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IMMEDIATE NON-OCCLUSAL *VERSUS* EARLY LOADING OF DENTAL IMPLANTS IN PARTIALLY EDENTULOUS PATIENTS - —15-YEAR FOLLOW-UP OF A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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PURPOSE. To compare peri-implant bone and soft-tissue levels at immediately non-occlusally loaded *versus* non-submerged early-loaded implants in partially edentulous patients 15 years after loading.

MATERIALS AND METHODS. Fifty-two patients from five Italian private practices were randomised, 25 to immediate loading and 27 to early loading. To be immediately loaded, single full Osseotite implants had to be inserted with a torque of at least 30 Ncm, and splinted implants with a torque of at least 20 Ncm. Immediately loaded implants were provided with non-occluding temporary restorations within 48 hours, which were brought into full occlusion after 2 months. In the early loading group, implants were loaded after 2 months. Definitive restorations were provided 8 months after implant placement in both groups. Outcome measures were prosthesis failures, implant failures and complications, recorded by non-blinded assessors, and peri-implant bone and soft-tissue levels, as evaluated by blinded assessors.

RESULTS. Fifty implants were loaded immediately and 54 early. Twelve patients with 24 implants dropped out from the immediate group *versus* 11 patients with 22 implants from the early loaded group, but all remaining patients were followed up for at least 15 years after loading. One single implant with its provisional crowns and one definitive prothesis failed in the immediate loading group. Seven patients with immediately loaded and two with early loaded implants reported complications.
There were no statistically significant differences between groups in terms of implant failures (Fisher's exact test P = 0.481; diff. = -0.04, 95% CI: -0.16 to 0.08), prosthesis failures (Fisher's exact test P = 0.226; diff. = -0.08, 95% CI: -0.21 to 0.06), or complications (Fisher's exact test P = 0.066; diff. = -0.22, 95% CI: -0.41 to 0.01). There were also no statistically significant differences in peri-implant bone (diff. = 0.28 mm, 95%CI: -0.35 to 0.91; P = 0.368) or soft-tissue level changes (diff. = 0.34 mm, 95%CI: -0.32 to 1.00; P = 0.292) between the two groups. Specifically, after 15 years immediately loaded patients had lost an average of 1.75 mm, and early loaded patients an average of 1.44 mm of peri-implant marginal bone.

CONCLUSIONS. The long-term prognosis of prostheses supported by both immediately and early-loaded implants seems favourable.

INTRODUCTION

The fitting of an immediate prosthesis after placement of a dental implant is highly appreciated by patients, as it drastically reduces treatment times and enables them to live a normal life with minimal discomfort[1,2]. Although immediate and early loading procedures can be successful in carefully selected cases[3], not all authors have demonstrated predictably high success rates[4-8].

Several randomised controlled trials (RCTs) have compared peri-implant marginal bone level changes at implants loaded immediately, early and delayed[1, 2, 4, 9-20]. While it is interesting to observe that a meta-analyses of these RCTs showed a statistically significant 0.1 mm less bone loss in favour of immediate loading when compared to conventional loading, such a difference is unlikely to have any clinical impact[3]. Less information is available on the stability of peri-implant soft tissues when comparing different loading strategies[3]. There is also very little reliable information on the long-term effectiveness of implants loaded at different times, especially on the long-term maintenance of hard and soft peri-implant tissues. Such information is essential to properly understand the actual prognosis of implant-supported prostheses.

The primary aim of this RCT was therefore to compare immediate non-occlusal loading *versus* early loading of implants in partially edentulous patients. The secondary aim was to provide long-term data on the stability of peri-implant tissues. Immediate non-occlusal loading was defined as the seating within 48 hours after implant placement of a provisional prosthesis not in occlusal contact for about 2 months. Early loading was defined as placing a provisional prosthesis after a 2-month period unloaded.

This report presents the clinical data at 15 years after implant loading. Previous publications have reported on 14-month[21,22], 48- and 60-month[23], and 10-year[24] outcomes. This 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/).

MATERIALS AND METHODS
Study design

The study was designed as a parallel-group multicentre randomised controlled trial to compare outcomes of patients who had implants loaded immediately, albeit not in occlusion, with patients having implants loaded after 2 months, via blind assessment of peri-implant marginal bone level and buccal soft tissue levels.

Inclusion/exclusion criteria

Any partially edentulous patient requiring at least one dental implant who was 18 or older and able to understand and sign an informed consent form was eligible for inclusion in this trial. All participants were informed of the nature of the study, and signed a written informed consent form before their enrolment. For patients with multiple edentulous areas to be restored, the operator was free, at the screening visit, to select one area to be included in the trial.

