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Immediate, early (6 weeks) and delayed loading (3 months) of single, partial and full fixed implant supported prostheses: 1-year post-loading data from a multicentre randomised controlled trial

Key words *Calcium-incorporated titanium, early loading, randomised controlled trial, RBM surface, surface modification*

Purpose: To compare the clinical outcome of single, partial and complete fixed implant supported prostheses immediately loaded (within 48 h), early loaded at 6 weeks, and conventionally loaded at 3 months (delayed loading).

Materials and methods: A total of 54 patients (18 requiring single implants, 18 partial fixed prostheses, and 18 total fixed cross-arch prostheses) were randomised in equal numbers at 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 up to 1 year post-loading. No implant or prosthesis failed and three complications occurred, one in each loading group. Peri-implant marginal bone loss was 0.19 ± 0.44 mm at immediately loaded implants, 0.18 ± 0.66 mm at early loaded implants and 0.25 ± 0.28 mm at conventional loaded implants. There were no statistically significant differences in complications ($P = 1.000$) and bone loss ($P = 0.806$) between the three loading strategies.

Conclusions: All loading strategies were highly successful and no differences could be observed for implant survival and complications when loading implants immediately, early or conventionally.

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Introduction

Osseointegrated dental implants are placed traditionally following a two-stage protocol[1]. With this approach, implants are left to heal unloaded for 3 to 4 months in mandibles and 6 to 8 months in maxillae. Successful osseointegrated dental implants are anchored directly to the 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 minimise the risk of soft-tissue encapsulation[1]. This traditional approach requires a longer treatment period, and according to the procedures used, a second surgical intervention may be needed to uncover submerged implants to

allow abutment connection. Early 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 the patients if the healing period could be shortened without jeopardising implant success. In 1990, the first longitudinal study was published suggesting that implants could be loaded immediately or early in mandibles of selected patients[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 important 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]. Occasionally immediately[5,6] and early[7] loaded implants have been associated with clinically relevant 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, for example in the case of a 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 h (test group 1) vs early loading (test group 2) at 6 weeks vs delayed (or conventional) loading at 3 months (control group). Groups were also balanced for type of edentulism, in fact three subgroups of identical number of patients requiring the replacement of a single tooth, partial edentulism and full edentulism, 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.

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.

This report presents data at 1 year post-loading. At protocol stage, it was planned to follow-up these patients to the third year of function. The present article is reported following the CONSORT statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/). A previous publication presented the 4-month post-loading data of the same patient materials by 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, and after repeated requests, it was decided the centre should be excluded[8]. The full data from the excluded centre is described in the previous publication[8].

■ Materials and methods

This was a multicentre randomised controlled trial (RCT) of parallel group design with three arms, balanced randomisation and blind assessment. After implant placement, equal number of 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 h), early loading at 6 weeks, and conventionally loading at 3 months (delayed loading).

Patients were recruited and treated at two private dental clinics located in Larissa, Greece, and Roma, Italy, both having extensive experience with immediate loading procedures. Originally, five centres agreed to participate into the study but two centres withdrew before initiating the study without treating any patient and the third centre provided only data to 4 months post-loading. One experienced surgeon at each centre performed all the operations and patients were randomised in equal numbers into three groups according to a parallel group design: immediate loading (within 48 h), early loading at 6 weeks and conventional loading at 3 months.

Any partially or fully edentulous patient requiring at least one implant-supported prosthesis, who was 18 years of age or older, and able to understand and sign an informed consent form was eligible for inclusion in this trial. Only patients having sufficient bone allowing placement of one or more implants with minimal dimensions of 7.0 mm × 3.5 mm were

included. A maximum of six implants were to be placed in an edentulous jaw. All patients received thorough explanations and signed a written informed consent form prior to being enrolled in the trial to document that they understood the scope of the study (including procedures, follow-up evaluations, and any potential risks involved). Patients were allowed opportunities to ask questions pertaining to this investigation, and were informed about treatment alternatives. The study was open to qualifying patients regardless of 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 visit. Only one prosthesis per patient was entered in the study. Pre-operative radiographs (periapical, panoramic, cone-beam CT scans or other radiographic examinations at discretion of the operators) together with clinical inspections were used to determine bone volumes and anatomic landmarks. Patients were not accepted into the study if any of the following exclusion criteria was present:

