several periapical radiographs may also have played a role. Our finding that implants loaded conventionally lost about 0.3 mm more bone within 3 years after loading than early and conventionally loaded implants, should also be interpreted with caution, as this difference may not be considered clinically relevant. Nonetheless, even taking into consideration the problems of periapical radiographic assessment previously described, a Cochrane systematic review also reported 0.1 mm more bone loss at conventionally loaded implants than immediately loaded ones 1 year after loading[4]. This difference was not considered to be clinically relevant, and was explained by the fact that conventionally loaded implants may undergo more abutment changes during the prosthetic phase, which may cause some minor trauma at the peri-implant tissues, causing the slightly greater bone loss observed in some RCTs[38].

All that being said, the difference in marginal bone loss between the two centres of 0.38 ± 0.19 mm (P = 0.0049) observed at 3 years after loading, while unlikely to be clinically significant, is difficult to explain. However, it should be pointed out that at the Rome centre, panoramic radiographs rather than periapical radiographs were often taken at implant placement and loading for fully and some of the partially edentulous patients. Being less reliable, bone levels on panoramic radiographs were not measured, and the lack of baseline periapical radiographs could have affected the precise evaluation of bone levels changes at the Rome centre. It may also be hypothesized that there were differences between the two centres in terms of implant placement depths.

Although we recognise that there was also an unexpected difference for bone levels at implant placement between the three groups, we are unable to find any reasonable explanation for this discrepancy. Considering the small number of patients included, however, it might be simply due to chance. Alternatively, the lack of many baseline radiographs from one centre may have had an influence.

As mentioned, this trial was originally designed to report post-loading data from three centres, in Greece, Lithuania and Italy. Unfortunately, after presenting their 4-month findings[8], the Lithuanian centre failed to provide any data for the 1- and 3-year follow-up, and therefore had to be excluded. The advantages of multicentre trials are twofold: more patients can be included, increasing the precision of the results, and findings are more generalisable when several centres achieve similar results. On the other hand, as we experienced, the logistics of organising of multicentre trials is more complex, and there is always the risk that some centres may inadvertently operate differently.

The main limitation of this trial is the limited sample size. The number of included patients was too low to detect any significant difference, if any. Unfortunately, in addition to losing the Lithuanian centre, the two additional centres which originally agreed to participate in this trial failed to recruit any patients. Nonetheless, our findings should prove useful to future meta-analyses, which can pool our data with those of other RCTs, thereby increasing the sample size. Another important limitation was the high number of panoramic, unreadable or missing radiographs, especially at implant placement and loading of fully and partially edentulous patients at the Rome centre, which may explain some of the apparent baseline diffe-

rences between groups. Finally, the substantial number of protocol deviations reported may have had some influence on the findings.
Nevertheless, it should be recognised that these procedures were tested in real-world clinical conditions and that patient inclusion criteria were broad. Hence our results may be generalisable to a wider population, bearing in mind, however, that our operators were highly experienced with immediate loading procedures.

## CONCLUSIONS

Although this trial had its limitations, especially a small sample size, all loading strategies were successful, and there were not clinically relevant differences between them. Nonetheless, immediate and early loading achieved similar results in a shorter period of time. Hence, if treatment duration is an issue for the patient, then immediate loading could be a preferable option if implants are placed with sufficient insertion torque.

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