Smokers were included, and patients were grouped according to their declaration into i) non-smokers; ii) moderate smokers (if smoking up to 10 cigarettes per day); or iii) heavy smokers (if smoking more than 10 cigarettes per day).

Patients were not accepted into the study if any of the following exclusion criteria were present:
— General contraindications to implant surgery;
— Irradiation in the head and neck area;
— Poor oral hygiene and motivation;
— Untreated periodontal disease;
— Uncontrolled diabetes;

— Pregnancy or lactation;
— Substance abuse;
— Psychiatric problems or unrealistic expectations;
— Lack of opposing occluding dentition in the area intended for implant placement;
— Severe bruxism or clenching;
— Infection or severe inflammation in the area intended for implant placement;
— Need for bone-augmentation procedures, including sinus lift.

Patients were recruited and treated at five private dental clinics located in northern Italy: Como (2 centres), Milan (2 centres), and Monza (1 centre), all having extensive experience in the treatment of patients using immediate loading procedures. The investigators worked as part of the same team for at least five years before the initiation of this study, and are still working together at the IRCCS Galeazzi, University of Milan, so they developed similar clinical operating procedures. One experienced surgeon at each centre performed all the operations. Patients were randomised to have implants non-occlusally loaded immediately (test group) or early (control group) in a parallel-group study design. Only one prosthesis in the area selected at screening was considered for each patient.

Patients were instructed to use chlorhexidine mouthwash 0.2% for one minute, twice a day, starting three days before the intervention and thereafter for two weeks. All patients received prophylactic antibiotic therapy, specifically amoxicillin 2 g one hour before the intervention and 2 g six hours postoperatively. Patients allergic to penicillin were given clarithromycin 500 mg one hour before the intervention. Ibuprofen 600 mg was given one hour prior to intervention and then twice a day for 3 days.

Full-thickness crestal flaps were raised after crestal or paracrestal incisions, with minimal extension to minimise patient discomfort. Tooth extractions were performed as atraumatically as possible to preserve the buccal alveolar bone. The choice of the implant diameter and length was left up to the surgeon. At four centres, Full Osseotite Tapered Implants FNT, Zimmer Biomet 3i, Palm Beach, FL, USA) with external hexagon connection were used, and inserted according to the manufacturer's instructions. At the Como 1 centre, 16 of the 35 implants placed were the FNT configuration, while 19 out of the 35 were tapered implant prototypes with identical surface characteristics from the same manufacturer. Implant diameters used were 4, 5, and 6 mm; lengths used were 8.5, 10, 11.5, 13, and 15 mm.

Bone density at drilling was subjectively evaluated and the bone at the implant site was classified as either "'hard'", "'medium'", or "'soft"[25]'. Resistance to implant insertion was objectively recorded using Osseocare equipment (Nobel Biocare, Kloten, Switzerland). In the protocol-formulation phase, it was decided that single implants with a torque resistance of less than 30 Ncm, or splinted implants with a torque resistance of less than 20 Ncm that were randomised to the immediately loaded group could be treated as belonging to the early loaded group according to an intention-to-treat analysis. However, the minimal insertion torque required was achieved at all implants, even though 2 implants placed at 20 Ncm in the same patient which should have been loaded immediately, were early loaded instead.

In soft bone, under-preparation was performed using a shaping drill one size smaller than the drill suggested by the manufacturer. In general, implants were placed at the crestal level in healed edentulous ridges, or 1 mm subcrestally in immediate post-extraction sockets. In the event of a residual gap greater than 1.5 mm between the implant surface and bone wall, the gap was filled with granular anorganic bovine bone (Bio-Oss, Geistlich Pharma, Wolhusen, Switzerland). A non-submerged technique was employed. Before placing the abutments, the envelope containing the randomisation code was opened, informing the surgeon whether the

implants were to be loaded immediately or early. Impression copings or healing screws were placed accordingly, and interrupted sutures were placed using a monofilament thread. An impression with the pick-up impression copings was made for the implants to be immediately loaded, and healing abutments were fitted. Ice packs were provided, and a soft diet was recommended. Smokers were told to avoid smoking for 48 hours postoperatively.

Acrylic resin provisional restorations were provided to patients from the immediately loaded group the following day. The occlusal surface of the provisional restoration was ground to avoid any static or dynamic occlusal contact with the opposing dentition. All provisional prostheses in the immediately loaded group were fitted within 48 hours. Sutures were removed 2 weeks after implant placement.

Two months after implant placement, resin was added to the immediate non-occlusally loaded restorations to bring them into full occlusion. Patients from the early loading group received provisional restorations identical to those of the immediate loading group, with full occlusal contact two months after implant placement. Definitive metal-ceramic restorations were cemented eight months after implant placement.

Patients were recalled for oral hygiene maintenance and prosthesis checks every 3 months up to the first year, and thereafter every 6 months.

