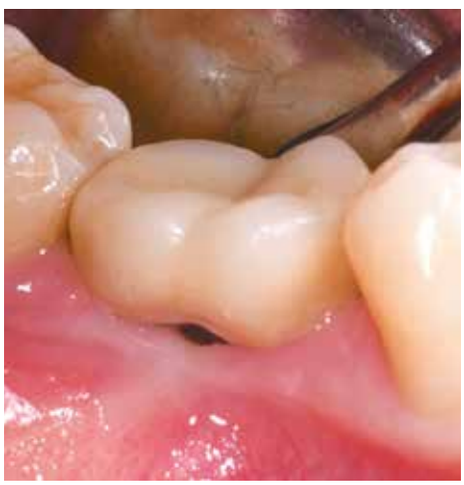
VOLUME **01** NUMBER **1** **DECEMBER** 2019

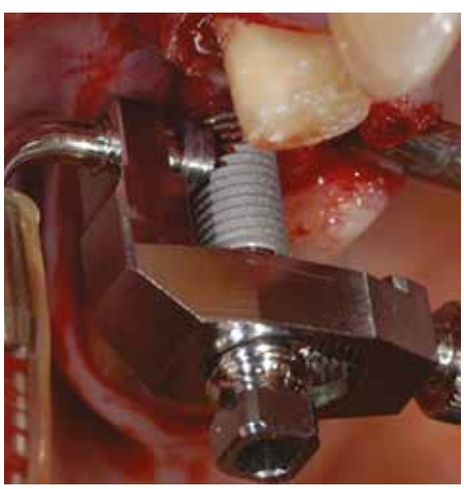
CLINICAL TRIALS *in* DENTISTRY

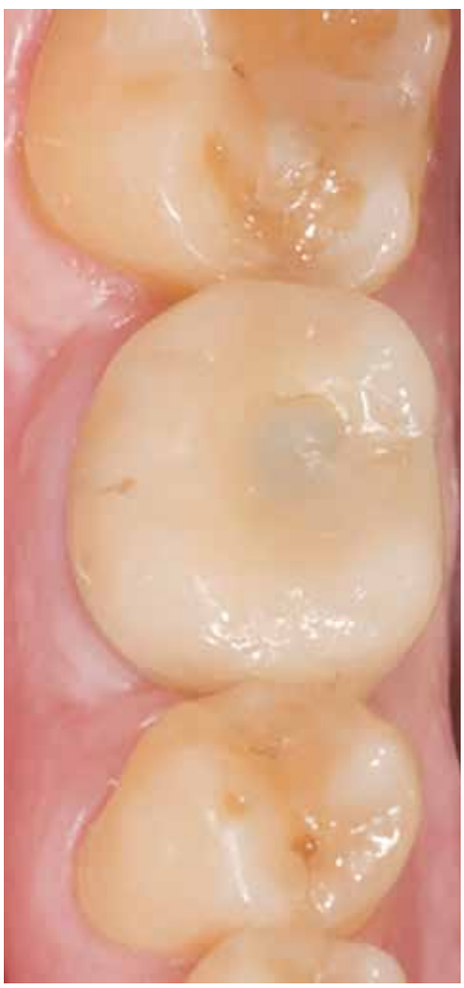
IMMEDIATE *VERSUS* EARLY *VERSUS* DELAYED **POST-EXTRACTIVE IMPLANTS**

4 X 4 MM *VERSUS* LONGER IMPLANTS IN POSTERIOR JAWS

3 MM *VERSUS* 4 MM DIAMETER IMPLANTS IN HORIZONTALLY AUGMENTED BONE







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CLINICAL TRIALS IN DENTISTRY, A NEW EVIDENCE-BASED JOURNAL FOR THE DENTAL PROFESSION

I am proud to present a new scientific clinical journal "Clinical Trials in Dentistry".
The focus of this new journal is to provide reliable scientific evidence to clinicians and patients on the most effective interventions in dentistry.
Why a new journal? This is the most common question I am asked. A new journal is needed because there are no other journals in dentistry specifically publishing reliable clinical trials in a broad range of dental specialties, keeping in mind that the relevance of clinical research will increase in the near future also for the industry due to new European regulations soon to be implemented.
Relevant and transparent randomised controlled trials, cohort studies, case-control studies and systematic reviews focussing on patient treatments in dentistry are warmly welcomed.
The journal will be published by the Italian publisher EDRA. EDRA is an emerging publishing house in the scientific world that strongly believes in this project, sharing our vision and ambitions and is courageously supporting us in this new adventure.
Our aim is not to publish a mass of articles but filter relevant and honest papers that will help all of us in taking evidence-informed clinical decisions for better patient care. It will take some time to be listed in Scopus, Science Citation Index, Medline and to obtain an impact factor, but as we did it before, we shall do it again.
I will be assisted by two valid and prepared Associate Editors: Michele Nieri and Jacopo Buti. Both have an extensive experience in international research, additional degrees in statistics and are from the town where Renaissance was born, Florence.
We shall try our best to select impartially and promote the best manuscripts according to scientific standards. We are optimistic and strongly motivated so time will tell about this new adventure, hoping that the loyal, the brave and the bold readers will follow us.

Happy reading
Marco, Michele and Jacopo

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IMMEDIATE, EARLY (6 WEEKS) AND DELAYED (4 MONTHS) SINGLE POST-EXTRACTIVE IMPLANTS: 3-YEAR POST-LOADING DATA FROM A RANDOMISED CONTROLLED TRIAL

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PURPOSE. To compare the clinical outcome of single implants placed immediately after tooth extraction with those placed 6 weeks after tooth extraction (early placement), and those placed 4 months after extraction and socket healing (delayed placement).

MATERIALS AND METHODS. Two hundred and ten patients requiring one single implant-supported crown to replace a tooth to be extracted were randomised into 3 groups of 70 patients each to receive immediate, early (at 6 weeks), or delayed (after 4 months of healing) post-extraction implants, according to a parallel-group design. When needed, patients from the immediate and early groups had bone substitute grafts in the extraction socket, covered with a resorbable membrane, at implant placement. Sockets randomised to delayed implants were grafted in the same manner if poorly preserved, or in the "aesthetic" areas (from second upper premolar to second upper premolar). Implants inserted with at least 25 Ncm torque were left to heal unloaded for 4 months, whereas those inserted with less than 25 Ncm were left to heal unloaded for 6 months. Temporary crowns were delivered, and were to be replaced by definitive ones after 4 months. Outcome measures were crown and implant failures; complications; peri-implant marginal bone level changes; aesthetics, as assessed using the pink aesthetic score (PES); and patient satisfaction, recorded by blinded assessors. Patients were followed-up for 3 years post-loading.

RESULTS. Three years after loading, drop-outs were: five (7.1%) patients from the immediate, nine (12.9%) from the early, and eight (11.4%) from the delayed group. Five implants (9.2%) failed in the immediate, four (6.6%) in the early, and one (1.6%) in the delayed group (P [Freeman-Halton] = 0.282). Apart from the crowns that failed due to implant losses, no other definitive crown had to be remade. Complications affected eleven patients from the immediate group, 12 from the early, and eight from the delayed group (P [chi-square test] = 0.596). Mean peri-implant marginal bone loss after 3 years was -0.33 ± 0.22 mm at immediate, -0.43 ± 0.26 mm at early, and -0.49 ± 0.30 at delayed implants; (P [Kruskal Wallis test] <0.001); there were significant pairwise differences between immediate and early (0.10 mm; CI 95% -0.02; 0.22; P [Dunn-Bonferroni post-hoc] = 0.0391) and immediate and delayed implants (0.16 mm; CI 95% 0.04; 0.27; P [Dunn-Bonferroni post-hoc] = 0.0004), but no difference between early and delayed implants (0.06 ± 0.05 mm; CI 95% -0.06; 0.18; P [Dunn-Bonferroni post-hoc] = 0.6015). Three years after loading, the mean overall PES were 12.25, 11.98 and 11.17 in the immediate, early and delayed groups, respectively (P [Kruskal Wallis test] <0.001); there were significant pairwise differences between immediate and delayed (1.08 ± 0.27 mm; CI 95% 0.45; 1.72; P [Dunn-Bonferroni post-hoc] = 0.0006), and early and delayed implants (0.81 ± 0.27 mm; CI 95% 0.17; 1.46; P [Dunn-Bonferroni post-hoc] = 0.0099), but no difference between immediate and early implants (0.27 ± 0.27 mm; CI 95% -0.37; 0.90; P [Dunn-Bonferroni post-hoc] = 1.0000). There were no significant diffe-

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rences in patient satisfaction regarding function (P = 0.353) or aesthetics (P=0.531), and all patients would undergo the same procedure again.

CONCLUSIONS. No statistically significant differences in failure, complications or patient satisfaction were observed when placing single implants immediately, 6 weeks or four months after tooth extraction, even though failures were more frequent in immediate and early implants. Bone loss was significantly smaller at immediate implants, and aesthetic evaluation scores were higher for immediate and early implants.

CONFLICT OF INTEREST STATEMENT. This trial was partially funded by Nobel Biocare Services AG (code: 2010-894), the manufacturer of the implants evaluated in this investigation; however, the data belonged to the authors and the manufacturer by no means interfered with the conduct of the trial or the publication of the results. Bone substitutes and membranes were generously provided by Tecnoss (OsteoBiol, Giaveno, Italy).

INTRODUCTION

Osseointegrated dental implants were traditionally placed in healed ridges[1]. Delayed implant placement after healing of the socket is preferred as it may minimise the risk of implant failures and complications, leaving post-extraction sockets to heal for 3 to 6 months before placing dental implants. However, with the traditional approach, long treatment periods and a second surgical intervention are required for implant placement. In addition, removable temporary prostheses are often used during the implant healing period, which many patients find uncomfortable. It would therefore be beneficial if the healing period could be shortened without jeopardizing implant success.

It is possible to place implants immediately after tooth extraction, in the fresh extraction socket. The main advantage of immediate implant placement is to shorten treatment, although immediate post-extraction implants might be at higher risk of complications and failures[2]. As a compromise between placing implants immediately (immediate post-extraction implants) and waiting for 4 to 6 months to obtain complete or almost complete bone healing in the socket (delayed implants), there is the third option of placing implants after soft tissue healing (early approach), usually after 2 to 6 weeks. The rationale behind this approach is to obtain sufficient soft tissue healing to facilitate its closure around/over the implants, and thereby to decrease the risk of implant failure due to infection associated with the extracted tooth. This risk needs to be further weighed against that of another physiological phenomenon, the alveolar bone remodelling and resorption that occurs after tooth extraction[3-6]. Indeed, within 1 year of extraction, the clinical width of the alveolar ridge is reduced by approximately 50%, two-thirds of which is lost within the first 3 months[3-6]. The mean vertical tissue loss at single extraction sites ranges from 1 to 4 mm[3-6], depending on site location, but varies among different individuals in rate and degree, and in some cases may be very advanced[3-6]. This localised alveolar bone resorption may affect both the possibility of placing dental implants and their aesthetic outcome, particularly in frontal areas, and in those patients exposing visible portions of their gums when speaking and smiling, potentially causing social discomfort and embarrassment.

Nevertheless, the naturally occurring bone resorption can be countered by subjecting sockets to a ridge preservation procedure just after extraction. Various ridge preservation techniques are currently used, ranging from soft tissue grafts to autogenous or bone substitute grafts[5-19]. The number of reliable RCTs is limited[3,6,16], but they appear to show that various ridge preser-

vation procedures are effective at reducing bone resorption[3,5-7,12]. That being said, some preservation techniques have been associated with a substantial number of failures and complications[5,20,21], and some appeared to be ineffective altogether[10].

It is, however, possible that immediate post-extraction implantation could reduce the bone resorption that occurs after tooth extraction, thereby improving the final aesthetic outcome, although this had yet to be proven[2] before the early findings of the present trial were published. Indeed, at that time there had only been a few randomised controlled trials (RCTs)[22-26] comparing immediate and delayed placement of single implants in post-extraction sockets. No statistically significant differences were observed between the two procedures, with the exception of a greater frequency of complications at immediate with respect to delayed implant placement reported in one of the trials[24], and better aesthetics and less bone loss at delayed implants in another trial[26]. However, in the latter study 6 to 8-mm-wide diameter implants were used in the post-extraction sites *versus* delayed implants of conventional 4 to 5 mm diameter in preserved sockets.

Even fewer RCTs have compared immediate *versus* early implants[27,28] and early *versus* delayed implants[29], and reported evidence is therefore inconclusive. To the best of our knowledge, there had been no RCTs comparing all three procedures at the time of initiation of the current trial. It would, however, be very useful to know whether a better clinical outcome could be achieved by placing delayed implants after bone healing, or by waiting for few weeks to allow soft tissues to heal, or whether similar results could be yielded by placing implants immediately after tooth extraction, shortening the treatment time by several months. Hence, the aim of this RCT was to compare the clinical outcome of single implants placed immediately after tooth extraction with those placed 6 weeks (early placement) and 4 months after extraction (delayed placement), following socket healing. The null hypothesis was that there would be no difference in success rates, complications, peri-implant marginal bone level changes, aesthetics or patient satisfaction between the three procedures, against the alternative hypothesis of a difference. Articles reporting data at 4 months[30] and 1 year[31] after loading were previously published, and the present article is their continuation to report the data at 3 years after loading. . At protocol stage, it was planned to follow the patients up to 5 years after loading. 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/).

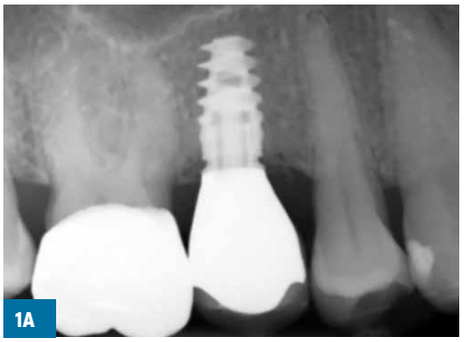
MATERIALS AND METHODS

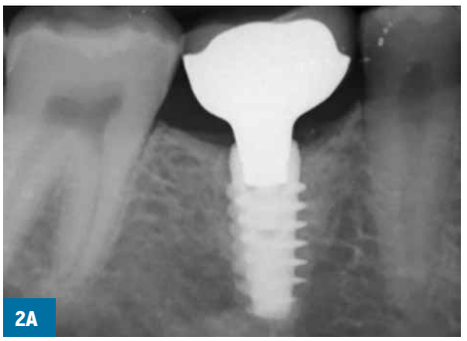
Trial design

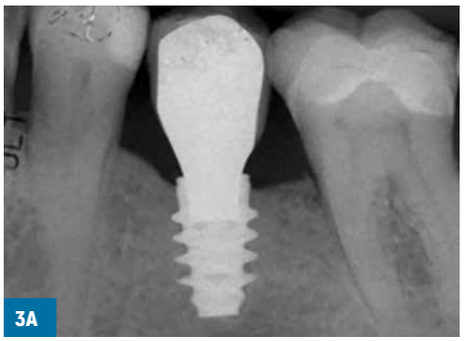
This was a single-centre RCT of parallel-group design with three arms, balanced randomisation and blind assessment. After tooth extraction, patients were randomised in equal numbers into three groups according to a parallel-group design: immediate post-extraction implant **(FIGS. 1A-C)**, early implantation after 6 weeks **(FIGS. 2A-C)**, and delayed implantation after 4 months **(FIGS. 3A-C)**.