- General contraindications to implant surgery;
- Irradiated in the head and/or neck with more than 70 Gray;
- Immunosuppressed or immunocompromised;
- Treated or under treatment with intravenous amino-bisphosphonates;
- Uncontrolled diabetes;
- Pregnant or nursing;
- Substance abusers;
- Psychiatric problems and/or unrealistic expectations;
- Poor oral hygiene and motivation;
- Untreated periodontitis;
- Acute infection/inflammation in the area intended for implant placement;
- Need of bone augmentation at implant insertion except for filling bone-to-implant gaps at immediate post-extractive implants;
- Lack of opposite occluding dentition/prosthesis in the area intended for implant placement;
- Severe bruxism or clenching;
- Participation to other investigations, if the present protocol could not be properly adhered to;
- Unable to commit to a 3-year follow-up;
- Referred only for implant placement if the patient could not be followed at the treatment centre.

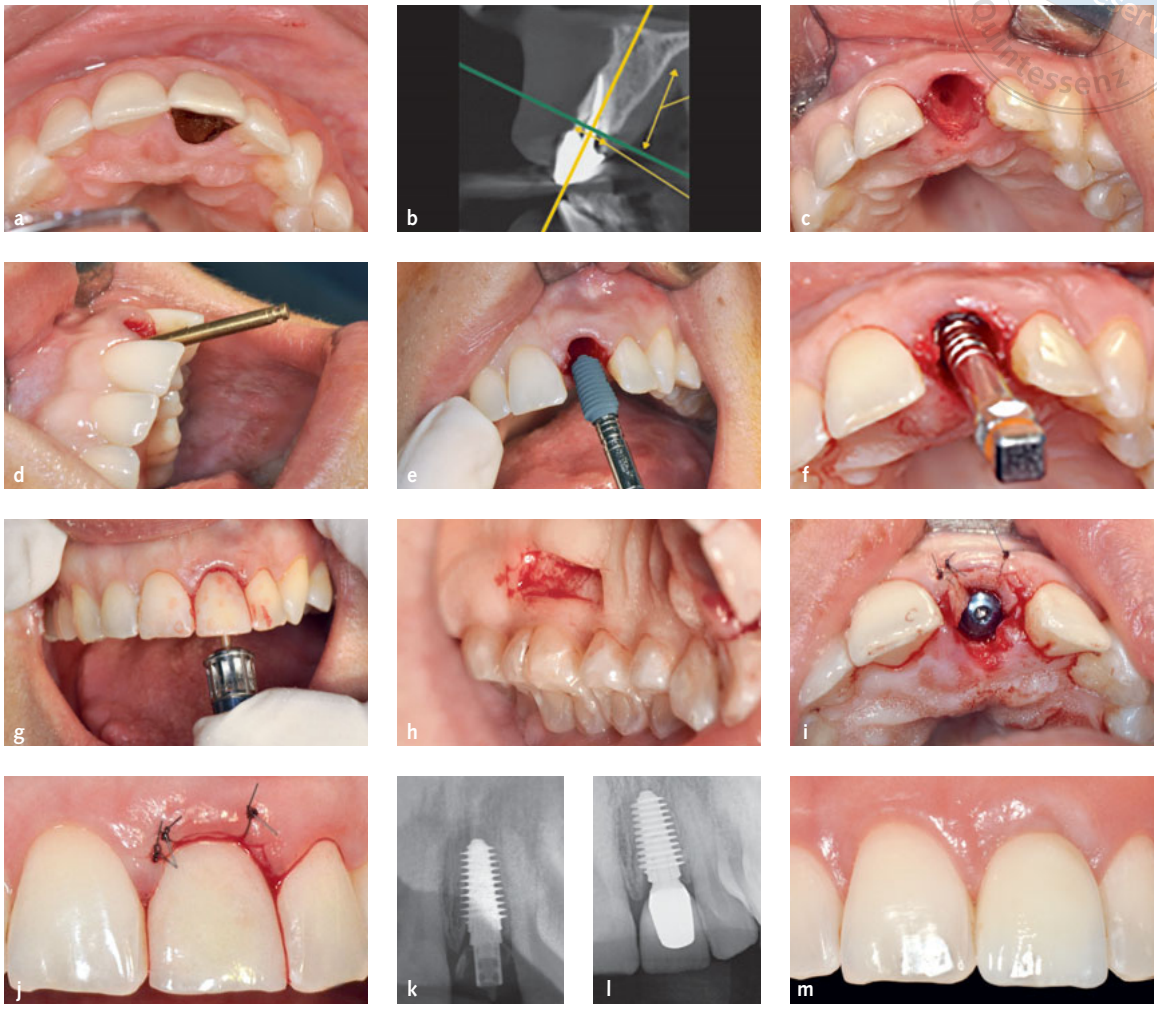
Patients were categorised into three groups according to what they declared: i) non-smokers, ii) moderate smokers (up to 10 cigarettes per day), and iii) heavy smokers (more than 10 cigarettes per day). Patients were also categorised into two groups: i) whether the opposite jaw had natural dentition/fixed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