Primary outcome measures, assessed by the treating dentists, who were therefore not blinded, were the following.

— Prosthesis failure: the planned prosthesis could not be placed or was lost because of implant failure, or was replaced for any reason.

— Implant failure: any mobility of the individual implant (assessed manually by rotating the implant) at insertion of the provisional or definitive prostheses, and/or any infection dictating implant removal, as well as implant fracture or any mechanical complication rendering the implant unable to support a prosthesis. After insertion of the definitive restorations, prostheses were not removed to assess clinical mobility of individual implants.

— Any biological or prosthetic complications. Examples of possible biological complications were: numbness of the lower lip and chin, peri-implant mucositis (heavily inflamed soft tissue without bone loss), peri-implantitis (bone loss with suppuration or heavily inflamed tissues), fistulas, etc. Examples of possible prosthetic complications were: fracture of the implant, abutment screw, framework, occlusal material, etc.

Secondary outcome measures were the following.

— Peri-implant marginal bone-level changes on intraoral radiographs made using the paralleling technique. Periapical radiographs were taken at implant placement, at 2, 8, 14, 48 and 60 months, and 10 and 15 years after implant placement. Non-digital radiographs were scanned (HP Scanjet 3c/t, Hewlett Packard, Cernusco sul Naviglio, Italy), digitized into JPG, converted to TIFF format with 600-dpi resolution, and stored on a desktop computer. Peri-implant marginal bone levels were measured using Scion Image (Scion Corporation, Frederick, MD, USA) software, calibrated for every single image using the known distance between two consecutive threads (0.9 mm for FNT implants, and 0.6 mm for the prototype implants). Measurements of the mesial and distal bone-crest level adjacent to each implant were made to the nearest 0.01 mm. Reference points for the linear measurements were: the coronal margin of the implant collar and the most coronal point of bone-to-implant contact. Measurements of mesial and distal sides were averaged at implant level, then at patient level, and finally at group level.

— Vestibular soft tissue recessions (height of the clinical crown), measured with a digital calliper (Calliper IP54, Sham, Guillin, China) on hard plaster models. Impressions were ta-

ken at 8 months (after fitting and adjustment of the final restorations), 14 months, and 5, 10 and 15 years using a high dimensional stability alginate (Zhermack, Hidrogum 5, Badia Polesine, Italy). Plaster models were immediately prepared using extra-hard plaster (type 4). For incisors the reference point was the middle of the incisal margin; for canines and premolars it was the tip of the cuspid; and for molars the deepest vestibular occlusal margin between the two cusps. Measurements were made vestibularly from the occlusal reference point, perpendicular to the gingival margin.

Up to 1 year, all radiographic and soft tissue measurements were made in duplicate, after at least a 15-day interval, and the two values were averaged. However, after the first year, since the previous difference between the two assessments was negligible, only one assessment was taken. These measurements were made by two independent, blinded, calibrated outcome assessors. One measured all radiographs and the other the clinical crown heights on plaster models up to one year after loading. For the 48- and 60-month assessments, the assessors were switched, i.e., the one who had performed the bone level assessment up to 1 year performed the soft tissue assessment, and vice-versa. For the 10-year assessment, two new, trained assessors blindly evaluated the peri-implant bone and soft tissue levels. Finally, for the 15-year assessment, one trained assessor evaluated both soft tissue and peri-implant radiographic bone levels blind. All radiographs were coded so that outcome assessors were blind to which group the implants belonged to, and no assessor was informed of the aims of the study. Since the assessors did not know which crowns to measure on the plaster models, the study implant-supported crowns were marked with a black spot.

The sample size was chosen based on calculations of the number of patients likely to have at least one restoration failure (primary outcome measure). In a study of partially edentulous patients, the proportion of failures in the immediately loaded group was 0.39, as compared to 0.04 in the conventionally loaded group[5]. Accordingly, it was calculated that a two-group continuity-corrected chi-squared test with a 0.050 two-sided significance level would have 80% power to detect the difference between a proportion of 0.39 and a proportion of 0.04 (odds ratio of 0.065) with a sample size in each group of 26 patients. It was therefore planned to include 30 patients in each group to allow for potential drop-outs.

A restricted randomisation list was manually generated to create two groups with equal numbers of patients. Only one of the investigators (Dr. Esposito), not involved in the selection and treatment of the patients, was aware of the randomisation sequence and had access to the randomisation list, stored on a password-protected laptop. The randomisation codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially only after the implants to be included in the trial were inserted, thereby concealing treatment allocation 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. Two biostatisticians and one medical doctor analysed the data from the previous reports[21-24]. One dentist with expertise in statistics (Dr. Jacopo Buti) analysed the data in the current report, without knowing the group allocation. Differences in the proportion of failures and other complications between the groups were compared using Fisher's Exact probability test. Radiographic mesial and distal implant surface values and buccal crown lengths were then averaged for each patient. Comparisons between each time point and the baseline measurement were made using paired tests to detect any changes in bone or soft-tissue levels. Analysis of covariance was used to compare the mean radiographic and soft-tissue values at 15 years (outcome variable), with the baseline value as a covariate.