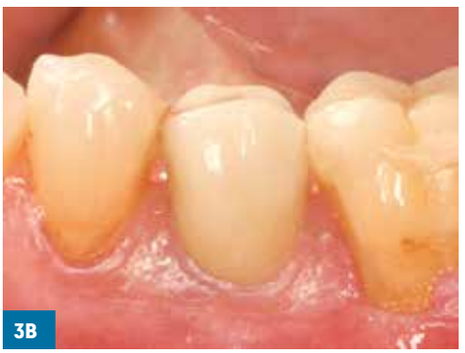
Eligibility criteria for participants

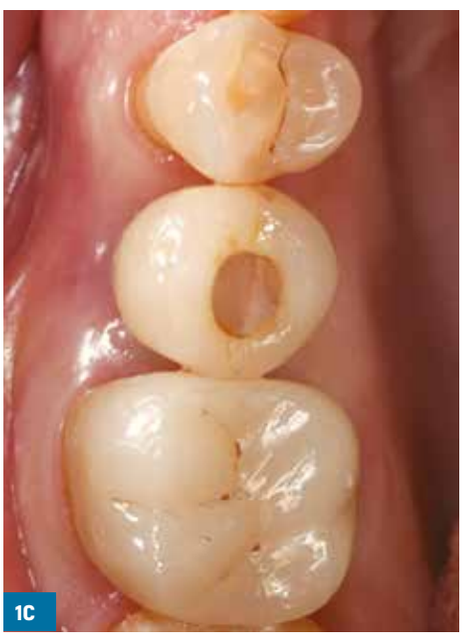
Any patient requiring at least one single immediate post-extraction implant, being at least 18 years old and able to sign an informed consent form, was eligible for inclusion. Sites were required to have sufficient bone to allow the placement of a single implant of at least 8.5 mm in length with a minimal diameter of 3.5 mm. Each patient provided only one implant site for the study. For patients with multiple edentulous areas to be restored, the operator was instructed to select the implant site in the most "aesthetic" area at the screening visit. Pre-operative radiographs (intraoral, panoramic, cone-beam computed tomography [CBCT] scans

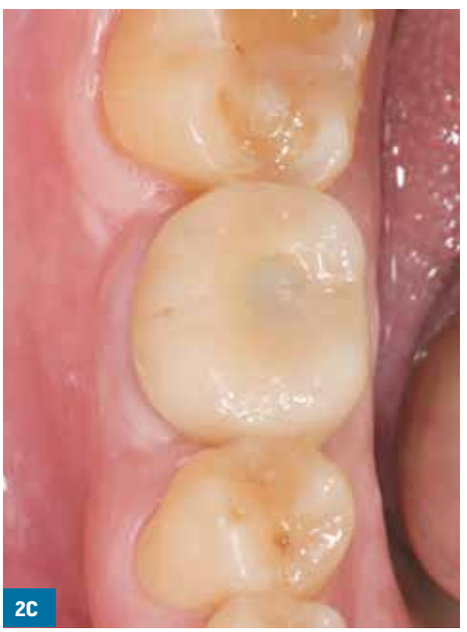


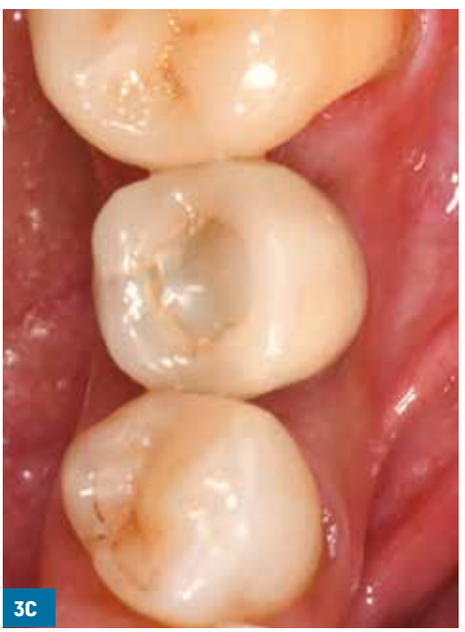












Figs. 1A-C: *Three-year post-loading results pertaining to one patient randomly allocated to immediate post-extraction implants: A) radiographic, B) vestibular and C) occlusal clinical views.*

Figs. 2A-C: *Three-year post-loading results pertaining to one patient randomly allocated to early implant placement: A) radiographic, B) vestibular and C) occlusal clinical views.*

Figs. 3A-C: *Three-year post-loading results pertaining to one patient randomly allocated to delayed implant placement: A) radiographic, B) vestibular and C) occlusal clinical views.*

or other radiographical investigations, at the discretion of the operator), together with clinical examination, were used to determine bone volumes and anatomical landmarks.
Exclusion criteria were:

- General contraindications to implant surgery;
- Immunosuppressed or immunocompromised status;
- Irradiation to the head or neck area;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;
- Untreated periodontitis;
- Poor oral hygiene and motivation;
- Alcohol or drug addiction;
- Psychiatric disorders;
- Acute infection (abscess) in the site intended for implant placement;
- Need to lift the maxillary sinus epithelium;
- Inability to commit to 5-year post-loading follow-up;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Participation in other studies interfering with the present protocol.

Patients were categorised into three groups based on the number of cigarettes they declared smoking per day: non-smokers, moderate smokers (up to 10 cigarettes per day) and heavy smokers (more than 10 cigarettes per day).

Setting and locations

Patients were recruited and treated by a single experienced operator (Pietro Felice) at the University of Bologna Dental Clinic and three private dental clinics, two located in Bologna and one in Conselice, Italy, following identical and standardised procedures. 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 evaluations, and any potential risks involved). The patients were given the opportunity to ask questions pertaining to this study, and were fully apprised of treatment alternatives. Ethical approval was obtained from the independent ethics committee of the Policlinic S. Orsola-Malpighi in Bologna on 22nd December 2011 (Prot. n. 2726/2011).

Interventions

Patients received a single dose of prophylactic antibiotic 1 hour prior to the intervention: 2 g of amoxicillin or 600 mg of clindamycin, if allergic to penicillin. Patients rinsed with 0.2% chlorhexidine mouthwash for 1 minute prior to the intervention. Patients were treated under local anaesthesia using articaine with 1:100,000 adrenaline. No intravenous sedation was used. Teeth were extracted as atraumatically as possible, using periotomes and small levers, attempting to preserve the buccal alveolar bone, when present. Flaps were raised only if necessary, after intrasulcular incision. Vertical releasing incisions were sometimes performed, but full-thickness flaps with minimal extension were attempted in order to minimise patient discomfort. Any remaining granulation tissue was carefully cleaned from sockets. The widest diameter of the socket was measured in mm, rounded to half mm, using a graduated periodontal probe.
Post-extraction sockets were categorised into:

- Well preserved, when the buccal plate was intact;
- Partially preserved, when up to 4 mm of buccal bone was missing;
- Poorly preserved, when more than 4 mm of buccal bone was missing.

The height of the buccal bone was assessed using the highest peak of the palatal wall as a reference point. After socket assessment, the sequentially numbered sealed envelope corresponding to the patient's recruitment number was opened to determine whether to place the implant immediately or to wait for 6 weeks or 4 months. In the situation that the investigator judged that no implant could be placed, the patient was excluded from the study and no envelope was opened.
NobelActive TiUnite implants (Nobel Biocare, Göteborg, Sweden) with conical internal connection were used. The operator was free to choose implant lengths (8.5, 10.0, 11.5, 13.0 and 15.0 mm) and diameters (3.5, 4.3 and 5.0 mm) according to the clinical indications and his preference.

Immediate post-extraction implants

Sites allocated to immediate implant placement were prepared using drills of increasing diameters, as recommended by the implant manufacturer. In brief, a lance drill was used to mark the exact implant entrance point, usually on the palatal wall of the socket, followed by drills of increasing diameter (2.0, 2.4/2.8, 3.2/3.6 and when needed 3.8/4.2 mm). Implants were placed crestally, but in "aesthetic" areas, the operator placed the head of the implant subcrestally, about 1 to 2 mm below the most coronal bone peak, and slightly palatally. Implant insertion torque was evaluated using the drilling unit motor and reported as equal to or higher than 25 Ncm or lower than 25 Ncm.
Once the implant was placed, clinical photographs were taken, the largest gap between the bony wall and the neck of the implant was measured (rounded to half mm) with a periodontal probe, and all "poorly preserved" sockets and "partially preserved" sockets in "aesthetic" areas (from second to second upper premolar) were reconstructed with bone substitute granules. The bone substitute used was a sticky paste made of 600–1000 micron pre-hydrated collagenated corticocancellous granules of porcine origin, properly mixed with collagen gel in a sterile syringe (OsteoBiol mp3, Tecnoss, Giaveno, Italy). The grafted area was then covered with a resorbable membrane derived from equine pericardium (Fine 20 x 20 mm, OsteoBiol Evolution). The membrane was trimmed and adapted to cover the entire socket and at least 2 mm of the surrounding crestal bone, and fixed using Frios titanium tacks (Dentsply-Friadent, Mannheim, Germany). Soft tissues were sutured with a cross suture without mobilising the flaps, and barriers were therefore left partially exposed, since full soft tissue coverage was not achieved.

Early implant placement group (6 weeks)

Patients randomised to the early implant placement group had sockets closed with flaps just after tooth extraction, whenever possible. After 6 weeks of soft tissue healing, a mucoperiosteal flap was raised, the widest diameter of the socket was measured using a graduated periodontal probe (in mm, rounded to the nearest 0.5 mm), and implants were placed as previously described. Once the implant was placed, clinical photographs were taken, the largest gap between the bony wall and the neck of the implant was measured (rounded to the nearest 0.5 mm) with a periodontal probe, and the operator reconstructed all "poorly preserved" sockets and "partially preserved" sockets in the "aesthetic" areas (from second upper premolar to second upper premolar) with granules of bone substitute (mp3). The grafted area was then covered with a resorbable membrane (Evolution) fixed with tacks. The wound was completely covered by soft tissues.

Delayed implant placement group (4 months)

At tooth extraction, patients randomised to the delayed implant placement group had their sockets augmented with bone substitute (mp3) when the alveoli were "poorly preserved", and

only in "aesthetic" areas when sockets were "partially preserved". The grafted areas were then covered with resorbable collagen membranes (Evolution) fixed with tacks. No other sites were augmented. The wound could be left partially open if complete soft tissue closure was difficult to achieve. After 4 months, implants were placed as previously described, and the surgeon could decide whether an additional augmentation procedure was required.

For all patients in all groups, a baseline periapical radiograph of the implant was taken using the paralleling technique after implant insertion/site augmentation. If the marginal bone levels were not clearly discernible or the implant image was too distorted, a second periapical radiograph was taken. Flaps were sutured with 4-0 Vicryl (Ethicon, Johnson & Johnson, Sint-Stevens-Woluwe, Belgium). Implants in reconstructed areas were left to heal submerged, whereas implants in non-reconstructed areas could be left to heal transmucosally, at the discretion of the operator. Implants were to be left to heal unloaded for 4 months, but for implants inserted with less than 25 Ncm torque, the loading-free healing period was prolonged to 6 months.

Postoperative antibiotics were prescribed only after augmentation procedures: amoxicillin 500 mg 4 times a day for 6 days. Patients allergic to penicillin were prescribed clindamycin 300 mg twice a day for 6 days. Ibuprofen 400 mg (or paracetamol 1 g for patients allergic to non-steroidal anti-inflammatory drugs) was prescribed after all surgical interventions, but patients were instructed not to take analgesics in the absence of pain. Chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks was prescribed after all surgical interventions. Patients were recalled and checked at weeks 1 and 2 and month 1 after tooth extraction and implant placement. Sutures were removed 1 week after their placement. No prosthesis compressing the implant or the augmented areas was used throughout the healing period.

Prosthetic procedures

All prosthetic procedures were identical in the three groups. Before abutment connection, a blinded outcome assessor measured the height of the vestibular keratinised mucosa in mm (to be rounded to 0.5 mm) at the study implant site using a graduated periodontal probe. If the implant was submerged, the assessor used the middle of the crest as a reference point for the measurement. When needed, implants were exposed after local anaesthesia, and if the height of keratinised mucosa was 2 mm or less, soft tissues were augmented using the roll technique[32]. If no keratinised mucosa was present at all, a connective tissue graft from the palate was placed[33]. The stability of the implants was manually tested by tightening the abutment screw with a torque of 20 Ncm, and a healing abutment was placed. Two weeks after abutment connection, an impression with the pick-up impression copings was made using a polyether material (Impregum 3M/ESPE, Neuss, Germany) and individual resin impression trays. Provisional crowns in acrylic resin were screwed onto temporary abutments (Temporary Abutment Engaging Conical Connection, Nobel Biocare), and a periapical radiograph of the study implant was taken. If the peri-implant marginal bone levels were difficult to measure, a second radiograph was taken. At this point the operator subjectively assessed the profile of tissues vestibular to the implant-supported crown in aesthetic areas only. If he judged that profile to be deficient, he harvested a connective tissue graft from the palate and placed it into a pouch made with a horizontal incision two to three mm below the implant sulcus without releasing incisions, to increase tissue thickness and thereby improve aesthetics. Oral hygiene instructions were delivered.

Four months after initial loading, provisional crowns were removed, implants were manually tested for mobility by tightening the abutment screws with 20 Ncm torque by a blinded assessor, and definitive screw-retained metal-ceramic, metal-resin, metal-composite, zirco-

nia-stratified ceramic or monolithic zirconia single crowns were delivered on different types of abutments (Abutments Titanium, Procera Abutments Zirconia, Procera Abutments Titanium; Nobel Biocare). Occlusion was carefully checked. Periapical radiographs were taken of the study implants, and if the marginal bone levels were not readable, a second radiograph was taken. Vestibular and occlusal pictures of the study crown, including, when possible, one adjacent tooth per side, were taken for the aesthetic evaluation, and the blind assessor assessed patient satisfaction. Oral hygiene instructions were reinforced. Patients were recalled at least every 6 months for oral hygiene maintenance and prosthetic controls.

Outcome measures

Primary outcome measures were the following:

- Crown failure: cases in which it was not possible to place the crown due to implant failures or secondary to implant losses, or replacement of the definitive crown 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 abutment connection and definitive crown delivery using 20-Ncm torque. At 1 and 3 years after loading, stability was tested by attempting to rock the implant using the metal handles of two metal instruments.
- Any complication or adverse event: recorded and reported by study group.