All patients received prophylactic antibiotic therapy at the dental practice: 2 g amoxicillin given 1 h before implant placement. Patients allergic to penicillin were given 600 mg clindamycin 1 h before implant placement. Patients rinsed with 0.2% chlorhexidine mouthwash for 1 min prior to any intervention. Local anaesthesia was obtained using articaine with adrenaline 1:100.000. Intravenous sedation could be also used. In the presence of a tooth 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 elevated with a minimal extension to minimise patient discomfort. Teeth extractions were performed as atraumatically as possible to preserve the buccal alveolar bone, using periotomes and small levers. Extraction sockets were carefully cleaned of any granulation tissue.

AnyRidge Xpeed (MegaGen Implant Co, 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 preferences.

After initial drilling of the implant site, a 2.0 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 last drill, one diameter smaller than the one suggested; and in case of soft bone, sites were underprepared using a last drill, two diameters smaller than suggested.

Implants were inserted in the osteotomy site with the motor set with a torque of 40 Ncm and, once the motor stopped, manually with a dedicated ratchet until seated at level with the alveolar bone

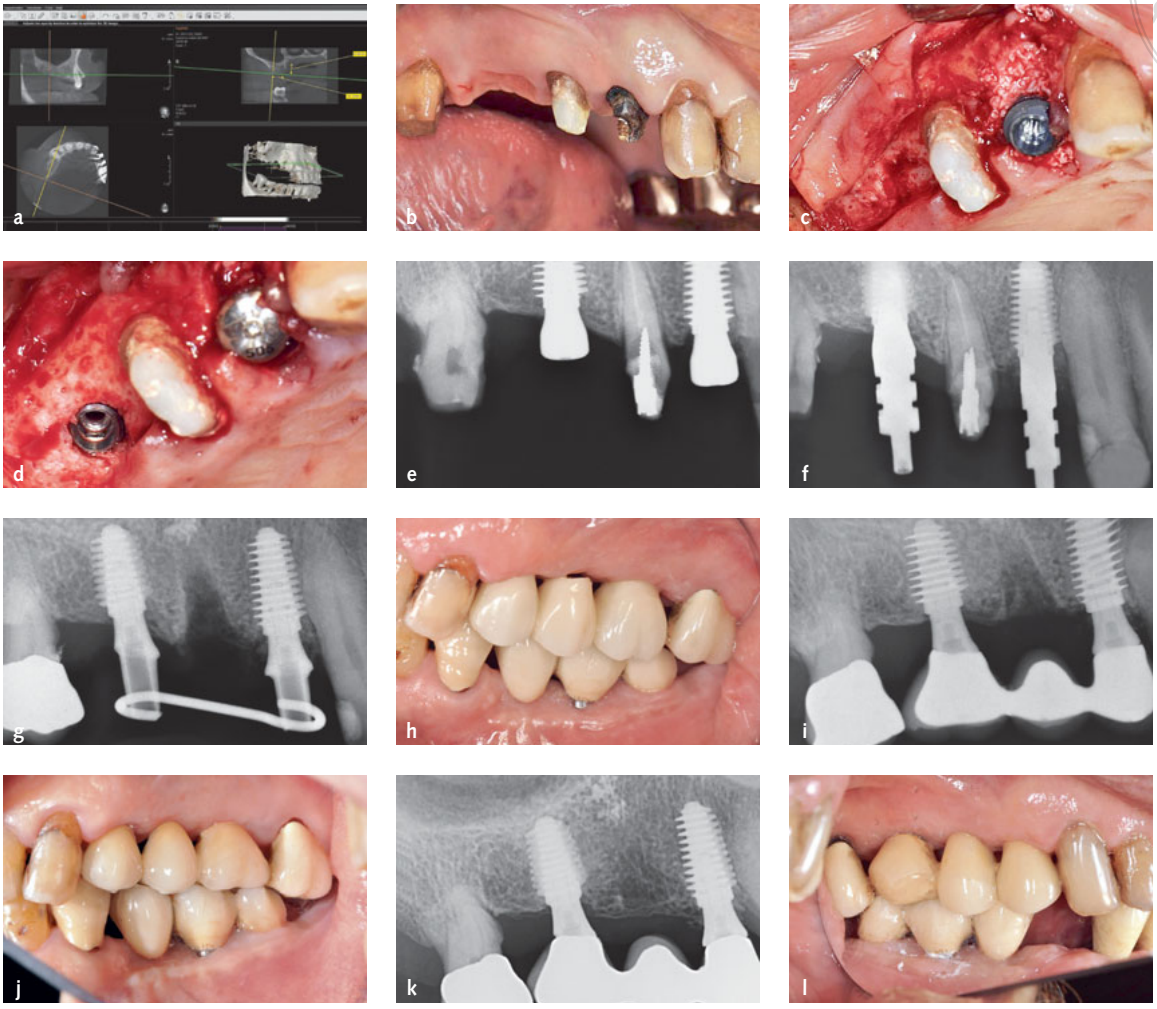