Differences among centres for dichotomous outcomes were calculated using the chi-squared test or the Freeman-Halton extension of Fisher's Exact test (when cell count <5). Between-centre differences in mean radiographic and soft tissue values at 10 years were calculated using an analysis of covariance with the baseline value as covariate. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

All patients eligible for this trial agreed to participate. Fifty-two patients were consecutively enrolled in the trial and randomised, 25 to the immediate loading group and 27 to the early loading group. The planned number of 30 patients per group was not reached, since the centres decided to stop patient recruitment at the end of May 2005. All patients were treated according to the allocated interventions. The minimal insertion torque required was achieved at all implants.

Twenty-three patients dropped out during the entire follow-up period (**TABLE 1**): twelve patients with 24 implants dropped out from the immediate group *versus* 11 patients with 22 implants from the early loading group. Unfortunately, one investigator (Como 2) moved to another country after the 10-year follow-up. All his patients were contacted, but only one agreed to attend the 15-year follow-up. More precisely the drop-outs were the following.

Immediate loading group
— Patient #55, with two implants, died of a heart attack between years 5 and 10.
— Patient #53, with three implants, died of cancer around year 8.
— Patient #43, with one implant, moved. Last seen in year 11.
— Patient #7, with 2 implants, become unreachable. Last seen in year 12.
— Patient #51, with three implants, did not attend the 15-year follow-up. Last seen in year 13.
— For Patients #16, 18, 20, 23, 31, 34 and 59, the centres did not provide either the reason for dropping out, with exception of Patient #23, who become unreachable, or when patients were seen last time. Nonetheless, all these patients were seen at the 10-year follow-up.

Early loading group
— Patient #48, with one implant, moved to another town. Last seen in year 6.
— Patient #44, with two implants, did not want to attend the 15-year follow-up but reported that everything was fine. Last seen in year 9.
— Patient #46, with two implants, moved. Last seen at year 9 and 6 months.

TABLE 1 NUMBER OF PATIENTS RANDOMLY ALLOCATED IN THE TRIAL AND, IN PARENTHESIS, NUMBER OF DROP-OUTS ACROSS CENTRES. ORIGINALLY SIX CENTRES WERE SUPPOSED TO TREAT 10 PATIENTS EACH

CENTRE	IMMEDIATE (N = 25)	EARLY (N = 27)
Como 1 (Dr. Testori)	9 (4 patients with 10 implants)	6 (1 patient with 1 implant)
Como 2 (Dr. Ritzmann)	2 (2 patients with 3 implants)	5 (4 patients with 10 implants)
Milan 1 (Dr. Zuffetti)	6 (4 patients with 7 implants)	6 (1 patient with 2 implants)
Milan 2 (Dr. Capelli)	4 (1 patients with 3 implants)	4 (1 patient with 1 implant)
Monza (Dr. Galli)	4 (1 patient with 1 implant)	6 (4 patients with 8 implants)

- Patient #45, with three implants, moved. Last seen at year 10 and 6 months.
- For Patients #6, 17, 22, 32, 33, 35 and 36, the centres did not provide either the reason for dropping out, with exception of Patient #22, who become unreachable, or when patients were seen for the last time. Nevertheless, all these patients were seen at the 10-year follow-up.
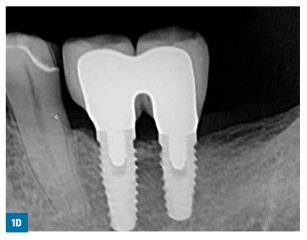
Patients were recruited and treated from October 2004 to May 2005, and were followed up for at least 15 years after initial loading (**FIGS. 1A-D, 2A-F**). Initially, six centres agreed to participate by treating ten patients each; however, two centres withdrew before starting the trial, and a new centre was added as partial replacement. The remaining envelopes containing the randomisation codes were redistributed among the centres with higher recruitment capacities. The patient distribution across the various centres is shown in **TABLE 1**. The main baseline patient characteristics are presented in **TABLE 2**. Patients were generally healthy. Three patients suffered from hypertension and one from hepatitis C. By chance, these four patients were all randomised to the early loading group.