Secondary outcome measures were the following:

- Peri-implant marginal bone level changes: assessed on periapical radiographs taken using the paralleling technique at implant placement, and at 4 months and 1 and 3 years after loading. In the case of unreadable radiographs, new radiographs were taken. Non-digital radiographs were scanned in TIFF format with a 600-dpi resolution. Peri-implant marginal bone levels were measured using OsiriX (Pixmeo Sarl, Bernex, Switzerland) software. The software was calibrated for each individual image using the known height of the implant collar. Measurements of the mesial and distal bone crest levels 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. Mesial and distal measurements of each implant were averaged, and a mean was calculated for each group.
- Aesthetic evaluation of the vestibular and occlusal clinical pictures including the two adjacent teeth, taken at 4 months and 1 and 3 years after loading was performed on a computer screen. The aesthetic evaluation was carried out using the pink aesthetic score (PES)[34]. In brief, seven variables were evaluated: mesial papilla, distal papilla, soft tissue level, soft tissue contour, alveolar process deficiencies, soft tissue colour and texture. A 0, 1, 2 scoring system was used; 0 being the lowest and 2 being the highest value, with a maximum achievable score of 14 per implant.
- Patient satisfaction: at 4 months and 1 and 3 years after loading, the blind outcome assessor provided a mirror to the patients, who were asked to express their opinions about the implant-supported crown. Specifically, the patients were asked “are you satisfied with the function of your implant-supported tooth?”. Possible answers were “yes absolutely”, “yes partly”, “not sure”, “not really”, and “absolutely not”. Then they were asked “are you satisfied with the aesthetic outcome of the gums surrounding this implant?”. Again, possible answers were “yes absolutely”, “yes partly”, “not sure”, “not really”, and “absolutely not”. Finally, patients were asked whether they would undergo the same therapy again. Possible answers were: “yes” or “no”. The questions were always posed with exactly the same wording.

Implant stability and patient satisfaction were assessed by blinded outcome assessors (by Stefano Chersoni up to 4 months after loading and then by Carlo Barausse), whereas marginal bone levels and PES score were assessed by a single experienced and blinded assessor (Carlo Barausse). Complications were assessed by the treating dentist, who was therefore not blinded.

Sample size, random sequence and allocation concealment

The sample size was calculated on the primary outcome measure as the proportion of patients experiencing implant failure. A two-group continuity-corrected chi-square test with a 0.050 two-sided significance level has 80% power to detect the difference between a Group 1 proportion of 0.100 and a Group 2 proportion of 0.200 (*odds ratio* of 0.184) when the sample size in each group is 162. However, our recruitment capacity could not match the required sample size, and it was therefore decided to include 70 patients per group.

A single computer-generated restricted randomisation list was created with three groups having an equal number of patients. Only one of the investigators, not involved in the selection and treatment of the patients (Marco Esposito), was aware of the random sequence, and had access to the randomisation list, which was stored in a password-protected laptop computer. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially following tooth extraction, and treatment allocation was therefore concealed to the investigator in charge of enrolling and treating the patients included in the trial.

Statistical methods

All data analysis was carried out according to a pre-established analysis plan. The patient was the statistical unit of the analyses. A dentist (Jacopo Buti) with expertise in biostatistics analysed the data, without knowing group allocation. The chi-square test (or the Freeman-Halton extension of the Fisher Exact test when 20% of cells with expected count <5) was used to compare dichotomous variables (failures and complications), and the Kruskal Wallis test for continuous (bone level changes and PES) and ordinal (patient satisfaction) outcomes, with the post-hoc Dunn-Bonferroni adjustment for pairwise multiple comparisons, was applied. Comparisons between each time point and baseline measurements were made in each study group using the Wilcoxon signed-rank test, to detect any changes in marginal peri-implant bone levels. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Two hundred and thirty-one patients were screened for eligibility, but 17 patients did not accept the treatment for financial reasons (the implant and the surgery was offered for free, but patients were required to pay for the crown and the prosthetic components), and four patients did not want to be randomised since they were not willing to wait for long treatment periods, preferring immediate rehabilitation. Two hundred and ten patients were consecutively enrolled in the trial and randomised: 70 to the immediate, 70 to the early, and 70 to the delayed placement group. All patients were treated according to the allocated interventions. Patients were recruited and treated from January 2012 to December 2014. The follow-up focused on the time between implant placement and 3 years after loading.

Twenty-two patients dropped out **(TABLE 1)**. Available data from all remaining patients were evaluated in the statistical analyses. Deviations from the operative protocol were the following.

TABLE 1 DROP-OUTS UP TO 3-YEAR POST-LOADING BY STUDY GROUP, WITH REASONS

Group	Reason	Last seen
Immediate	Moved	Provisional delivery
	Health problems	Provisional delivery
	Moved abroad	2 months after provisional delivery
	Uncontactable	1 year after loading
	Moved	1 year after loading. Contacted by phone at 3 years–reported that the crown was fine
Early	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Moved abroad	Provisional delivery
	Moved	1 month after provisional delivery. Contacted by phone at 3 years–reported that the crown was fine
	Uncontactable	1 year after loading
	Uncontactable	1 year after loading
	Health problems	1 year after loading
	Moved abroad	1 ½ years after loading. Contacted by phone at 3 years–reported that the crown was fine
Delayed	Moved	1 month after implant placement
	Moved abroad	1 month after implant placement
	Moved	Provisional delivery
	Moved abroad	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	Provisional delivery
	Uncontactable	1 ½ years after loading
	Health problems	1 ½ years after loading. Contacted by phone at 3 years–reported that the crown was fine

Immediate group

- Fifteen patients refused the definitive crowns at four months post-loading for financial reasons. However, one patient received it after 10 months, one patient after 11 months, one after 1 year and 6 months, one after 1 year and 7 months, two after 1 year and 8 months, one after 1 year and 9 months, one after 2 years, one after 2 years and 2 months, and two after 2 years and 3 months.
- In four patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- In three patients, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- One patient delayed loading by 3 months for work reasons.
- One patient, lacking keratinised mucosa, refused connective tissue harvesting from the palate because he was afraid of post-operative pain.
- For the third year of follow-up, two patients had radiographs and pictures taken with a delay of 7 months, and 1 year and 2 months, respectively, and for four patients no pictures were taken, since the camera was not available; no radiographs were taken for two further patients.

Early group

- Twelve patients refused definitive crowns at four months post-loading for financial reasons. However, one patient received it after 8 months, one after 1 year and 4 months, one after 1 year and 5 months, two after 1 year and 6 months, one after 1 year and 7 months, one after 1 year and 8 months, one after 2 years and 1 month, and one after 2 years and 3 months.
- In four patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- One patient delayed loading by 5 months because she moved abroad, and the implant was mobile when she returned.
- One patient, lacking keratinised mucosa, refused connective tissue harvesting from the palate because she was afraid of post-operative pain.
- In one patient, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- For the third year of follow-up, two patients had radiographs and pictures taken with delays of 8 months, and 1 year and 9 months, respectively, and for three patients no pictures were taken since the camera was not available; no radiographs were taken for one patient.

Delayed group

- Sixteen patients refused definitive crowns at four months post-loading for financial reasons. However, one patient had theirs fitted after 10 months, one after 1 year and 2 months, one after 1 year and 5 months, two after 1 year and 6 months, one after 1 year and 8 months, one after 1 year and 9 months, one after 2 years, one after 2 years and 1 month, two after 2 years and 3 months, and one after 2 years and 4 months.
- In eight patients, short healing abutments were used instead of flat cover screws, since the latter were not available.
- Two patients, lacking keratinised mucosa, refused connective tissue harvesting from the palate because they were afraid of post-operative pain.
- One implant was placed flapless because the patient was under treatment with aspirin for a cardiological issue, and, according to the treating physician, this treatment could not be suspended.
- In one patient, no sutures were given for aesthetic reasons, and the wound was closed by the provisional crown.
- For the third year of follow-up, six patients had radiographs and pictures taken with a delay ranging from 6 months to 1 year and 9 months, and for seven patients no pictures were taken since the camera was not available.

The main baseline patient characteristics are presented in **TABLE 2**. No relevant differences between the three groups were noted at baseline, with the exception for fewer immediate (30%) than delayed implants (78.6%) in mandibles and more immediate (70%) than delayed implants (21.4%) in maxillae.

Implant failures: ten implants failed; five from the immediate group, four from the early group and one from the delayed group **(TABLE 3)**. However, there were no statistically significant differences in implant failures between the three procedures (P [Freeman-Halton] = 0.282). All failed implants were successfully replaced, but data pertaining to the replaced implants were not recorded since they were outside the scope of this study.

Crown failures: apart from the crowns lost due to implant failures, no additional crowns had to be remade.

Complications (TABLE 4): a total of 33 complications affected 11 patients treated with imme-

TABLE 2 PATIENT AND INTERVENTION CHARACTERISTICS

	Immediate (n = 70)	Early (n = 70)	Delayed (n = 70)
Females	36 (51.4%)	34 (48.6%)	33 (47.1%)
Males	34 (48.6%)	36 (51.4%)	37 (52.9%)
Mean age at implant insertion ± SD (range)	55.3±11.0 (34-79)	53.5±13.4 (29-76)	55.8±11.6 (34-75)
Smoking up to 10 cigarettes/day	18 (25.7%)	20 (28.6%)	21 (30%)
Smoking more than 10 cigarettes/day	4 (5.7%)	5 (7.1%)	7 (10%)
Well preserved sites	47 (67.1%)	39 (55.7%)	41 (58.6%)
Partially preserved sites	18 (25.7%)	27 (38.6%)	24 (34.3%)
Poorly preserved sites	5 (7.1%)	4 (5.7%)	5 (7.1%)
Mean buccal bone vertical loss in mm ± SD	1.1±1.8	1.1±1.5	1.1±1.6
Implants inserted in mandibles	21 (30%)	40 (57.1%)	55 (78.6%)
Implants inserted in maxillae	49 (70%)	30 (42.9%)	15 (21.4%)
Implants inserted in incisor sites	15 (21.4%)	12 (17.1%)	4 (5.7%)
Implants inserted in canine sites	8 (11.4%)	10 (14.3%)	11 (15.7%)
Implants inserted in premolar sites	26 (37.1%)	17 (24.3%)	24 (34.3%)
Implants inserted in molar sites	21 (30%)	31 (44.3%)	31 (44.3%)
Implants with 3.5 mm diameter	31 (44.3%)	32 (45.7%)	17 (24.3%)
Implants with 4.3 mm diameter	24 (34.3%)	30 (42.9%)	36 (51.4%)
Implants with 5.0 mm diameter	15 (21.4%)	8 (11.4%)	17 (24.3%)
Implants 8.5 mm long	21 (30%)	15 (21.4%)	16 (22.9%)
Implants 10 mm long	14 (20%)	23 (32.9%)	25 (35.7%)
Implants 11.5 mm long	21 (30%)	14 (20%)	22 (31.4%)
Implants 13 mm long	14 (20%)	18 (25.7%)	7 (10%)
Mean implant length ± SD	10.6±1.7	10.8±1.7	10.4±1.4
Mean implant diameter ± SD	4.1±0.6	4.0±0.5	4.3±0.5
Horizontal gap buccal bone-implant in mm ± SD	1.2±1.3	0±0	0±0
Bone augmentation	35 (50%)	0	0
Submerged implants	65 (92.9%)	63 (90%)	57 (81.4%)
Non-submerged implants	5 (7.1%)	7 (10%)	13 (18.6%)
Complete flap closure	28 (40%)	33 (47.1%)	20 (28.6%)
No provisional during unloaded phase	21 (30%)	28 (40%)	30 (42.9%)
Adhesive prosthesis during unloaded phase	20 (28.6%)	15 (21.4%)	17 (24.3%)
Removable prosthesis during unloaded phase	16 (22.9%)	16 (22.9%)	11 (15.7%)
Tooth crown attached to adjacent teeth during unloaded phase	13 (18.6%)	11 (15.7%)	12 (17.1%)
Incomplete wound closure 1 week after extraction	42 (60%)	38 (54.3%)	50 (71.4%)
Incomplete wound closure 2 weeks after extraction	42 (60%)	38 (54.3%)	50 (71.4%)
Incomplete wound closure 1 month after extraction	41 (58.6%)	36 (51.4%)	50 (71.4%)
Mean keratinised mucosa height in mm at abutment connection ± SD	3.6±0.9	3.8±1.1	3.3±0.8*
No graft at abutment connection	69 (98.6%)	65 (92.9%)	65 (95.6%)*
Roll technique at abutment connection	0	0	0*
Connective tissue graft at abutment connection	1 (1.4%)	5 (7.1%)	3 (4.4%)*
Connective tissue graft at provisional delivery	0	0	0*
Implants initially inserted with at least 25 Ncm torque	53 (75.7%)	54 (77.1%)	59 (84.3%)
Implants initially inserted with less than 25 Ncm torque	17 (24.3%)	16 (22.9%)	11 (15.7%)
Metal-resin/composite crowns	18 (36%)	23 (46%)	20 (41.7%)*
Metal-ceramic crowns	26 (52%)	24 (48%)	25 (52.1%)*
Zirconia crowns	6 (12%)	3 (6%)	3 (6.3%)*

**68 patients, since two patients never came back for abutment connection.*

TABLE 3 IMPLANT FAILURES UP TO 3 YEARS POST-LOADING IN CHRONOLOGICAL ORDER, BY STUDY GROUP, AND RELATED TREATMENT

Immediate implants			
Pat #	**Time***	**Implant/Tooth #; symptoms**	**Treatment and outcome**
#203	6 m.p-i	#46; implant mobile at surgical exposure	Successfully replaced
#17	3 m.p-l	#45; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#98	4 m.p-l	#26; 3 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#109	3 m.p-l	#24; slight pain on chewing, implant mobile	Successfully replaced
#20	19 m.p-l	#26; slight pain on chewing, crown removed and implant was mobile when counter-torqueing	Successfully replaced
Early implants			
#86	6 m.p-i	#36; implant mobile at surgical exposure	Successfully replaced
#16	9 m.p-i	#46; implant mobile at surgical exposure	Successfully replaced
#78	3 m.p-l	#22; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
#154	3 m.p-l	#36; 2 months after loading, slight pain on chewing, no mobility or radiographic signs, implant removed from occlusion for one month, pain still present	Successfully replaced
Delayed implants			
#54	6 m.p- i	#16; implant mobile at surgical exposure	Successfully replaced

Legend *m.p-i = month post-implantation; m.p-l = month post-loading; *Failure time = when the implant was actually removed.*

diate, 12 with early and eight with delayed implants. There were no statistically significant differences between the three procedures in the number of patients with complications (P [chi-square test] = 0.596).

Marginal bone level changes (TABLES 5 AND 6): at implant placement there was no statistically significant difference between the three groups: bone levels were 0.02 ± 0.03 mm (CI95% 0.01; 0.03) at immediate, 0.03 ± 0.04 mm (CI95% 0.02; 0.04) at early implants, and 0.03 ± 0.04 mm (CI95% 0.02; 0.04) at delayed implants (P [Kruskal Wallis test] = 0.635; **TABLE 5**).

However, three years after loading, there was a statistically significant difference between the three groups in terms of peri-implant bone levels, which were 0.35 ± 0.23 mm (CI 95% 0.29; 0.41) at immediate, 0.46 ± 0.27 mm (CI 95% 0.39; 0.53) at early, and 0.52 ± 0.32 mm (CI 95% 0.44; 0.60) at delayed implants (P[(Kruskal Wallis test] = <0.001); there were significant pairwise differences between immediate and early (0.11 mm; CI 95% -0.01; 0.23; P [Dunn-Bonferroni post-hoc]) = 0.0241) and immediate and delayed implants (0.18 mm; CI 95% 0.06; 0.29; P [Dunn-Bonferroni post-hoc]) = 0.0002), but no difference between early and delayed implants (0.07 mm; CI 95% -0.05; 0.19; P [Dunn-Bonferroni post-hoc]) = 0.5988) **(TABLE 5)**.