Figs 1a to m Treatment sequence of one of Dr Pistilli's patients requiring an immediate post-extractive single tooth replacement, randomly allocated to immediate loading after implant placement: a) preoperative clinical view of crowned tooth in position 21 which had a root fracture; b) preoperative CBCT scan showing the fracture along the long post; c) preparation of the implant site on the palatal wall to allow proper angulation of the implant; d) check of the proper inclination of the preparation site; e) implant placement; f) ideal inclination of the positioned implant; g) check of the immediate provisional crown; h) since the operator was a bit concerned about the possible aesthetic outcome, he decided to take a soft tissue graft from the palate (protocol deviation); i) soft tissue graft fixed with sutures; j) clinical view and k) periapical radiograph at delivery of the provisional crown; l) periapical radiograph and m) clinical view 1 year after loading.

crest. In the case that an implant was inserted with a torque inferior to 40 Ncm, operators were free to decide whether to prepare an alternative implant site, to replace it with a larger diameter or longer implant to attempt to obtain the required insertion torque, or loading it conventionally after 3 months of healing.

Post-extractive implants were placed 1.0 mm to 2.0 mm below the most coronal bone of the surrounding crest and slightly palatally. In case of a bone-to-implant gap, the centres had different strategies: the Greek centre did not used any 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 was opened to inform when to load the implant, immediately (Figs 1a to m), early (after 6 weeks; Figs 2a to l), or conventionally (after three months; Figs 3a to h). According to the random allocation, impression copings or cover screws were placed. Implants