Fifty-two implants were allocated to the immediate loading group, and 52 to the early loading group. The lengths and diameters of the implants inserted are presented in **TABLE 3**, while the

FIGS. 1A-D: *Treatment outcome in Patient # 42, randomly allocated to early loading: clinical (A) and radiographic (B) images at definitive prosthesis fitting, and clinical (C) and radiographic (D) images at the 15-year post-loading follow-up. Note the healthy peri-implant tissues and the minimal buccal recession and peri-implant bone loss at implants in positions 36 and 37. More recessions occurred at natural teeth 34 and 35, most likely due to toothbrush abrasion over a 15-year period*

TABLE 2 PATIENT AND INTERVENTION CHARACTERISTICS

	IMMEDIATE (N = 25)	EARLY (N = 27)
Females	12	17
Mean age at implant insertion (range)	51.6 (27–74)	51.3 (34–73)
Smokers	9 moderate	3 moderate & 1 heavy
Total number of implants inserted	52*	52
Total number of prototype implants inserted (only by 1 centre)	11	8
Implants inserted in mandibles	38	21
Implants inserted in anterior areas (canine to canine)	3	3
Implants inserted in fresh extraction sockets	6	9 (1 grafted)
Number of patients receiving single implants	7	10
Number of patients receiving two implants	10	9
Number of patients receiving three implants	7	8
Number of patients receiving four implants	1	0

Two out of four implants placed in the same patient with an insertion torque of 20 Ncm which should have loaded immediately were early loaded instead

bone density, subjectively evaluated, and the maximum insertion torque (primary implant stability) appear in **TABLE 4**. There were no apparent significant baseline imbalances between the two groups, with the exception of more smokers and mandibles receiving immediately loaded implants.

Deviations from the operating protocol identified were the following.

— One centre (Como 1) also used some prototypes of tapered implants with identical surface characteristics made by the same manufacturer (19 out of 35 implants inserted).
— The centres asked to use only autogenous bone chips to fill bone-to-implant gaps at immediate post-extraction implants, but actually used a bone substitute instead.
— One patient from the immediate loading group who received four implants had the two distal prototype implants inserted with a 20 Ncm torque, and loading was delayed instead of being conducted immediately as per protocol (**FIGS. 2A-F**).
— One patient from the immediate loading group was fitted with his final restoration after 2 months instead of the planned 8 months.
— One patient from the early loading group received his definitive prosthesis 14 months after implant placement due to cardiac disease. However, that patient's implants were assessed for stability at the planned 8-month interval.
— One patient from the immediate loading group had no impressions taken at 15-year follow-up to evaluate buccal soft tissue recession.
— Four patients from the early loading group had no impressions taken, and two no periapical radiographs at 15-year follow-up.

Prosthesis failures

Two prostheses failed in the immediate loading group *versus* no prosthesis in the early loaded group. There were no statistically significant differences in prosthesis failures between the two interventions (Fisher's Exact test P = 0.226; diff. = -0.08, 95% CI: -0.21 to 0.06).

TABLE 3 LENGTH AND DIAMETERS OF THE IMPLANTS INSERTED

IMPLANT LENGTH	IMMEDIATE (N = 52)	EARLY (N = 52)
8.5 mm	8	2
10 mm	18	16
11.5 mm	13	15
13 mm	11	17
15 mm	2	2
Implant diameter	Immediate (n = 52)	Early (n = 52)
4 mm	38	33
5 mm	12	18
6 mm	2	1

TABLE 4 BONE DENSITY, EVALUATED CLINICALLY AND WITH THE OSSEOCARE DEVICE (PRIMARY IMPLANT STABILITY)

TACTILE BONE DENSITY	IMMEDIATE (N = 52)	EARLY (N = 52)
Hard	1	2
Medium	43	40
Soft	8	10
Insertion torque	Immediate (n = 52)	Early (n = 52)
20 Ncm	3*	4
30 Ncm	6	14
40 Ncm	18	20
50 Ncm	22	14
60 Ncm	3	0

Two out of four implants placed in the same patient with an insertion torque of 20 Ncm, which should have loaded immediately, were early loaded instead

One provisional crown failed two months after placement due to failure of its supporting implant (see below; Patient #21), and one definitive prosthesis supported by 3 implants in position 44, 45 and 46 had its ceramic lining fractured about three years after loading; the prosthesis was remade (Patient #14).

Implant failures

A single implant and its provisional crown, inserted in position 25 (second left upper premolar) in medium bone density with a primary stability of 50 Ncm, failed 2 months after placement in the immediate loading group (Patient #21). The failed implant was successfully replaced with another implant after six months of healing. There were no statistically significant differences in implant failures between the two interventions (Fisher's Exact test P = 0.481; diff. = -0.04, 95% CI: -0.16 to 0.08).