Similarly, there was a statistically significant difference between the three groups in terms of bone loss, which was -0.33 ± 0.22 mm (CI 95% -0.39; -0.27) at immediate, -0.43 ± 0.26 mm (CI 95% -0.50; -0.36) at early, and -0.49 ± 0.30 (CI 95% -0.57; -0.41) at delayed implants; P (Kruskal-Wallis test) = <0.001; there were significant pairwise differences between immediate and early (0.10 mm; CI 95% -0.02; 0.22; P [Dunn-Bonferroni post-hoc] = 0.0391) and immediate and delayed implants (0.16 mm; CI 95% 0.04; 0.27; P [Dunn-Bonferroni post-hoc] = 0.0004), but no difference between early and delayed implants (0.06 mm; CI 95% -0.06; 0.18; P [Dunn-Bonferroni post-hoc] = 0.6015) **(TABLE 6)**.

TABLE 4 COMPLICATIONS UP TO 3 YEARS POST-LOADING IN CHRONOLOGICAL ORDER BY STUDY GROUP AND RELATED TREATMENT

Immediate implants			
Pat #	**Time**	**Complication**	**Treatment**
#66	day 0	Late haemorrhage after extraction of tooth #35	1 suture + compression with gauze soaked with hemostatic
#17	2 m.p-l	Pain at 45 implant #45 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#97	3 m.p-l	Discomfort at implant #26 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#8	4 m.p-l	Mobility of crown #15 due to screw loosening	Retightened at 35 Ncm
#109	4 m.p-l	Pain at implant #24 when chewing; no mobility or radiographic alterations	Implant replacement
#40	12 m.p-l	Mobility of crown #13 due to screw loosening	Retightened at 35 Ncm
#20	19 m.p-l	Discomfort at implant #26 when chewing; mobile implant	Implant replacement
#131	21 m.p-l	Mobility of provisional crown #14 due to screw loosening	Retightened at 35 Ncm
#34	24 m.p-l	Chipping of provisional crown #47	Repaired chairside
#131	25 m.p-l	Facture of provisional crown #14	Repaired chairside
#170	26 m.p-l	Facture of provisional crown #35	Repaired in lab
#112	29 m.p-l	Mobility of crown #24 due to screw loosening	Retightened at 35 Ncm
Early implants			
#16	9 m p-i*	Discomfort and mobility at implant #46	Implant replacement
#78	2 m.p-l	Pain at implant #22 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#154	2 m.p-l	Pain at implant #36 when chewing; no mobility or radiographic alterations	Out of occlusion for 1 month, no resolution, implant replacement
#10	3 m.p-l	Chipping of provisional crown #46	Repaired chairside
#111	3 m.p-l	Mobility of crown #47 due to screw loosening	Retightened at 35 Ncm
#37	4 m.p-l	Mobility of crown #46 due to screw loosening	Retightened at 35 Ncm
#94	18 m.p-l	Chipping of provisional crown #45	Made definitive crown
#135	25 m.p-l	Peri-implant mucositis #46	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks; suggested maintenance every 3 months
#42	27 m.p-l	Peri-implant mucositis #17	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks; suggested maintenance every 3 months
#183	29 m.p-l	Chipping of provisional crown #15	Repaired chairside
#209	36 m.p-l	Mobility of crown #36 due to screw loosening	Retightened at 35 Ncm
#13	36 m.p-l	5 mm of vestibular recession #12	Patient refused surgical treatment
#10	36 m.p-l	Mobility of crown #46 due to screw loosening	Retightened at 35 Ncm
Delayed implants			
#116	5 days post-op	Throbbing pain at extraction site of ankylotic #46; dry socket with minor exudate	Curettage of the socket; 0.2% chlorhexidine rinse + local chlorhexidine gel three times a day for 2 weeks; pain killer (naproxen 550 mg) twice a day for 3 days, and afterwards as required; augmentin 1g twice a day for 1 week; complete resolution after 1 week
#91	2 m.p-l	Chipping of provisional crown #46	Repaired chairside
#152	2 m.p-l	Mobility of crown #36 due to screw loosening	Retightened at 35 Ncm
#190	10 m.p-l	Mobility of crown #14 due to screw loosening	Retightened at 35 Ncm
#118	24 m.p-l	Mobility of crown #24 due to screw loosening	Retightened at 35 Ncm
#124	27 m.p-l	Mobility of crown #14 due to screw loosening	Retightened at 35 Ncm
#14	31 m.p-l	Chipping of the provisional crown #14	Repaired chairside
#189	36 m.p-l	Peri-implant mucositis #24	Scaling + local chlorhexidine gel twice a day for 2 weeks; complete resolution after 2 weeks

Legend *m.p-l = month post-loading; m.p-i = month post-implantation; *patient moved abroad and come back 9 months after implantation with the implant still to be restored.*

TABLE 5 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS BETWEEN GROUPS AND TIME PERIODS UP TO 3 YEARS POST-LOADING

	Implant placement	4 months after loading	1 year after loading	3-year after loading	
	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	Within-group P-value
Immediate	70 0.02±0.03 (0.01; 0.03)	63 0.19±0.12 (0.16; 0.22)[a]	63 0.26±0.18 (0.22; 0.31[a]	58 0.35±0.23 (0.29; 0.41)[a]	<0.001*
Early	70 0.03±0.04 (0.02; 0.04)	61 0.23±0.10 (0.20; 0.25)[a,b]	61 0.31±0.14 (0.28; 0.35)[a,b]	56 0.46±0.27 (0.39; 0.53)[b]	<0.001*
Delayed	70 0.03±0.04 (0.02; 0.04)	63 0.27±0.13 (0.24; 0.30)[b]	63 0.34±0.17 (0.30; 0.39)[b]	60 0.52±0.32 (0.44; 0.60)[b]	<0.001*
Between-Group P-value	0.635	0.001*	0.007*	<0.001*	

**Statistically significant difference; all within-group pairwise differences were statistically significant; for between-group pairwise comparisons, subsets not connected by the same letter are significantly different.*

TABLE 6 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVEL CHANGES BETWEEN GROUPS AND TIME PERIODS UP TO 3 YEARS POST-LOADING

	Placement – 4 months	Placement – 1 year	Placement – 3 years	
	N Mean±SD (95% CI)	N Mean±SD (95% CI)	N Mean±SD (95% CI)	Within-group P-value
Immediate	63 -0.17±0.11 (-0.20; -0.15)[a]	63 -0.25±0.17 (-0.29; -0.20)[a]	58 -0.33±0.22 (-0.39; -0.27)[a]	<0.001*
Early	61 -0.20±0.09 (-0.23; -0.18)[a,b]	61 -0.29±0.14 (-0.32; -0.25)[a,b]	56 -0.43±0.26 (-0.50; -0.36)[b]	<0.001*
Delayed	63 -0.24±0.12 (-0.27; -0.21)[b]	63 -0.31±0.16 (-0.35; -0.27)[b]	60 -0.49±0.30 (-0.57; -0.41)[b]	<0.001*
Between-Group P-value	0.006*	0.015*	<0.001*	

**Statistically significant difference; all within-group pairwise differences were statistically significantly different; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.*

All three groups had gradually lost statistically significant amounts of marginal peri-implant bone at 3 years post-loading: P (Wilcoxon signed-rank test) < 0.001 for all groups.

PES score: four months after loading **(TABLE 7)**, the average total PES score, as assessed by a blind assessor, was 12.48 for immediate, 12.38 for early and 11.71 for delayed implants, the difference being statistically significant (P [Kruskal Wallis test] < 0.001)**.** More specifically, soft tissue levels and alveolar process deficiencies scored better at immediate and early implants than at delayed implants, with no difference in the five remaining aesthetic variables. The average total PES scores one year after loading **(TABLE 8)**, as assessed by a blind assessor, was 12.52 for immediate, 12.49 for early and 11.78 for delayed implants, the difference being statistically significant (P [Kruskal Wallis test] < 0.001). More specifically, soft tissue levels scored better at immediate implants than at delayed implants, and alveolar process deficiencies scored better at immediate and early implants than at delayed implants, with no difference for the five remaining aesthetic variables.

Three years after loading **(TABLE 9)**, the average total PES score, assessed by a blind assessor, was 12.25 for the immediate, 11.98 for early and 11.17 for delayed implants, the difference being statistically significant (P [Kruskal Wallis test] <0.001); there were significant pairwise differences between immediate and delayed (1.08 mm; CI 95% 0.45; 1.72; P [Dunn-Bonferroni post-hoc]) = 0.0006) and early and delayed implants (0.81 mm; CI 95% 0.17; 1.46; P [Dunn-Bonferroni

TABLE 7 MEAN PES SCORES AT 4-MONTHS POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 63	1.95 (0.22)	1.87 (0.34)	1.90 (0.30)[a]	1.95 (0.22)	1.71 (0.46)[a]	1.86 (0.40)	1.22 (0.46)	12.48 (0.95)[a]
Early = 61	1.95 (0.22)	1.84 (0.37)	1.92 (0.28)[a]	1.98 (0.13)	1.70 (0.46)[a]	1.87 (0.34)	1.11 (0.32)	12.38 (0.93)[a]
Delayed = 63	1.94 (0.25)	1.73 (0.45)	1.73 (0.45)[b]	1.94 (0.25)	1.49 (0.50)[b]	1.75 (0.44)	1.14 (0.35)	11.71 (1.11)[b]
Between-Group P-value	0.910	0.104	0.005*	0.422	0.014*	0.110	0.244	<0.001*

**Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.*

TABLE 8 MEAN PES SCORES AT 1-YEAR POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 63	1.90 (0.30)	1.84 (0.37)	1.89 (0.32)[a]	1.97 (0.18)	1.70 (0.46)[a]	1.87 (0.38)	1.35 (0.51)	12.52 (1.08)[a]
Early = 61	1.93 (0.25)	1.82 (0.39)	1.87 (0.34)[a,b]	1.98 (0.13)	1.69 (0.47)[a]	1.90 (0.30)	1.30 (0.46)	12.49 (0.96)[a]
Delayed = 63	1.90 (0.30)	1.70 (0.46)	1.71 (0.46)[b]	1.95 (0.22)	1.43 (0.50)[b]	1.81 (0.40)	1.27 (0.45)	11.78 (1.10)[b]
Between-Group P-value	0.795	0.110	0.020*	0.616	0.002*	0.273	0.586	<0.001*

**Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.*

TABLE 9 MEAN PES SCORES AT 3-YEAR POST-LOADING BY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; STANDARD DEVIATIONS ARE IN BRACKETS

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Immediate = 56	1.82 (0.39)	1.66 (0.51)	1.86 (0.35)[a]	1.91 (0.29)	1.64 (0.48)[a]	1.88 (0.38)	1.48 (0.54)	12.25 (1.25)[a]
Early = 54	1.72 (0.45)	1.67 (0.48)	1.81 (0.44)[a]	1.93 (0.26)	1.65 (0.48)[a]	1.87 (0.34)	1.33 (0.48)	11.98 (1.37)[a]
Delayed = 54	1.70 (0.46)	1.57 (0.54)	1.54 (0.50)[b]	1.81 (0.39)	1.35 (0.48)[b]	1.83 (0.42)	1.35 (0.52)	11.17 (1.59)[b]
Between-Group P-value	0.309	0.586	<0.001*	0.148	0.002*	0.818	0.217	<0.001*

**Statistically significant difference; for between-group pairwise comparisons, subsets not connected by the same letter are statistically significantly different.*

post-hoc]) = 0.0099), but no difference between immediate and early implants (0.27 ± mm; CI 95% -0.37; 0.90; P [Dunn-Bonferroni post-hoc] = 1.0000). In other words, soft tissue levels at immediate and early implants scored better than at delayed implants, and alveolar process deficiencies scores were better for immediate and early implants than for delayed implants, there being no differences in the five remaining aesthetic variables.

Patient satisfaction: patient satisfaction was assessed at 4 months, and 1 and 3 years after loading, but only in those patients who did not experience implant failure. At 4 months and at 1 year, the vast majority of patients declared that they were fully satisfied with both the function and aesthetics of their implant-supported prostheses, and that they would undergo the same procedure again; there were, however, four exceptions (one from the immediate, one from the early and two from the delayed group), who were only partially satisfied with the aesthetics (P [Kruskal Wallis test] = 0.785).

Similarly, at three years, almost all patients declared that they were fully satisfied with both function and aesthetics, and would undergo the same procedure again. The only exceptions were one patient from the early group who was only partially satisfied with the function (P [Kruskal Wallis test] = 0.353), and 10 patients who were not fully satisfied with the aesthetics (three from the immediate, one from the early and five from the delayed group who were only partially satisfied; and one from the early group who was uncertain) (P [Kruskal Wallis test] = 0.531).

DISCUSSION

This investigation was designed to evaluate whether immediate and early implant placement 6 weeks after tooth extraction of single implants could provide similar clinical outcomes to delayed implant placement in a healed ridge, since shorter treatment periods are highly appreciated and requested by many patients. Roughly 9.2% of the immediately placed implants and 6.6% of those placed after 6 weeks failed over a 3-year post-loading period, as compared to only one (1.6%) of the delayed implants. Although we found no statistically significant difference between groups in terms of implant failures or complications, these results suggest that delayed implant placement should remain the gold standard, especially when fitting single implants. Such observations are in agreement with other, similar studies[22-26].

Regarding bone level changes, at 3-year post-loading delayed implants had lost 0.17 mm more bone than immediate implants. While such a difference was statistically significant (P = <0.001), it is unlikely to have any clinical significance. Our results are similar to those from another RCT, also conducted by our group, where significantly more bone loss (0.06 mm) was observed at delayed implants[24]. A similar difference (0.05 mm), though not significant, was observed in another RCT[25], but the opposite trend was observed when 6 to 8-mm wide implants were used as immediate post-extraction implants[26].

With respect to aesthetics, at 3 years post-loading immediate and early implants scored significantly better than delayed implants. In particular, only differences in soft tissue levels and alveolar process deficiencies were observed. This is in agreement with the results of another trial[22], but contrasts with those reported in three other RCTs conducted by our group[24-26]. In particular, one trial[26] showed the opposite result at 1 year, i.e., better aesthetics for delayed implants. This can be explained by the fact that the immediate implants considered in that case were of wider diameter (6 to 8 mm), which may have caused more peri-implant bone resorption.

There are two plausible explanations for the present findings which could act synergistically; first, delayed sites were not subjected to any bone preservation procedures unless in "aesthetic" areas, or if severely damaged, as per typical clinical practice. It is known that site

preservation procedures are able to better preserve the site dimensions than not implementing any[15]. In addition, the immediate or early placement of an implant in a post-extraction site might also contribute to partial preservation of the width and height of the surrounding tissues. In order to better understand these mechanisms, however, further trials with larger sample sizes are needed.

Nevertheless, there could be some potential aesthetic advantages to deciding to place an implant immediately or a few weeks after tooth extraction. In addition, such an option greatly reduces the treatment time. Therefore, the decision on which procedure to choose remains in the hands of clinicians and patients, who have to decide between a potentially higher risk of failures and complications associated with immediate and early implants, against shorter treatment times and slightly better aesthetic outcomes.

Despite being the largest RCT ever published on implant placement timing, the main limitation of this trial remains the limited sample size. However, in future systematic reviews this limitation could hopefully be overcome by increasing the sample size by combining patients from different RCTs.