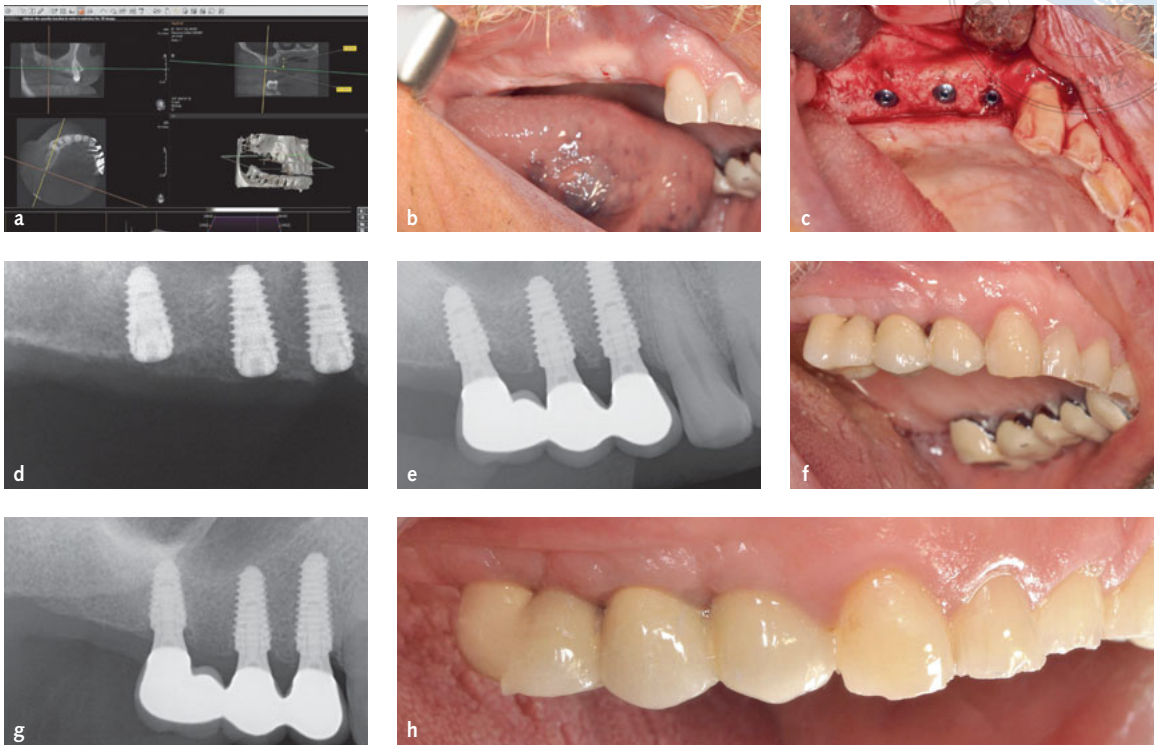
Figs 2a to l Treatment sequence of one of Dr Pistilli's partially edentulous patients who was allocated to the early loading group: a) preoperative CBCT: it was planned to place two implants in positions 16 and 14 and to extract 15 and 14; b) preoperative clinical view after prosthesis removal; c) placement of implant in post-extractive site 14 filled with anorganic bovine bone; d) placement of the second implant in position 16; e) post-implantation periapical radiograph of the implant with healing abutments (protocol deviation since the implants were to be submerged); f) radiograph at impression-taking 6 weeks after implant placement; g) radiograph at delivery of the provisional prosthesis, 15 was extracted; h) provisional in place; i) radiograph and j) clinical view at delivery of the definitive prosthesis 4 months after initial loading; k) radiograph and l) clinic view at 1 year after loading: both vestibular cusp of 16 fractured.

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 resulted too distorted a second periapical radiograph was 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:

- A cold and soft diet was recommended for 1 week.
- No removable prosthesis compressing the surgical wound should be used for 1 week.
- Ibuprofen 400 mg (or paracetamol 1 g for patients allergic to NSAIDs) to be taken two to four times a day during meals, only if needed.
- Patients were prescribed chlorhexidine mouthwash 0.2% for 1 min 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



Figs 3a to h Treatment sequence of one of Dr Pistilli's partially edentulous patients who was randomly allocated to the conventional loading group: a) preoperative CBCT and b) clinical view of the first quadrant to be rehabilitated; c) clinical view and d) baseline radiograph at placement of implants in positions 14, 15 and 16; e) radiograph and f) clinical view at initial loading, 3 months after implant placement, with the definitive prosthesis (protocol deviation since the patient should have received a provisional prosthesis for 4 months); g) periapical radiograph and h) clinical view at 1 year post-loading: a minor chipping of the ceramic occurred distally to 16.

cut and modified on implant analogues. Implants of the early-loaded group were exposed at 6 weeks and implants of the conventionally loaded group at 3 months and were subjected to identical prosthetic procedures.

At 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 with the dedicated manual ratchet at 35 Ncm.

Patients were to be recalled at least every 6 months for oral hygiene maintenance and prosthetic controls.

■ Primary outcome measures were:

Prosthesis failure

- Whether it was not possible to place the prosthesis due to implant failures or secondary to implant losses, or replacement of the definitive prosthesis for any reasons.

Implant failure

- Implant failure was 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 using a manual wrench with a 35 Ncm force. Rotating implants were to be considered failures.
- Any complication and adverse event was to be recorded and reported.

- Peri-implant marginal bone levels changes evaluated on periapical radiographs taken with the paralleling technique at implant placement, at initial loading, and 1 year after loading. Radiographs were scanned into TIFF format with a 600 dpi resolution, and stored in a personal computer. Peri-implant marginal bone levels were measured using the OsiriX (Pixmeo Sàrl, Bernex, Switzerland) software. The software was calibrated for every 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, whereas complications were assessed by the treating dentists who were therefore not blinded.