FIGS. 2 A-F: *Treatment outcome in Patient # 3, randomly allocated to immediate loading: occlusal (A), buccal (B) and radiographic (C) images at provisional prosthesis fitting, and lingual (D), buccal (E) and radiographic (F) images at the 15-year post-loading follow-up. Note the two protocol deviations in the treatment of this patient: the two distal implants were of different types to those to be used, and despite being placed with a torque of 20 Ncm, they were not immediately loaded as they should have been per the protocol. More bone loss occurred at the two distal implants loaded early, and crown margin become visible at implants in position 33 and 35*

Complications

Eleven complications affecting nine different patients were reported, seven from the immediate (nine complications) and two from the early loading group (two complications). There were no statistically significant differences in patients having complications between the two interventions (Fisher's Exact test P = 0.066; diff. = -0.22, 95% CI: -0.41 to 0.01).

The following complications occurred at immediately loaded implants:

— Patient #14 had a fracture of the ceramic lining of the prosthesis supported by 44, 45 and 46 around 3-year follow-up. The prosthesis was remade;

— Patient #53 had peri-implantitis at implant 16, noticed at 7 years and 5 months after loading. However, the patient was severely ill, and died of unrelated causes before proper treatment could be administered;

— Patient #59 had mucositis around implants in position 45, 46 and 47 nine years after loading. It was successfully treated with intrasulcular 0.2% chlorhexidine irrigation;

— Patient #41 had recession of the soft tissues around implants in position 45 and 46, exposing the titanium abutments, nine years after loading. No treatment was attempted;

— Patient #47 had recession of the soft tissues around the implant in position 16, exposing the titanium abutment, nine and half years after loading. No treatment was attempted;

— Patient #1 displayed severe peri-implantitis at the implant in position 36, noticed on the periapical radiograph taken at the 15-year follow-up. Treatment will be attempted;

— Patient # 3 had recession of the soft tissues, exposing the titanium abutments, around implants in positions 33 and 35 15 years after loading. No treatment was attempted.

The following complications occurred at early loaded implants:

— Patient #44 was affected by peri-implantitis around two implants in positions 36 and 37, detected 33 months after implantation. The patient did not show up for regular recalls between months 14 and 33. On the control periapical radiograph, bone loss up to the fourth threads was observed, despite the peri-implant tissues appearing clinically healthy, with no evident sign of pathology. A flap was immediately raised, revealing the presence of cement around the exposed margins of the prosthesis. The excess cement was removed, the defect carefully debrided, and the implant surface thoroughly cleaned with a bicarbonate jet. The defect was filled with granular anorganic bovine bone (Bio-Oss, Geistlich Pharma, Wolhusen, Switzerland), and covered with a resorbable collagen membrane (Bio-Gide, Geistlich Pharma). The post-operative healing was uneventful, and health was maintained over time;

— Patient #58 chipped his partial mandibular prosthesis supported by implants in positions 45, 46 and 47 eight years after loading. The prosthesis was polished, resolving the problem.

Peri-implant marginal bone level changes

Both groups gradually lost marginal peri-implant bone in a highly statistically significant way (P <0.001) at 2, 8, 14, 48 and 60 months, and 10 and 15 years (**TABLE 5**). After 2 months, patients in the immediate loading group had lost an average of 0.5 mm peri-implant bone, *versus* 0.6 mm in patients from the early loading group (**TABLE 6**). After 8 months, patients in the immediate loaded group had lost an average of 0.9 mm of peri-implant bone *versus* 1.0 mm for the patients in the early loading group (**TABLE 6**). After 14, 48 and 60 months, patients from both had groups lost an average of 1.1, 1.2 and 1.2 mm of peri-implant bone, respectively (**TABLE 6**). After 10 years, immediately loaded patients had lost an average of 1.34 mm, and early loaded patients an average of 1.42 mm of peri-implant marginal bone (**TABLE 6**). Finally, after 15 years, immediately loaded patients had lost an average of 1.75 mm and early loaded patients 1.44 mm of peri-implant marginal bone (**TABLE 6**). Fifteen years after loading, there was no statistically significant difference in peri-implant bone-level changes between the two loading strategies when analysis of covariance was applied (diff. = 0.28 mm, 95%CI: -0.35 to 0.91; P = 0.368).