With respect to the generalisability (external validity) of these findings, it should be recognized that these procedures were tested in real clinical conditions, and that patient inclusion criteria were broad, mean that the results could be generalised to a wider population. However, it should be borne in mind that the operator who performed the immediate post-extraction procedures was highly experienced.

CONCLUSIONS

No statistically significant differences in failures, complications or patient satisfaction were observed when placing single implants immediately, 6 weeks or four months after tooth extraction. However, the absolute frequency of failures was greater at implants placed immediately and early. Nonetheless, bone loss was significantly smaller at immediate implants, and aesthetics was better at immediate and early implants.

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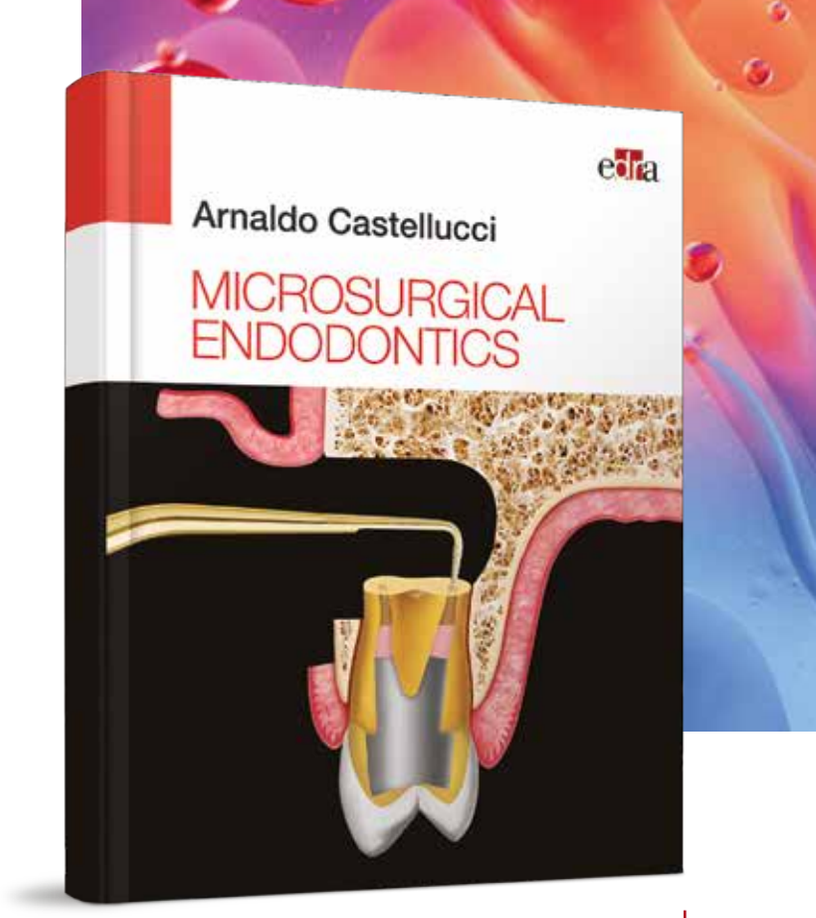

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POSTERIOR JAW REHABILITATION USING PARTIAL PROSTHESES SUPPORTED BY IMPLANTS 4.0 X 4.0 MM OR LONGER: THREE-YEAR POST-LOADING RESULTS OF A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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PURPOSE. To evaluate whether 4.0 x 4.0-mm dental implants could be viable alternatives to implants of length at least 8.5 mm when placed in posterior jaws with adequate bone volumes.

MATERIALS AND METHODS. One hundred and fifty patients with posterior (premolar and molar areas) jaws having at least 12.5 mm bone height above the mandibular canal or 11.5 mm below the maxillary sinus, as applicable, were randomised according to a parallel-group design and received one to three 4.0 mm-long implants or one to three implants which were at least 8.5 mm-long at three treatment centres. All implants had a diameter of 4.0 mm. Implants were loaded with permanent screw-retained prostheses after 4 months. Patients were followed-up until 3-year post-loading, and outcome measures considered were prosthesis and implant failure, any complications, and changes in peri-implant marginal bone levels.

RESULTS. Seventy-five patients were randomly allocated to each group. Drop-outs at 3-year post-loading assessment were five patients from the long implant group and three from the short implant group. Up to 3 years post-loadings, three patients lost one 4.0 mm-long implant each, in comparison to two patients who lost one long implant each (difference in proportion = -0.013; 95% CI: -0.079 to 0.054; P = 1). All failures occurred before loading; failed implants were replaced, delaying delivery of two prostheses in each group by several months (difference in proportion = 0; 95% CI: -0.061 to 0.062; P = 1). Five short-implant patients experienced six complications *versus* the three complications seen in three long implant patients (difference in proportion = -0.026; 95% CI: -0.103 to 0.053; P = 0.719). There were no statistically significant differences between groups in prosthesis failures, implant failures or complications. Patients with short implants lost on average 0.55 mm of peri-implant bone, and patients with longer implants lost 0.61 mm. There were no statistically significant differences between short and long implants in bone level changes up to 3 years (mean difference = 0.05 mm; 95% CI: -0.05 to 0.16; P = 0.221).

CONCLUSIONS. Outcomes 3 years after loading were similar with 4.0 x 4.0 mm-long implants and 8.5 x 4.0 mm or longer implants in posterior jaws, in the presence of adequate bone volumes. However, 5 to 10-year post-loading data will be necessary before reliable recommendations can be made.

CONFLICT OF INTEREST STATEMENT. Global D (Brignais, France) partially supported this trial and donated the implants and prosthetic components. OsteoBiol (Tecnoss, Giaveno, Italy) donated the biomaterials used for bone augmentation. However, the data property belonged to the authors and neither Global D nor OsteoBiol interfered in any way with the conduct of the trial or the publication of the results.

INTRODUCTION

Rehabilitation of atrophic edentulous jaws with implant-supported prostheses is challenging because of inadequate bone volumes. However, several randomised controlled trials (RCTs) and systematic reviews have shown that in the presence of 4 to 8 mm of bone height, short implants can be successfully used as an alternative to the more invasive bone augmentation procedures required for placement of longer implants[1-11]. In particular, findings of ongoing trials with a follow-up up to 8-years that 4.0 to 8.5-mm long implants can be a viable, if not better, alternative to augmentation procedures, especially in posterior sectors of both jaws. This raises the clinical issue of whether short implants might also be a viable option in situations in which long implants are possible, and just how short an implant could be in order to be able to provide good long-term outcomes.

There are at least two manufacturers (Straumann and Global D) marketing 4.0 mm-long transmucosal implants, and one of these implant types has been evaluated in a non-controlled single-cohort multicentre prospective 2-year post-loading study[12]. In this study, 100 4.0 mm-long implants were placed in the posterior jaws of 32 partially edentulous patients (three or four implants in each patient). Seven implants failed before loading in four patients, and two additional patients were excluded for unclear reasons (most likely because of implant failures), so only 26 patients received their prostheses. Two years after loading, one patient had died, and one requested to have all his implants removed[12]. This meant that 2 years after loading, the treatment with short implants had failed in 23% (seven out of 31) of the treated patients.

Despite this less than encouraging preliminary report, the aim of this RCT was to compare the outcomes of partial fixed prostheses supported using 4.0 x 4.0-mm implants with respect to those of length at least 8.5 x 4.0 mm when placed in posterior jaws with bone volumes sufficient for placement of medium-to-long implants. This report presents the clinical outcomes up to 3 years' post-loading, according to the original research protocol and following the previous publication of 4-month[13] and 1-year post-loading data[14]. The present article has been drafted 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

This study was designed as a multicentre randomised controlled trial of parallel-group design with two arms, using blinded outcome assessors whenever possible.

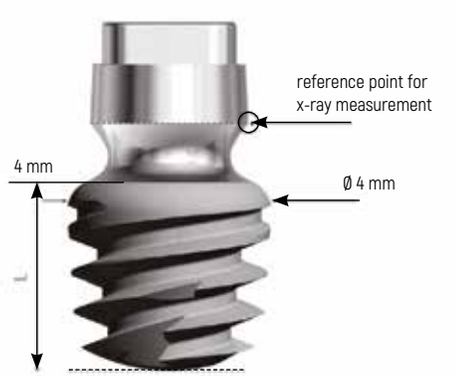
Any partially edentulous patient missing teeth in the premolar and molar areas requiring one to three dental implants aged 18 years or older and able to sign an informed consent form was eligible for inclusion in this trial. Vertical bone heights at implant sites had to be at least 12.5 mm above the mandibular canals and 11.5 mm below the maxillary sinuses, as applicable. Bone thickness had to be at least 6.0 mm, as measured on cone-beam computed tomography (CBCT) scans. Each patient was treated on only one side of the jaw, and received one prosthesis only, according to a parallel-group design.

Exclusion criteria were:

- General contraindications to implant surgery;
- Any irradiation to the head and neck area;
- Immunosuppressed or immunocompromised status;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Untreated periodontitis;
- Poor oral hygiene and motivation;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;

- Substance misuse;
- Psychiatric problems or unrealistic expectations;
- Lack of opposite occluding dentition to the area intended for implant placement;
- Acute or chronic infection/inflammation in the area intended for implant placement;
- Participation in other trials, if precluding adherence to the present protocol;
- Referral solely for implant placement, and having the prosthesis or maintenance procedures performed at other treatment centres;
- Inability to attend follow-up visits for 3 years after loading;
- Post-extraction sockets, if upper portion of the buccal wall was 4 mm lower than the palatal wall.

Patients were categorised into three groups according to their declared smoking habits: non-smokers, moderate smokers (up to 10 cigarettes per day), and heavy smokers (more than 10 cigarettes per day). Patients were to be recruited and treated in three different centres (50 patients per centre) by three different operators. However, one operator recruited and treated only four patients, so his remaining quota of patients was taken over by one of the two other operators (Pietro Felice, PF), who treated patients in two Italian private practices and one university hospital, whereas the other operator (Roberto Pistilli, RP) treated patients in both a hospital and a private practice. All operators followed a similar, standardised, protocol. The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to, and the study design was approved by the ethical committee of the Ospedale Maggiore in Bologna, Italy, on 14th June 2013 (Prot.N.554/CE). All patients received thorough explanation and provided informed written consent prior to being enrolled in the trial. Approximately 10 days before implant placement, patients received at least one professional tooth cleaning session.



1A

1B

Figs. 1A, B: *Illustration of a 4.0-mm (A) and a 13.0-mm (B) conical transmucosal Global D TwinKon Universal SA2 implants, as used in this study. Implants are made of Ti4V6Al alloy, have a sand-blasted acid-etched surface and a distinctive external connection.*

Implant placement procedures

One hour prior to implant placement, 2 g of amoxicillin (or 100 mg minocycline for patients allergic to penicillin) was administered, and before the procedure patients rinsed for one minute with 0.2% chlorhexidine. The area was locally anaesthetised via infiltration of articaine with 1:100,000 adrenaline. After crestal incision and flap raising, or after curettage of the socket in case of post-extraction implants, patients were randomly allocated, by opening the sequentially numbered envelope corresponding to the patient recruitment number, to receive either one to three 4.0 x 4.0 mm-long implants **(FIG. 1A)** or one to three implants which were at least 8.5 mm-long (8.5, 10, 11.5 and 13-mm long; **FIG. 1B**) and 4.0 mm in diameter, according to the standard procedures as recommended by the manufacturer (TwinKon Universal SA2, Global D, Lyon, France). Surgical stents were used to optimise implant positioning after flap lifting. Drills with stops of increasing diameters **(FIG. 2)** were used to prepare the implant sites, which were slightly under-prepared. At implant insertion, the surgical motor unit was set to a torque of 25 Ncm, and resistance at implant insertion was recorded as up to 25 Ncm or superior to 25 Ncm. The transition portion from machined to roughened surface of the implant neck **(FIGS. 1A, B)** was placed about 2 mm subcrestally.

In the case of post-extraction implants, teeth were extracted using a flapless approach in order to minimise surgical trauma and to spare the buccal wall of the socket. Sockets were carefully debrided from any remnants of granulation tissue. In the presence of a horizontal buccal bone-to-implant gap of 2 mm or more, gaps were filled with 600 to 1000-micron diameter granules of pre-hydrated corticocancellous porcine bone mixed with approximately 10% collagen gel (MP3, OsteoBiol, Tecnoss, Giaveno, Italy) covered with a resorbable haemosta-

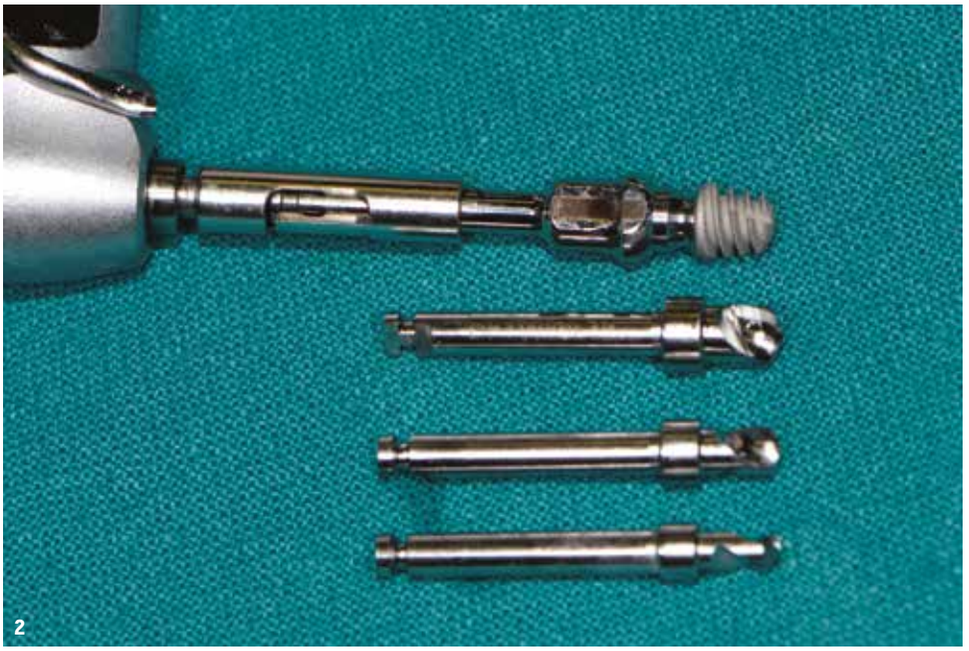


Fig. 2: *Sequence of drills used to prepare the implant sites for shorter implants. Please note the presence of stops with the drills.*

tic collagen sponge (Spongostan, 1 x 1 x 1 cm, Ethicon, Johnson & Johnson, Somerville, NJ, USA) of porcine origin, blocked with a cross-suture.

Healing abutments were placed on implants not to be submerged, and healing screws on implants to be submerged. Flaps were closed around non-submerged implants or over submerged implants with Vicryl 4/0 sutures (Ethicon). The decision on whether to submerge the implant or not was based on the thickness of the mucosa. Ideally, all implants were to be submerged, but since these implants have a transmucosal design, they could be only submerged when soft tissues were sufficiently thick. Periapical radiographs (baseline) were taken using the paralleling technique. If bone levels around the study implants were hidden or difficult to estimate, a second radiograph was taken.