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, therefore, it was decided to include 45 patients per group. Originally, five centres agreed to participate to the study, each agreeing to recruit 27 patients (nine patients per 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 1-year follow-up.

Five computer-generated restricted random lists were created with three groups with equal number of patients. Only one of the investigators (Dr Esposito), not involved in the selection and treatment of the patients, was aware of the random sequence and had access to the randomisation list stored on a password-protected portable computer. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially only after all implants were placed, therefore treatment allocation was concealed to 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 practitioner (Dr Trullenque-Eriksson) with expertise in dental biostatistics analysed the data, without knowing the group allocation and according to an intention to treat analyses. Fisher's exact 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 was used 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 the baseline measurements were made with the Wilcoxon signed rank test, to detect any changes in marginal peri-implant bone levels for each study group. All statistical comparisons were conducted at the 0.05 level of significance.

Results

Sixty-six patients were originally screened for eligibility, but 12 patients from the Italian centre were not enrolled into 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 number to the three different loading protocols. All patients were treated according to the allocated interventions. Two patients dropped out after the delivery of the definitive prostheses (4 months after initial loading), both from the Pistilli centre and involved two patients rehabilitated with conventionally loaded cross-arch fixed prostheses. One patient emigrated to Australia and the other was a 70-year-old woman who received

two mandibular implants instead of the four originally planned, and who was not willing to attend the follow-ups. Neither reported subjective problems. Data regarding all remaining patients was evaluated in the statistical analyses. Dr Pistilli did not achieve a torque of 40 Ncm in four implants for two fully edentulous patients: three implants were to be loaded immediately and one early. Therefore, the operator loaded the implants that achieved at least 40 Ncm torque according to the random scheme and loaded the other implants after 4 months, at the delivery of the definitive prostheses.

Deviations from the operative protocol were the following:

Dr Siormpas

- All patients in the conventionally loaded group were directly rehabilitated with definitive prostheses without using any interim provisional restorations, and one partially edentulous patient from the early loading group had his implants not submerged.

Dr Pistilli – immediate loading group

- One single implant was grafted with 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 still had tooth 27 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-extractive 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 membranes.

Dr Pistilli – early loading group

- One fully edentulous patient, who had post-extractive 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) membranes.
- One partially edentulous patient still had teeth 18 and 27 present, but never in occlusion.
- One fully edentulous patient had the provisional prosthesis made twice.

Dr Pistilli – conventional loading group

- Two fully edentulous maxillae received eight and seven instead of six implants.
- One fully edentulous mandible received only two of four planned implants. During surgery, the patient 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 rehabilitated 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 collagen resorbable membranes (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.
- Orthopantomographs, rather than periapical radiographs, were taken for fully edentulous patients at implant placement for all patients, whereas periapical radiographs were taken at initial loading for three patients.

Patients were recruited and treated from September 2012 to July 2015. The follow-up focused on the time between implant placement and 1 year 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 opposite jaw, more implants in the maxillae, less 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 more implants in soft quality bone, and more implants placed with a torque inferior to 40 Ncm.

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 a day	4 (22.2%)	4 (22.2%)	5 (27.8%)
Smoking more than 10 cigarettes a day	5 (27.8%)	6 (33.3%)	3 (16.7%)
Natural dentition/fixed prosthesis in opposite jaw	18 (100%)	17 (94.4%)	16 (88.9%)
Removable prosthesis/denture in opposite 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 bone quality	18 (29.5%)	23 (41.1%)	12 (21.8%)
Implants in medium bone quality	38 (62.3%)	28 (50%)	22 (40%)
Implants in soft bone quality	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%)

Prosthesis and implant failures

No prosthesis or implant failures were reported for any patients up to 1 year after loading.

Complications

After delivery of the definitive prostheses, only three complications occurred, all at Dr Pistilli's centre. There was one complication in each group, with no statistically significant differences between groups ($P = 1.000$). In the immediate loading group there was one metal framework misfit in a cross-arch maxillary prosthesis, which was solved by cutting and resoldering the framework. In the early-loaded group, the maxillary vestibular cusps in the ceramic of the partial fixed prosthesis fractured on tooth 16 (Fig 2l). The metal was not exposed and the ceramic was polished. Finally, in the conventionally loaded group, the distal cusp of a maxillary partial fixed prostheses fractured on tooth 16 (Fig 3 h). The metal was not exposed and again the ceramic was polished.