Vestibular soft tissue recessions

After 15 years, there was statistically significant recession of the vestibular soft tissues from baseline (fitting of the final restorations 8 months after implant placement) at immediately (0.55 mm; P <0.036) but not at early loaded implants (0.16 mm; P <0.461). There were no stati-

TABLE 5 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS IN MM BY GROUP AND TIME PERIODS

	BASELINE		2 MONTHS*		8 MONTHS*		14 MONTHS*		48 MONTHS*		60 MONTHS*		10 YEARS*		15 YEARS*	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Immediate loading	25	0.03 (0.09)	25	0.55 (0.50)	24	0.95 (0.56)	24	1.13 (0.56)	24	1.15 (0.55)	24	1.18 (0.56)	21	1.37 (0.57)	12	1.81 (0.85)
Early loading	27	0.07 (0.16)	27	0.67 (0.46)	27	1.04 (0.52)	27	1.18 (0.51)	26	1.25 (0.50)	26	1.28 (0.50)	25	1.49 (0.60)	14	1.54 (0.66)

All changes from baseline statistically different (P <0.001)

TABLE 6 COMPARISON BETWEEN GROUPS OF MEAN CHANGES IN PERI-IMPLANT MARGINAL BONE LEVELS IN MM AT DIFFERENT TIME PERIODS

	BASE.–2 MONTHS			BASE.–8 MONTHS			BASE.–14 MONTHS			BASE.–48 MONTHS			BASE.–60 MONTHS			BASE.–10 YEARS			BASE.–15 YEARS		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Immediate loading	25	0.52	(0.48)	24	0.92	(0.55)	24	1.10	(0.58)	24	1.12	(0.54)	24	1.15	(0.56)	21	1.34	(0.55)	12	1.75	(0.88)
Early loading	27	0.60	(0.46)	27	0.97	(0.50)	27	1.11	(0.54)	26	1.18	(0.49)	26	1.21	(0.49)	24	1.42	(0.64)	14	1.44	(0.64)
P -value																				0.368*	

*Base. = baseline (implant insertion); *Analysis of covariance for 15 years with baseline as a covariate*

stically significant differences between the two loading strategies in terms of soft tissue changes (diff. = 0.34 mm, 95%CI: -0.32 to 1.00; P = 0.292; **TABLE 7**).

Comparisons among centres revealed no statistically significant difference (**TABLES 8, 9**) in any of the outcomes considered.

DISCUSSION

The primary aim of this trial was to compare the clinical outcomes of immediate and early loading implants in partially edentulous patients; however, the long-term tissue stability of peri-implant tissues was also evaluated. The data reported here cover a follow-up period of 15 years after implant placement, and show that both loading strategies yielded good clinical outcomes which were maintained over a 15-year period of time. No statistically significant differences were observed between implants loaded immediately and early. Specifically, patients rehabilitated with immediately loaded implants lost an average of 1.75 mm, and those with early loaded implants lost 1.44 mm of peri-implant marginal bone. Values for buccal soft tissue recession were 0.55 mm and 0.16 mm, respectively. The mean peri-implant marginal bone loss across the entire sample was 1.58 mm, whereas buccal soft tissues receded by only 0.35 mm. The number of patients affected by complications was also reasonable seven immediately loaded *versus* two early loaded. Despite no statistically significant differences being observed, for all the parameters evaluated there was a slight trend in favour of loading implants early.

TABLE 7 COMPARISON BETWEEN GROUPS AND TIME PERIODS OF SOFT-TISSUE RECESSION IN MM

	8–14 MONTHS			8–60 MONTHS			8 MONTHS–10 YEARS			8 MONTHS–15 YEARS			P-VALUE 8 MONTHS vs. 15 YEARS	P-VALUE IMMEDIATE vs. EARLY LOADING
	N	Mean Diff	(SD)	N	Mean Diff	(SD)	N	Mean Diff	(SD)	N	Mean Diff	(SD)		
Immediate loading	24	0.13	(0.40)	24	0.20	(0.40)	21	0.38	(0.75)	11	0.55	(0.75)	0.036*	
Early loading	27	0.01	(0.37)	26	0.05	(0.37)	25	0.25	(0.45)	12	0.16	(0.72)	0.461	0.292§

Change statistically different from baseline (8 months after implant placement); §Analysis of covariance for 15 years with baseline as a covariate

TABLE 8 COMPARISON AMONG STUDY CENTRES OF DROP-OUTS, FAILURES AND COMPLICATIONS EXPRESSED AT PATIENT LEVEL (N = NUMBER OF PATIENTS) AT 15-YEAR POST-LOADING

	COMO1 (N = 15)	COMO2 (N = 7)	MILAN1 (N = 12)	MILAN2 (N = 8)	MONZA (N = 10)	TOTAL (N = 52)	P-VALUE[a]
Drop-outs	5	6	5	2	5	23	0.150
Patients with prosthesis failures	0	0	1	1	0	2	0.412
Patients with implant failures	0	0	0	1	0	1	0.288
Patients with complications	3	0	3	0	3	9	0.393