Ibuprofen 400 mg to be taken 2 to 4 times a day during meals was prescribed for pain relief as long as required. Patients were instructed to place 1% chlorhexidine gel on the wounds twice a day for two weeks, to avoid brushing and trauma to the surgical sites, and advised to ingest a soft diet for one week. No removable prostheses were allowed on treated areas. Sutures were removed after 10 days, and patients were checked at 20 days, and one and two months after placement of dental implants.

Prosthetic procedures

After 3 months of unloaded healing, implants were exposed when necessary, manually tested for stability, and impressions with the pick-up impression copings were taken using a polyether material (Impregum 3M/ESPE, Neuss, Germany) and customised resin impression trays. Impressions of submerged implants were taken after 2 weeks of soft tissue healing. Four months after placement, implants were manually tested for stability and definitive metal-composite or metal-resin screw-retained restorations, rigidly joining the implants, were connected directly to the implants in light occlusion with antagonistic dentition. Oral hygiene instructions were delivered. Periapical radiographs of the study implants were taken, and, in the case of unreadable radiographs, new radiographs were taken.

Patients were enrolled in an oral hygiene programme with recall visits every 6 months for the entire duration of the study. Follow-ups were conducted by independent outcome assessors (Vittorio Checchi, VC, at PF's and Luigi Checchi's centres, LC, and Roberto Cassoni, RC, at RP's centre) up to the first year, and thereafter by Cesare Berti (PF's and LC's centres) and Fabrizio Lisotti (RP's centre).

Outcome measures

This study tested the null hypothesis that there were no differences in the clinical outcomes between the two procedures against the alternative hypothesis of a difference.
Outcome measures were the following.

- Prosthesis failure: planned prosthesis which could not be placed due to implant failure(s), loss of the prosthesis secondary to implant failure(s), or replacement of the prosthesis for any reason.
- Implant failure: implant mobility, removal of stable implants dictated by progressive marginal bone loss or infection, or any mechanical complications rendering the implant unusable (e.g., implant fracture). The stability of each individual implant was measured at delivery of permanent prostheses (4 months after implant placement) by tightening the abutment screws using a manual wrench at force 25 Ncm. Implant mobility was checked by tightening the abutment screws for fixed partial prostheses 4 months, and 1 and 3 years after initial loading, whereas the stability of single implant-supported crowns was tested by attempting to rock the crown with the handles of two dental instruments.
- Any biological or prosthetic complications.
- Peri-implant marginal bone levels changes, as assessed on periapical radiographs taken with the paralleling technique at implant placement, at prostheses delivery, and at 4 months, and 1 and 3 years after loading. Non digital radiographs were scanned in TIFF format with a 600 dpi resolution and stored in 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 length. Measurements of the mesial and distal bone crest level adjacent to each implant, parallel to the implant axis, were made to the nearest 0.01 mm, and averaged at implant, patient and group levels. Reference points for the linear measurements were the apical margin of the implant collar **(FIGS. 1A, B)** and the most coronal point of bone-to-implant contact.

Methodological aspects

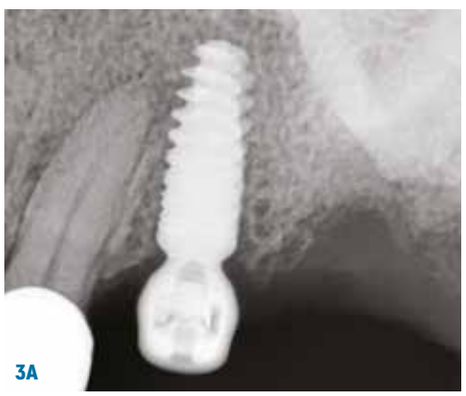
Four dentists (VC at RP's and LC's centres and RC at RP's centre) up to the first year and thereafter Cesare Berti (PF's and LC's centres) and Fabrizio Lisotti (RP's centre) performed all clinical measurements without knowing group allocation. One dentist (Carlo Barausse), not involved in patient treatment, performed all the radiographic assessments; note, however, that the different implant lengths could be easily identified on periapical radiographs.

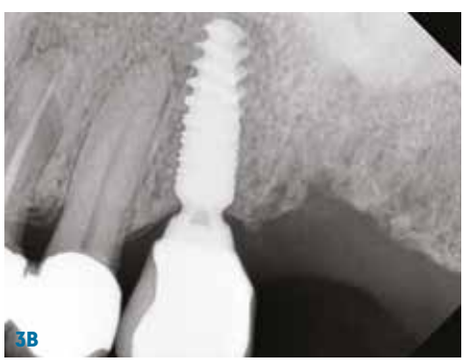
A sample size calculation was performed using patient experiencing at least one implant failure as the primary outcome measure with 80% power ($\beta = 0.2$) and one-sided $\alpha = 0.05$. No previous study on the same topic had been published at the time that the research protocol was devised. Consequently, the sample size was computed on the basis of a similar study,[15] which reported that 3 years after loading, 7% of patients had lost short implants and 10% long implants. A failure rate of 0.07 was therefore estimated for the control group. The minimal clinically relevant difference was set at 0.08, in agreement with the clinicians' opi-

nions. Based on this consideration, 160 patients would be required in total, but we had only resources to recruit 150 patients.

Hence 150 patients with partial edentulism, or to be rendered partially edentulous, in the posterior jaws were included in the trial: 75 patients received 4.0 x 4.0 mm-long implants (short implant group) and 75 patients in the 8.5 mm-long or longer implants (long implant group). Patients were allocated to groups on the basis of a computer-generated restricted randomisation list. Only one of the investigators (Maria Rosaria Gatto), not involved in the selection or treatment of the patients, was aware of the random sequence and had access to the random list, stored in a password-protected portable computer. Information on how to treat each patient was enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially after flap raising, and treatment allocation was thereby 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. A dentist with expertise in statistics (Jacopo Buti) analysed the data. The patient was the statistical unit of the analyses. Differences between the two groups in the proportion of patients with prosthesis failures, implant failures and complications (dichotomous outcomes) were compared using Fisher's exact test, and binomial 95% confidence intervals were computed. The non-Gaussian distribution of radiographic bone levels suggested the use of non-parametric tests. Differences between means for radiographic bone levels between groups were compared using Mann-Whitney U test, and bias-corrected and accelerated 95% confidence intervals were computed (IBM-SPSS Statistics Release 21, Armonk NY, USA). Comparisons between each time point and baseline measurements were made using a paired Wilcoxon test, to detect any changes in peri-implant marginal bone levels. A chi-square test was used to compare the number of patients with prosthesis failures, implant failures and complications, and the Kruskal-Wallis H test to compare the marginal bone level changes between centres. All statistical comparisons were conducted at the 0.05 level of significance.





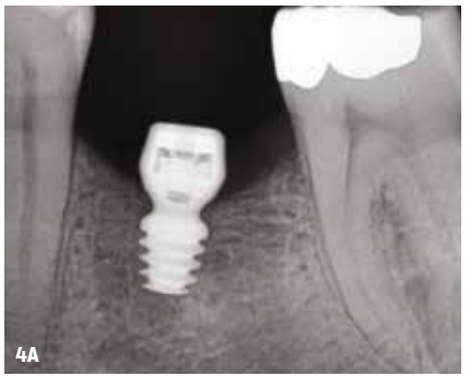
Figs. 3A, B: *Sequence of periapical radiographs of a patient randomly allocated to 8.5 x 4.0-mm or longer implants (long implant group) who received an implant in position 25: A) just after implant placement (baseline); B) at 3 years post-loading.*

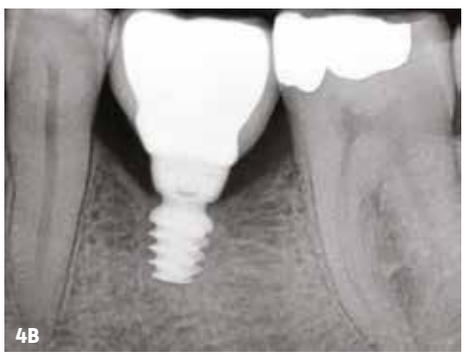
RESULTS

One hundred and sixty-four patients were screened for eligibility, but 14 patients were not included in the trial because they did not want to be randomised, and wished to have long implants. One hundred and fifty patients were considered eligible and were consecutively enrolled in the trial, four patients at LC's centre; 96 at PF's centre, which also treated the remaining 46 patients who should have been treated by LC's centre, and 50 patients at RP's centre. Seventy-five patients were treated using short implants **(FIGS. 3A, B)** and 75 patients using long implants **(FIGS. 4A, B)**. All patients were treated according to the allocated interventions.

Eight patients dropped-out during the three years of follow-up, three from the short implant group and five from the long implant group. Reasons for dropping out are listed below.

- Short implant group:
  Patient 14 (PF's) was last seen at 1-year follow-up. He changed dentist but was contacted by phone and reported no problems;
  Patient 84 (PF's) was last seen at 1-year follow-up. Her phone number was later disconnected;
  Patient 98 (PF's) was last seen at 1 year, 8-month follow-up. He moved away and could not come to the 3-year follow-up appointment, but was contacted by phone and reported no problems.
- Long implant group:
  Patient 56 (PF's) was last seen at 4-month follow-up. His phone number was later disconnected;





Figs. 4A, B: *Sequence of periapical radiographs of a patient randomly allocated to 8.5 x 4.0-mm or longer implants (long implant group) who received an implant in position 35: A) just after implant placement (baseline); B) at 3 years post-loading.*

Patient 27 (PF's) was last seen at 1-year follow-up. His phone number was later disconnected;
Patient 128 (RP's) was last seen at 1-year follow-up. He moved away and could not come to the 3-year follow-up appointment, but was contacted by phone and reported no problems;
Patient 23 (PF's) was last seen at 1½-year follow-up. He moved away and could not come to the 3-year follow-up appointment, but was contacted by phone and reported no problems;
Patient 134 (RP's) was last seen at 2-year follow-up. He moved away and could not come to the 3-year follow-up appointment, but was contacted by phone and reported no problems.

Data pertaining to all remaining patients were subjected to statistical analysis. No substantial deviations from the protocol occurred, with the exception that LC treated only four patients out of the 50 patients allocated, and the remaining quota of his patients were therefore treated by PF. In addition, one patient, from the long implant group, from PF's centre initially received a provisional resin prosthesis instead of the permanent one due to financial issues. The permanent prosthesis was delivered at the 1-year post-loading assessment.

Patients were recruited and had their implant placed from September 2013 to February 2014. Follow-up was 3-year post-loading in all patients.

The main baseline patient and intervention characteristics are presented in **TABLE 1**. Initially, 124 implants were placed in the short group and 116 in the long group. There were no apparent significant baseline imbalances between the two groups, with the exception that less 4 mm-long implants were placed in maxillae that longer implants.

The main results up to 3-year post-loading are summarised in **TABLE 2**.

- Prosthesis failures: in each group, two prostheses could not be placed when planned because of early implant failures. The difference in observed proportions for prosthesis failures was not statistically significant (difference in proportion = 0; 95% CI: -0.061 to 0.062; P = 1; **TABLE 2**). All four prostheses were successfully delivered with a 4-month delay once the failed implants had been replaced.
- Implant failures: five patients experienced one implant failure each: three short and two long implants failed. The difference in proportions for implant failures was not statistically significant (difference in proportion = -0.013; 95% CI: -0.079 to 0.054; P = 1; **TABLE 2**). In the short implant group, one implant in position 16, inserted with a torque lower than 25 Ncm, was found to be mobile and painful at percussion 3½ months after insertion. The implant was removed and immediately replaced by an identical implant 11.5-mm long, which was successfully loaded 4 months later. One immediate post-extraction implant, in position 44 and inserted with a torque lower than 25 Ncm, was found to be mobile four months after insertion, and immediately replaced with an identical 10 mm-long implant, which was successfully loaded 4 months later. Another implant, inserted with a torque lower than 25 Ncm in position 36, was found to be mobile and painful at impression-taking and was removed. It was not replaced since there were successful implants in positions 35 and 37. Two long implants failed: one 13 mm-long implant in position 26 was found to be mobile and painful at percussion after 4 months. It was removed and immediately replaced with a short but wider implant (6 x 4.7 mm, I-RES Shape 1, I-RES, Milan, Italy). After 4 months of submerged healing, the replacement implant was successfully loaded. Another 11.5 mm-long implant placed immediately post-extraction in position 35, with an insertion torque lower than 25 Ncm, was found to be mobile and painful 3½ months after placement. The patient confessed to having been worrying the implant with her tongue. The implant was removed and immediately replaced with an identical implant measuring 10.0 x 4.0 mm, inserted with a torque greater than 25 Ncm, and was successfully loaded after at 4 months.

Complications: eight patients experienced nine complications: six complications occurred in five patients with short implants and three complications occurred in three patients with long implants. There was no statistically significant difference between the two groups in the number of patients experiencing complications rate (difference in proportion = -0.026; 95% CI: -0.103 to 0.053; P = 0.719; **TABLE 2**). The following complications occurred with short implants: two patients experienced some pain when touching the implants. Both implants were mobile and were removed. Another patient lost the cover screw 20 days after surgery, but this was replaced without any consequences. Two years and 8 months after loading, the same patient complained of pain around his implants, in positions 34 and 35. These implants were seen to be surrounded by inflamed mucosa, and

TABLE 1 PATIENT AND INTERVENTION CHARACTERISTICS

	4 mm-long implants (75 patients)	8.5-mm or longer implants (75 patients)
Females	45 (60%)	39 (52%)
Mean age at recruitment (range)	53.7 (20-76)	55.5 (25-86)
Heavy smokers (smoking up to 10 cigarettes per day)	20 (26.7%)	13 (17.3%)
Moderate smokers (smoking >10 cigarettes per day)	1 (1.3%)	6 (8.0%)
# implants	124	116
# implants in upper jaws	46	69
# post-extraction implants	22	34
# of augmented post-extraction implants	14	18
# implants placed with < 25 Ncm torque	17	27
Mean implant length	4.00 mm	9.94 mm
# patients with submerged implants	39	38
# patients receiving 1 implant	32	38
# patients receiving 2 implants	37	33
# patients receiving 3 implants	6	4
# patients rehabilitated with metal-resin prostheses	11 (14.7%)	3 (4.1%)
# patients rehabilitated with metal-composite prostheses	64 (85.3%)	71 (95.9%)

TABLE 2 SUMMARY OF THE MAIN RESULTS EXPRESSED AS NUMBER OF PATIENTS WHO EXPERIENCED AT LEAST ONE NEGATIVE EVENT UP TO 3 YEARS AFTER LOADING. DROP-OUTS WERE EXCLUDED AND NONE EXPERIENCED A NEGATIVE EVEN

	Long implants 70 patients	Short implants 72 patients	Difference in proportions	95% CI	P-value
Patients with failed prostheses	2 (2.9%)	2 (2.8%)	0	-0.061 to 0.062	1
Patients with failed implants	2 (2.9%)	3 (4.2%)	-0.013	-0.079 to 0.054	1
Patients with complications	3 (4.3%)	5 (6.9%)	-0.026	-0.103 to 0.053	0.719

the prosthesis' screws were loose. The prosthesis was therefore removed and healing abutments placed on the implants. The patient was prescribed 1% chlorhexidine gel (Corsodyl, GlaxoSmithKline Consumer Healthcare, Baranzate, Italy) to be applied twice a day for 14 days. After 14 days the mucosa looked healthy, and the prosthesis was adjusted to facilitate oral hygiene procedures. Another patient complained about the mobility of her prosthesis, on implants in positions 35 and 37, at 2 years and 3 months after loading. Part of the resin prosthesis lining was missing. The prosthesis was unscrewed, and the connecting screw of implant 37 was found to be fractured at the level of its apical third. Since the broken portion of the screw could not be removed, it was abraded with a micro-drill. The prosthesis was screwed back into place, to see how it performed, before deciding whether to repair the missing resin lining. Finally, another patient presented with a mobile crown 2½ years after prosthesis loading. The connecting screw was loosened and was retightened at 25 Ncm.