Marginal bone level changes (Tables 2 and 3):

At implant placement, there were statistically significant differences between the three groups: bone levels were 0.52 ± 0.62 mm (CI 95% 0.15; 0.90) for immediately loaded; 0.26 ± 0.46 mm (CI 95% -0.02; 0.54) for early loaded; and 0.04 ± 0.13 mm (CI 95% -0.04; 0.11) for conventionally loaded implants (P (Kruskal Wallis test) = 0.003; Table 2). Pairwise comparisons showed statistically significant differences between the immediate and

Table 2 Mean radiographic peri-implant marginal bone levels between groups and time periods up to 1 year post-loading.

	Implant placement	Loading	1-year after loading	
	N Mean ± SD (95% CI)	N Mean ± SD (95% CI)	N Mean ± SD (95% CI)	*P*-value intra-group
Immediate	13 0.52 ± 0.62 (0.15; 0.90)[a]	12 0.59 ± 0.44 (0.30; 0.87)	17 0.54 ± 0.40 (0.33; 0.75)	Baseline – loading 0.214; baseline – 1 year 0.155; loading – 1 year 0.241
Early	13 0.26 ± 0.46 (-0.02; 0.54)	14 0.42 ± 0.37 (0.21; 0.63)	18 0.36 ± 0.39 (0.17; 0.56)	Baseline – loading 0.139; baseline – 1 year 0.285; loading – 1 year 0.859
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 (0.06; 0.47)	Baseline – loading 0.005*; baseline – 1 year 0.012*; loading – 1 year 0.093
P-value intergroup	0.003*	0.422	0.131	

*Statistically significant difference, subsets with statistically significant difference in pairwise comparisons. Regarding the missing cases: 14 patients at baseline and nine at loading only had orthopantomographs; in one case the loading radiographs were missing; in two cases at loading and three cases at the 1-year follow-up, the quality of the radiographs taken was not sufficient to be able to measure the marginal bone levels; there were two drop-outs at the 1-year follow-up.

Table 3 Mean radiographic peri-implant marginal bone level changes between groups and time periods up to 1 year post-loading.

	Difference placement – loading	Difference placement – 1 year
	N Mean ± SD (95% CI)	N Mean ± SD (95% CI)
Immediate	10 0.22 ± 0.53 (-0.16; 0.59)	12 0.19 ± 0.44 (-0.09; 0.47)
Early	12 0.20 ± 0.42 (-0.07; 0.46)	13 0.18 ± 0.66 (-0.23; 0.58)
Conventional	14 0.36 ± 0.30 (0.18; 0.53)	12 0.25 ± 0.28 (0.07; 0.43)
P-value intergroup	0.659	0.806

conventionally loaded groups (*P* = 0.002). At loading, there was no statistically significant difference between the three groups for peri-implant bone levels: 0.59 ± 0.44 mm (CI 95% 0.30; 0.87) at immediately loaded; 0.42 ± 0.37 mm (CI 95% 0.21; 0.63) at early loaded; and 0.39 ± 0.35 mm (CI 95% 0.20; 0.58) at conventionally loaded (*P* (Kruskal Wallis test) = 0.422; Table 2). For bone loss results were: 0.22 ± 0.53 mm (CI 95% -0.16; 0.59) at immediately loaded; 0.20 ± 0.42 mm (CI95% -0.07; 0.46) at early loaded; and 0.36 ± 0.30 mm (CI 95% 0.18; 0.53) for the conventionally loaded implants – *P* (Kruskal Wallis test) = 0.659; Table 3). One year after loading, there was no statistically significant difference between the three groups for peri-implant bone levels: 0.54 ± 0.40 mm (CI 95% 0.33; 0.75) at immediately; 0.36 ± 0.39 mm (CI 95% 0.17; 0.56) at early; and 0.27 ± 0.36 mm (CI 95% 0.06; 0.47) at conventionally loaded (*P* (Kruskal Wallis test) = 0.131; Table 2), For bone loss: 0.19 ± 0.44 mm (CI 95% -0.09; 0.47) at immediately loaded; 0.18 ± 0.66 mm (CI 95% -0.23; 0.58) at early loaded; and 0.25 ± 0.28 mm (CI 95% 0.07; 0.43) for conventionally loaded implants; *P* (Kruskal Wallis test) = 0.806; Table 3). Only the conventionally loaded group gradually lost statistically significant marginal peri-implant bone at 1 year post-loading (*P* (Wilcoxon signed rank test) = 0.012).