[a]*Freeman-Halton extension of Fisher Exact test (when cell count <5)*

TABLE 9 MEAN RADIOGRAPHIC AND SOFT TISSUE AND PERI-IMPLANT MARGINAL BONE CHANGE ESTIMATES, WITH BASELINE ASSESSMENTS AS COVARIATE PER CENTRE AT 15 YEARS (N = NUMBER OF PATIENTS)

	BONE LEVEL CHANGES			SOFT TISSUE LEVEL CHANGES		
	N	Mean	95%CI	N	Mean	95%CI
Como1	8	1.83	(1.13 to 2.52)	6	0.38	(0.03 to 0.74)
Como2	1	0.66	(- to -)	0	-	(- to -)
Milano1	7	2.04	(1.46 to 2.62)	7	0.06	(-0.54 to 0.66)
Milano2	5	0.89	(0.10 to 1.68)	5	0.08	(-0.81 to 0.97)
Monza	5	1.43	(1.01 to 1.84)	5	0.96	(-0.32 to 2.24)

No statistically significant differences between centres

It is interesting to observe that the implants used in the present investigation, roughened up to the neck (Dual Acid-Etched Full-Osseotite implant surface), performed well over a long time period. There were just three episodes of peri-implantitis, which affected about 10% of the patients who were prospectively followed up to 15 years. To better appreciate such an achievement, it should be considered that a retrospective study with a follow-up of 9 to 14 years on implants with a machined surface reported a 16% prevalence of peri-implantitis at patient level[26].

In our trial, the pattern of peri-implant bone loss was virtually identical for both groups. This is in agreement with a meta-analysis(3) including a previous report on this trial plus two other similar RCTs[2,27], which showed no statistically significant differences between the two loading strategies (P = 0.19; mean difference -0.06 mm, 95% CI from -0.16 to 0.03) at 1 year, with immediate loading being slightly superior.

We are unable to compare the long-term data presented here with that from other investigations using the same implants, because no such research could not be identified. However, another long-term RCT reported excellent clinical results at 10 years after loading and no significant differences between immediately and early loaded implants[28].

When interpreting the finding of statistically significant recession of vestibular soft-tissue levels after fitting of the definitive restorations clinically, it should be considered that an average of 0.55 mm (immediately loaded group) and 0.16 mm (early loaded group) after 15 years in function may not have a major clinical impact. It is possible, though, that some soft tissue recession may have occurred during the first 8 months, when the provisional restorations were in use. Subsequently, vestibular soft tissue levels remained stable over a 15-year period, with only five implants in three immediately loaded patients showing some visible titanium at 15 years after loading. It is also worth noting that recessions did not necessarily reflect the pattern of marginal bone loss (**TABLE 9**), though some recessions may also have occurred before fitting of the definitive prostheses.

The decision to avoid static and dynamic occlusal contacts on immediately loaded prostheses with the opposing dentition for the first 2 months was dictated by the desire to minimise the risk of early implant failures. This decision was based purely on clinical reasoning, even though, most likely, these restorations did bear loads during chewing. Surprisingly, two RCTs that have investigated this hypothesis[7,8] did not find any statistically significant difference, or even clinical trend, when comparing occlusal *versus* non-occlusal immediate loading. However another RCT[29], showed at least a clinical trend favouring non-occluding loading. Therefore, from a clinical point of view, it is tempting to recommend not placing provisional restorations in direct contact with the opposite dentition, when possible, particularly in those situations where clinicians fear that problems might arise (posterior regions, low implant insertion torques, signs of parafunctions, etc.).

The main limitations of this trial are the small sample size and the use by one of the centres of implant prototypes instead of the implants selected at the protocol stage. Nonetheless, the prototypes used were similar to the commercially available implants assessed in this trial, and were randomly placed, concealing group allocation, i.e., without the clinician knowing at placement into which group they were going to be included. As such, they were randomly distributed between the two groups in approximately equal numbers (**TABLE 2**), and it is therefore unlikely that this protocol violation significantly impacted the outcomes of the present study.

Another limitation was the high drop-out rates observed after year 10. Unfortunately, the longer the follow-ups are, the less likely it is that patients will be able to attend. In our case drop-out was mainly due to health issues, moving to other places, or the fear of exposure to COVID 19 during the pandemic. It should also be considered that the original plan was to follow these patients up for 5 years, but the follow-up period was later extended to 15 years after implant loading. It is also worth observing that the precision of the information provided by two centres deteriorated after the 10-year follow-up, since one investigator moved to another country and another centre was unable or unwilling to provide precise information on reasons for and timing of drop-outs.

Concerning the generalisability (external validity) of the present findings, patient inclusion criteria were broad, and both techniques were tested in real clinical conditions. Therefore, our results should be generalisable to a wider population.

CONCLUSIONS

The long-term prognosis of prostheses supported by dual acid-etched full Osseotite implants seems favourable, whether immediately or early loaded.

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