Two implants belonging to the long implant group caused pain when placed under pressure. Both implants were mobile, removed and immediately replaced. Failures were not considered as complications unless pain was present, and these events were therefore both considered as complications. Finally, one patient complained of discomfort at both implants 2 years and 5 months after loading. Both implants were affected by peri-implant mucositis. The prosthesis was unscrewed, the area was cleaned, 1% chlorhexidine gel was applied, and the prosthesis screwed back in place. The chlorhexidine gel was prescribed to be taken 3 times per day for 14 days, and the complication resolved.

Peri-implant marginal bone level changes **(TABLE 3 AND 4)**: both groups had gradually lost statistically significant marginal peri-implant bone (P <0.001) at loading (0.23 mm for short implants and 0.21 mm for long implants), at 4 months after loading (0.38 mm for short implants and 0.39 mm for long implants, at 1 year after loading (0.53 mm for short implants and 0.57 mm for long implants, and at 3 years after loading (0.55 mm for short implants and 0.61 mm for long implants; **TABLE 4**). There was no statistically significant difference between the two groups in terms of peri-implant bone level changes either between implant placement and loading (-0.01; 95% CI: -0.11 to 0.07; P = 0.304), implant placement and 4 months after loading (0.01; 95% CI: -0.08 to 0.11; P = 0.328), implant placement and 1 year after loading (0.04; 95% CI: -0.07 to 0.14; P = 0.198), or between implant placement and 3 years after loading (0.05; 95% CI: -0.05 to 0.16; P = 0.221) **(TABLE 4)**.

TABLE 3 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS BETWEEN GROUPS AND TIME PERIODS

	Implant placement	Loading	4 months after loading	1 year after loading	3 years after loading
	N Mean (SD)	N Mean (SD) 95% CI	N Mean (SD) 95% CI	N Mean (SD) 95% CI	N Mean (SD) 95% CI
Short implants	75 0.02 (0.08)	75 0.25 (0.26) 0.20; 0.30	75 0.40 (0.26) 0.35; 0.45	75 0.550 (0.257) 0.492; 0.608	72 0.58 (0.26) 0.52; 0.64
Long implants	75 0.05 (0.27)	74 0.26 (0.173) 0.23; 0.30	74 0.44 (0.25) 0.39; 0.50	73 0.616 (0.262) 0.556; 0.678	69 0.66 (0.30) 0.59; 0.73
Difference	-0.03	-0.02 -0.09; 0.05	-0.04 -0.12; 0.05	-0.066 -0.147; 0.023	-0.08 -0.18; 0.01
Mann-Whitney U-test P-value	0.859	0.131	0.172	0.127	0.133

TABLE 4 COMPARISON OF MEAN CHANGES IN PERI-IMPLANT MARGINAL BONE LEVELS AT LOADING, 4 MONTHS, AND 1 AND 3 YEARS AFTER LOADING

	Placement – loading	Placement – 4 months after loading	Placement – 1 year after loading	Placement – 3 years after loading
	N Mean (SD) 95% CI	N Mean (SD) 95% CI	N Mean (SD) 95% CI	N Mean (SD) 95% CI
Short implants	75 -0.225 (0.213) -0.278; -0.177	75 -0.380 (0.247) -0.447; -0.322	75 -0.528 (0.238) -0.592; -0.470	72 -0.554 (0.240) -0.611; -0.498
Long implants	74 -0.214 (0.254)-0.261; -0.152	74 -0.392 (0.312)-0.463; -0.310	73 -0.566 (0.338)-0.639; -0.479	69 -0.610 (0.368)-0.694; -0.517
Difference	-0.011 -0.109; 0.070	0.013 -0.083; 0.105	0.038 -0.068; 0.138	0.051 -0.052; 0.156
Mann-Whitney U-test P-value	0.304	0.328	0.198	0.221

TABLE 5 COMPARISONS BETWEEN THE THREE STUDY CENTRES AT 3 YEARS AFTER LOADING

	PF 96 patients	RP 50 patients	VC 4 patients	P-value
Drop-outs	6	2	0	0.755
Patients with implant failures	4	1	0	0.728
Patients with prosthesis failures	4	0	0	0.311
Patients with complications	7	1	0	0.352
Mean (95% CI) peri-implant bone level changes in mm from implant placement to 3 years after loading	-0.620 (-0.692; -0.548) A	-0.513 (-0.582; -0.443) B	-0.498 (-0.657; -0.338) AB	0.011*

**Statistically significant difference; centres not connected by the same letter are statistically significant different.*

There were no statistically significant difference in failure, complication or drop-out rates across centres, but there was a statistically significant difference in marginal bone level changes between RP's and PF's centres (P = 0.004) at 3-year post-loading **(TABLE 5)**. Specifically, PF's centre lost 0.1 mm more peri-implant marginal bone than RP's centre; however this difference would not be considered clinically significant.

DISCUSSION

This study assessed whether 4.0 x 4.0-mm implants supporting partial fixed prostheses could be at higher risk of failures than longer implants when placed in posterior jaws with adequate bone volumes. We were particularly interested in evaluating the clinical performance of very short implants (4.0 mm long) with the conventional diameter of 4.0 mm in order to determine the minimal amount of bone able to support functionally loaded dental implants.
Previous trials suggested that short implants can achieve clinical results that are as effective, if not more so, than longer implants placed in augmented bone up to 8 years after loading[1-11].

However, sometimes surgeons use short implants with wider bodies to compensate for the lack of implant height[2,10]. While it is still unclear whether this 'compensation' is actually necessary, results of this and many other trials in which 5.0 to 6.6 mm-long implants with diameters of 4.0 to 5.0 mm were used suggest that short implants with diameters of 4.0 to 5.0 mm also perform well, at least up to 8 years post-loading[1,3-9,11].

When comparing our data to those from previous similar RCTs[16-18], all trials showed identical trends: there were similar outcomes between 5.0 to 6.0 mm-long implants and 10.0-mm or longer implants up to 10 years post-loading in the presence of adequate bone volumes. In the present trial, five implants were lost in total: three 4 mm-long implants and two longer ones. All failures were detected at abutment connection, and four of the failed implants were replaced. No apparent signs of infection were noted, but failed implants were usually painful at percussion and mobile, indicating that osseointegration had not taken place[19].

The failures occurring earlier were easier to handle; in fact, four of the mobile implants were immediately replaced with other implants on the same day they were removed, minimising patient discomfort. That being said, in those patients delivery of the prostheses was delayed for up to 4 additional months. In at least one of these cases, the patient declared that she had been continuously touching the transmucosal portion of the implant with her tongue, and most of the failed implants were placed using insertion torques lower than 25 Ncm. It is possible that several undesirable movements disrupted the bone healing around these transmucosal implants, thereby causing fibrointegration[19]. To minimise the potential risk of such a complication, therefore, we suggest that a two-piece bone-level 4 mm-long implant be developed, and its clinical performance subsequently compared with that of 4 mm-long transmucosal implants.

Peri-implant marginal bone loss was minimal (about 0.6 mm) at 3 years after loading in both groups. It may be that this minimal bone loss could be partly explained by the lack of an implant-abutment junction at the level of the crest; indeed, such junctions could easily harbour bacteria that could enhance peri-implant marginal bone loss.

The main limitation of the present trial was the short duration of the follow-up, but longer follow-up findings will be presented at a later date. Another limitation is the limited sample size. Nonetheless, at the time of writing, this is the RCT comparing short with longer implants in sufficient bone volumes with the largest sample size ever published. Furthermore, as interventions tested were assessed in real-world clinical conditions and the patient inclusion criteria were rather broad, similar results should be obtained by other experienced operators treating patients with similar characteristics.

CONCLUSIONS

Three years after loading, 4.0 x 4.0 mm-long implants achieved similar results to 8.5 x 4.0 mm or longer implants in posterior jaws in the presence of adequate bone volumes. That being said, 5 to 10 years' post-loading data will be necessary before reliable recommendations can be made.

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KEY WORDS
dental implants, immediate loading, early loading, conventional loading, delayed loading

Randomised controlled trial

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 4th year of follow-up instead of the 3rd 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 Baseline – 1 year 0.204 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 Baseline – 1 year 0.311 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* Baseline – 1 year 0.008* 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 0.25 ± 0.70	N = 18 -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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KEY WORDS
small diameter implant, horizontal augmentation,
bone substitute, bone lamina

Randomised controlled trial

IMMEDIATE LOADING OF 3 MM-DIAMETER IMPLANTS AS AN ALTERNATIVE TO HORIZONTAL BONE AUGMENTATION FOR PLACING NORMAL DIAMETER IMPLANTS: FOUR-MONTH POST-LOADING RESULTS FROM A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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PURPOSE. To evaluate the effectiveness of immediately loaded 3 mm-diameter implants in alternative to horizontal bone augmentation procedures to allow placement of implants with a conventional diameter of 4 mm.

MATERIALS AND METHODS. Forty-five partially edentulous patients with a bone width of between 4 and 5 mm 3 mm below the crest in areas requiring one to three adjacent implants were randomised, according to a parallel-group design, to receive one to three 3.0 mm-wide implants to be loaded immediately (23 patients) or horizontal crest augmentation with a granular bone substitute covered with a bone lamina for placing, after 6 months of healing, one to three implants at least 4 mm wide (22 patients) at two centres. Implants at augmented sites were left to heal unloaded for 4 months. Four mm-diameter implants were restored using provisional screw-retained reinforced acrylic prostheses, replaced after 4 months by definitive prostheses. Three mm-diameter implants were loaded immediately (if the insertion torque was ≥ 35 Ncm) or after 4 months with definitive metal-composite prostheses. Patients were followed-up to 4-month post-loading. Outcome measures were: prosthesis and implant failures, any complication, peri-implant marginal bone level changes, and patient satisfaction.

RESULTS. No patient dropped out. In three patients, five 3 mm-diameter implants could not be inserted with a torque of 35 Ncm, so were submerged unloaded for 4 months. Two implants failed in two patients from the augmented group (P [Fisher's exact probability test] = 0.2333; difference in proportion = -0.09; CI 95% -0.24 to 0.07) and neither patient was fitted with a definitive prosthesis. Three patients with small diameter implants were affected by three complications *versus* nine augmented patients with 10 complications, the difference being statistically significant (P [chi-square test] = 0.0346; difference in proportion = -0.28; CI 95% -0.50 to -0.01). Patients with 3 mm-diameter implants lost on average 0.09 mm of peri-implant bone at 4 months, while augmented patients lost 0.26 mm, a statistically significant difference (mean difference = 0.17 mm, 95% CI 0.02 to 0.31, P = 0.0235). All patients were fully satisfied with both function and aesthetics, with two exceptions: one patient from the 3-mm group was only partially satisfied with both aesthetics and function, and one patient from the augmentation group was only partially satisfied with the aesthetics. However, all patients would undergo the same procedure again.

CONCLUSIONS. Four months after loading, patients treated using 3 mm-wide implants displayed better results than those horizontally augmented to receive 4 mm-wide implants. Three mm-wide implants might therefore be a preferable choice with respect to bone horizontal bone augmentation, the treatment being less invasive, faster, cheaper, and associated with less morbidity; however, 5- to 10-year post-loading data will be necessary before reliable recommendations can be made.

CONFLICT OF INTEREST STATEMENT. Global D (Brignais, France) partially supported this trial and donated the implants and prosthetic components. OsteoBiol (Tecnoss, Giaveno, Italy) donated the biomaterials used for bone augmentation. However, the data property belonged to the authors and neither Global D nor OsteoBiol interfered in any way with the conduct of the trial or the publication of the results.

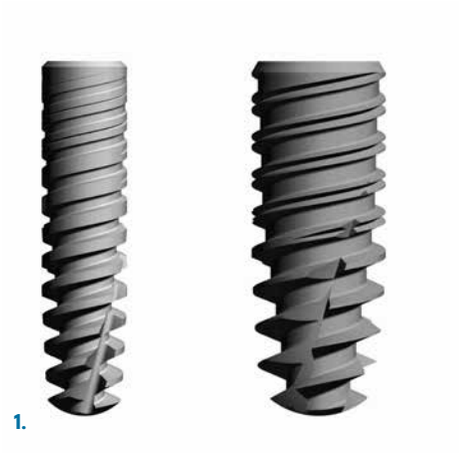
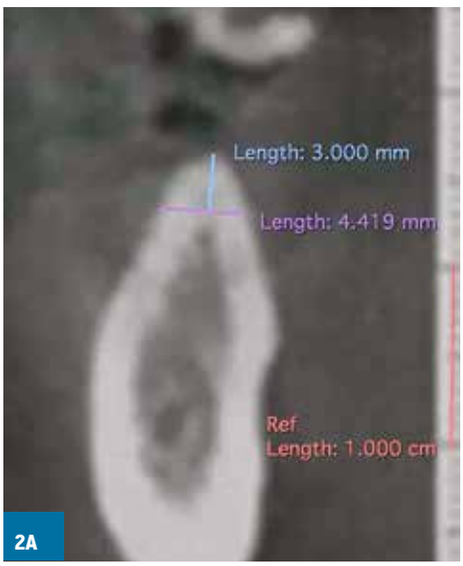
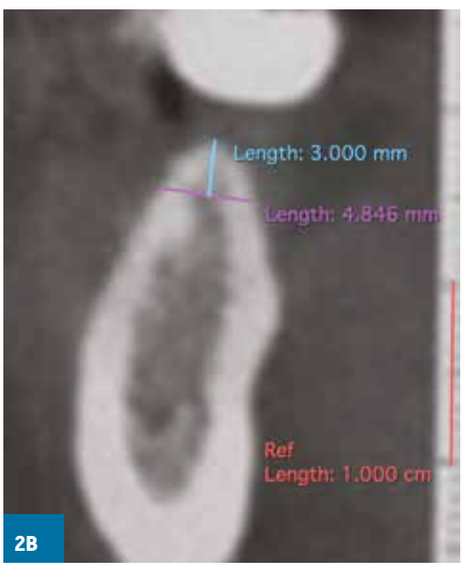


Fig. 1: *Drawings showing the difference in diameters of the implants used in the present study: on the left the 3 mm-diameter and on the right the 4 mm-diameter implant.*





INTRODUCTION

Dental implants are used to replace missing teeth for rehabilitating function and aesthetics in edentulous patients. However, in many patients it is not possible to place dental implants of "adequate" diameter because there is less than 5 mm of residual bone width due to resorption of the crestal bone. Clinicians, therefore, are faced with the dilemma of whether to attempt a horizontal augmentation procedure, or whether to place small implants having a diameter of 3 mm or less.