The comparison of the clinical outcome between the two clinicians is presented in Table 4. There were statistically significant differences of -0.42 between the two operators for marginal bone loss at 1 year after implant placement (*P* (Mann-Whitney U test) = 0.002).

■ Discussion

The present 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

Table 4 Comparison of the clinical outcomes of the two operators. Each operator treated 27 patients.

	Dr Siormpas	Dr Pistilli	*P*-value
Dropout	0	2	0.491
Patients with failed prostheses	0	0	NE
Patients with failed implants	0	0	NE
Patients with complications	0	3	0.104
Marginal bone loss ± SD	N = 24 (0.35 ± 0.48)	N = 13 (-0.07 ± 0.36)	0.002*

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

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 their preferred option.

There are many RCTs comparing immediate, early and conventional loading of dental implants[4,6,7,9-33]. Our results are in agreement with most of the published RCTs, with the exception of two trials[6,7] that reported higher failure rates of immediately loaded and early loaded implants, respectively.

The most relevant factor, which may explain the good results obtained in this trial, is the high insertion torque at implant placement. To qualify for the immediate and early loading, implants had to be inserted with torque superior to 40 Ncm. To achieve this in cases with medium and soft bone quality, implant sites were under-prepared with drills with a diameter one or two sizes smaller than the final implant diameter. This explanation is supported by the findings of two trials[5,34]. In a non-randomised controlled trial of split-mouth design, single implants were either immediately non-occlusally loaded or conventionally loaded. The authors found a strong correlation between low implant insertion torque and implant failures for immediately loaded implants. In fact, out of 10 single implants placed with an insertion torque of 20 Ncm, nine failed, whereas only one implant failed out of 10 implants inserted with a torque of at least 32 Ncm[5]. 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 superior to 80 Ncm. Seven implants inserted with a torque between 25 and 35 Ncm failed vs none of those implants placed with insertion torque superior to 80 Ncm[34]. The difference was statistically significant, which suggests 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)[34], and an accurate control of loading. Some authors also advocate the use of specific implant surface modifications to reduce the healing time[35], but no evidence yet supports this hypothesis[36]. 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 it is most likely that patients prefer immediate loading.

The 0.4 mm difference in marginal bone loss between the two centres observed at 1 year after loading is difficult to explain, although it may not have any clinical significance. However, Dr Pistilli often took panoramic radiographs instead of periapical radiographs at implant placement and loading in fully and in some partially edentulous patients. Bone levels on panoramic radiographs were not evaluated, since they are less reliable, and the lack of baseline periapical radiographs could have affected the precise evaluation of bone level changes at this centre.

While recognising there was also an unexpected difference at implant placement for bone levels between the three groups, we could not find any reasonable explanation for this. It might be simply due to chance, taking into account the small number of included patients.

The present trial originally included three centres in Greece, Lithuania and Italy. Unfortunately, the Lithuanian centre did not provide any data for

the 1-year follow-up and had to be excluded. The advantages of multicenter trials are twofold: more patients can be included, increasing the precision of the results, and the results are more general when more centres achieve similar results. On the other hand, the logistic organisation of multicenter trials is more complex, and there is always the risk that some centres may inadvertently operate in a different way. 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, two additional centres that originally agreed to participate in this trial did not recruit any patients. Hopefully putting together data from patients enrolled in different RCTs, thus increasing the sample size, in future meta-analyses, could overtake this limitation. 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 Dr Pistilli's centre, which may explain some of the baseline differences between groups that may not be real. The final limitation related to the substantial number of protocol deviations reported; it is impossible to say to what extent they could have affected the results, although the complexity of the interventions increased.

With regard to the generalisation (external validity) of these findings, it should be recognised that these procedures were tested in real clinical conditions and that patient inclusion criteria were broad. Therefore, results can be generalised to a wider population, keeping in mind that the operators were highly experienced in immediate loading procedures.

Conclusions

All loading strategies were successful, with no significant differences between them, although immediate and early loading achieved similar results in a shorter time frame. If treatment duration is an issue for the patient, then immediate loading could be a better choice, if implants are placed with a sufficient insertion torque.

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