Various techniques are currently used for horizontal bone augmentation, though only a few of these techniques have been evaluated in randomised controlled trials (RCTs)[1]. Augmentation procedures are more technically demanding than simple implant placement, and therefore require skilful operators; moreover, they are expensive, can also be associated with significant postoperative morbidity and complications, and may require a longer period (up to 1 year) before patients are able to chew on their implant-supported prostheses[1]. Small diameter implants, on the other hand, could be a simpler, cheaper, less invasive and faster alternative if they could provide similar clinical outcomes to conventional diameter implants placed in augmented bone.

While there have been two randomised controlled trials (RCTs) comparing 3.3-mm small-diameter implants with implants having a conventional 4.1 mm diameter placed in sufficient bone volumes with 3-year follow-up [2,3], there have been no RCTs comparing small-diameter implants placed in scarce bone volumes with conventional-diameter implants placed in similar bone volumes created by means of horizontal augmentation. Hence, the aim of this RCT was to compare the effectiveness of immediately loaded 3 mm-diameter implants (In-Kone Universal, Global D, Brignais, France) **(FIG. 1)** as an alternative to the placement of identical implants with a conventional diameter of 4 mm following horizontal bone augmentation using a mix of collagenated corticocancellous porcine bone (OsteoBiol mp3, Tecnoss, Giaveno, Italy) covered with lamina of cortical porcine bone (OsteoBiol Lamina, 1 mm thick) **(FIGS. 2A-K)**.

The study protocol foresees following-up patients to the fifth year of function in order to evaluate the success of the procedures over time; this preliminary report presents the clinical outcomes at 4 months after loading. The present article has been drafted in line with the CONSORT statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/).

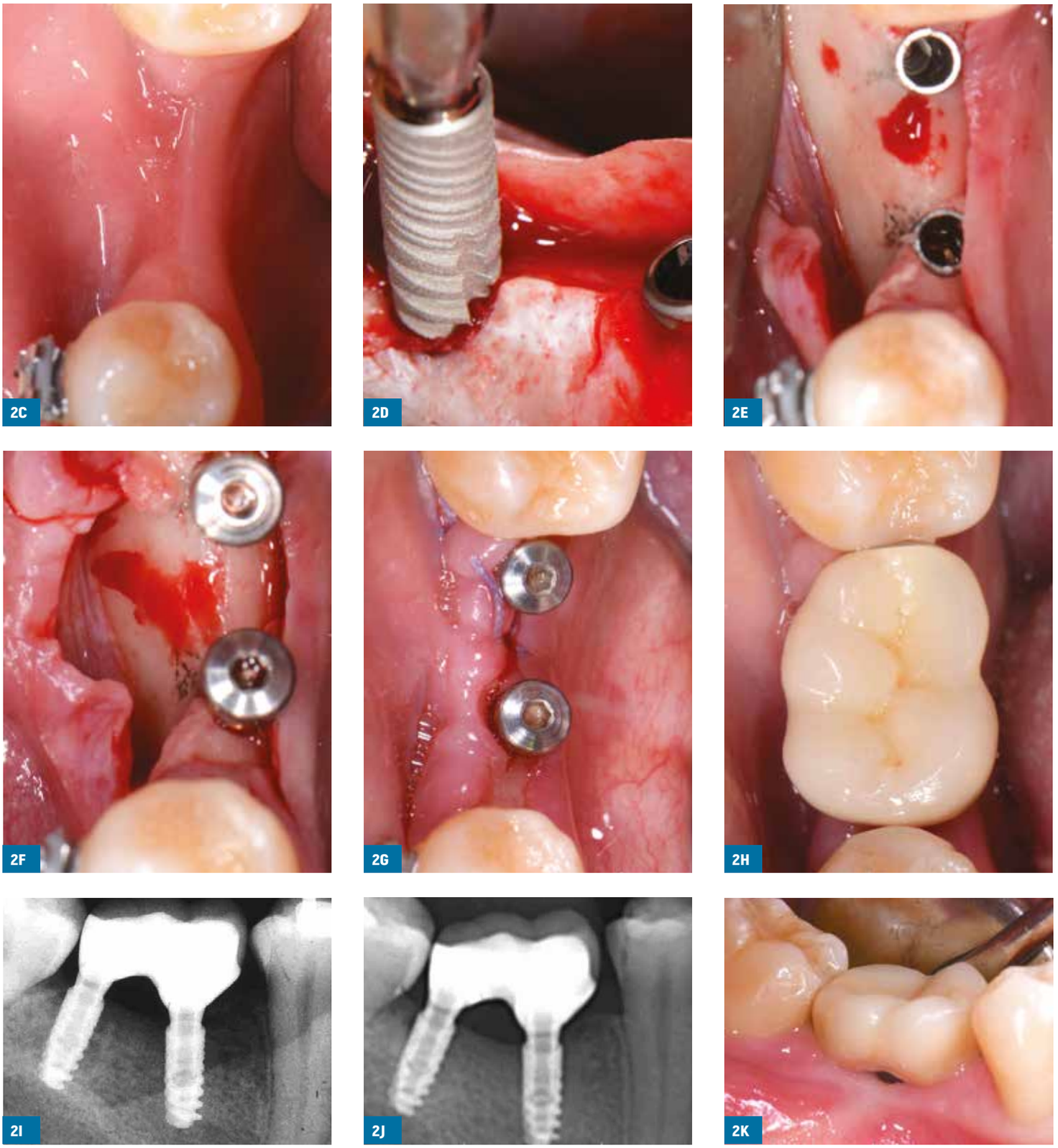
MATERIALS AND METHODS

Study design

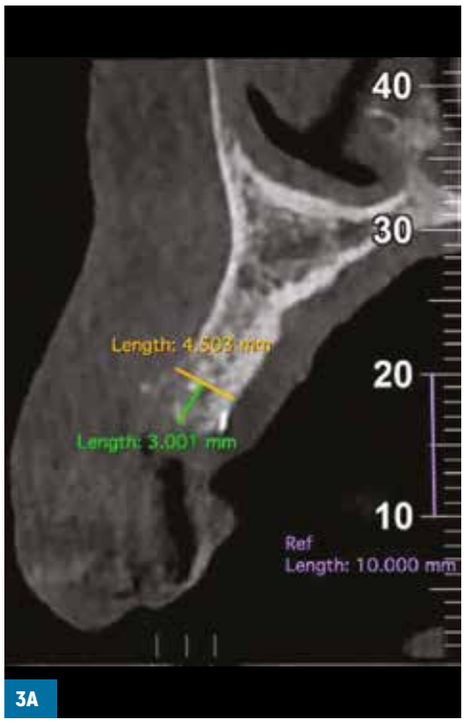
This parallel-group randomised controlled multicentre trial was designed with two arms. One arm received one to three immediately loaded 3 mm-diameter implants **(FIGS. 2A-K)**, while the other had crestal bone horizontally augmented and, after 6 months of healing, one to three 4 mm-diameter implants placed and left to heal submerged and unloaded for 4 months **(FIGS. 3A-M)**.

Inclusion and exclusion criteria

Any partially edentulous patient with crestal bone of buccolingual width of between 4 and 5 mm 3 mm below the crest at each future implant site, as measured on cone-beam computed tomography (CBCT) scans, in areas requiring one to three dental implants, being 18 years or older and able to understand and sign an informed consent form, was eligible for inclusion in this trial. The minimal implant length to be used was of 8.5 mm. In case of an eligible area



Figs. 2A-K: *Sequence of treatment of one of the patients randomly allocated to receive two 3 mm-diameter implants to replace a lower molar: A) and B) preoperative CBCT scans of the areas of the future implants for screening the patient; C) preoperative clinical view; D) two 3 mm-wide implants were placed in position of the molar roots; E) occlusal view; F) healing abutments in position; G) clinical view with sutures just before immediate loading; H) immediate loading with a definitive metal-composite crown; I) periapical radiograph at implant placement/immediate loading; J) periapical radiograph and K) clinical view 4 months after loading; note the tunnel to allow proper oral hygiene.*



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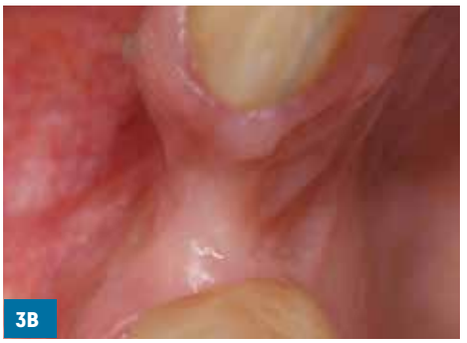
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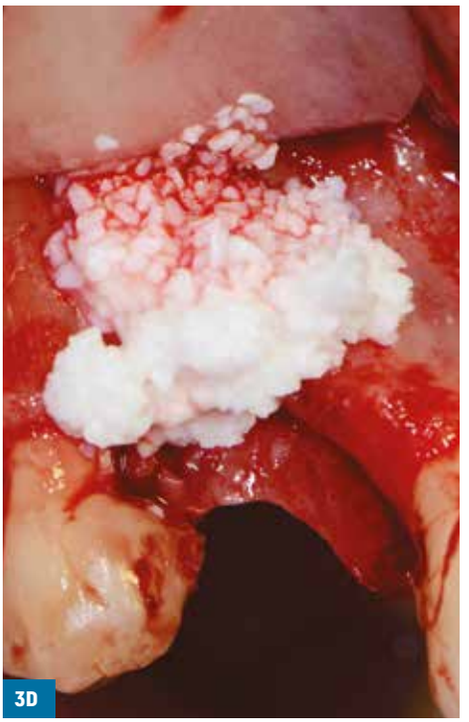
3C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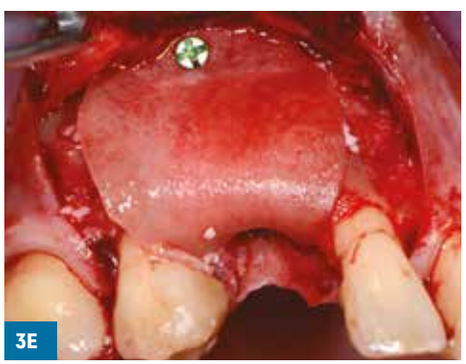
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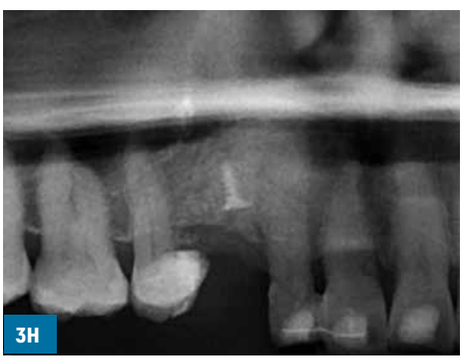
3F


3G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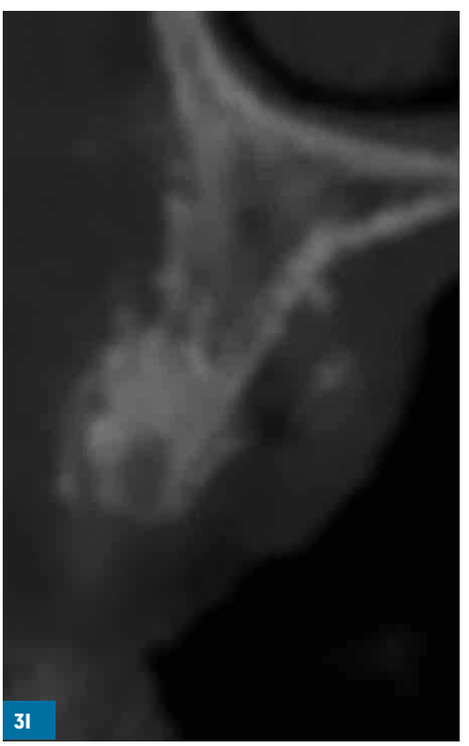
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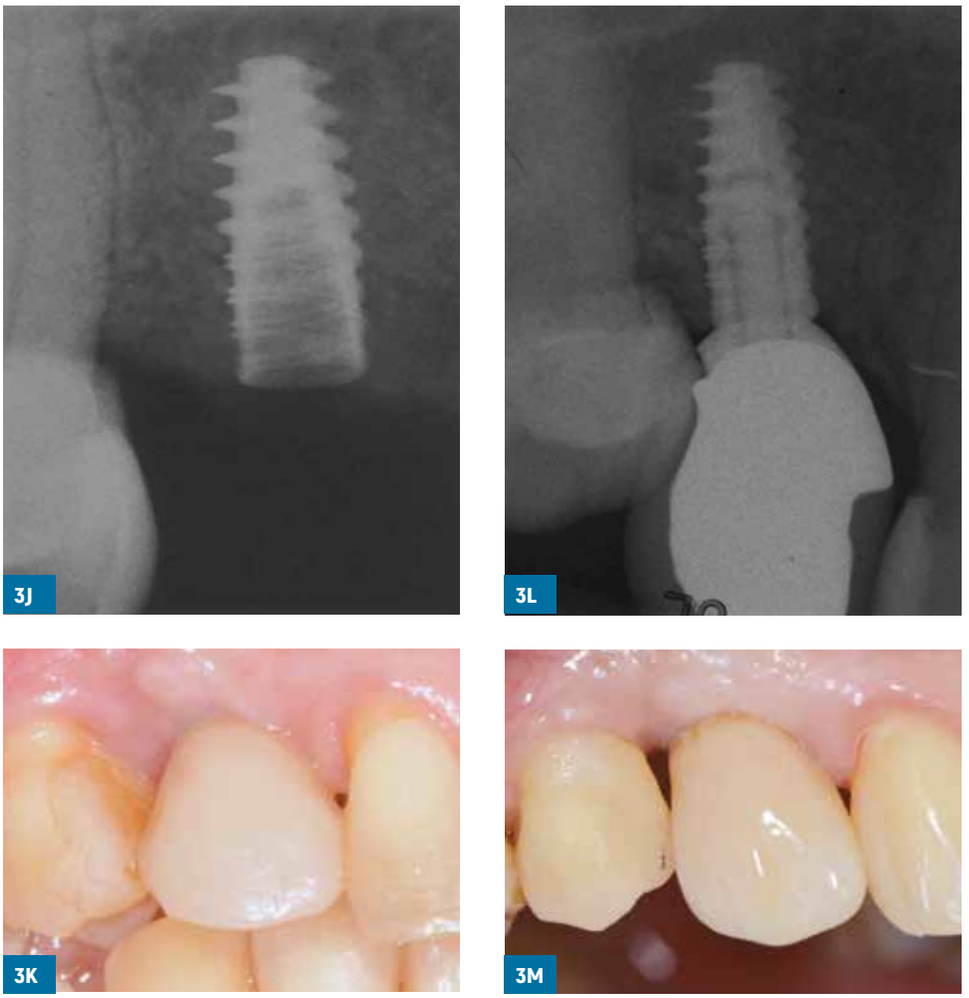

Figs. 3A-M: *Sequence of treatment of one of the patients randomly allocated to receive horizontal bone augmentation to place a 4 mm-diameter implant to replace an upper canine: A) preoperative CBCT scan of the area of the future implant used for screening the patient; B) preoperative clinical view; C) after flap raising the area was randomly allocated to horizontal augmentation; D) positioning the bone substitute; E) final fixation of the bone lamina; F) clinical evaluation of the horizontally augmented portion; G) sutures; H); postoperative control panoramic radiograph; I) CBCT scan after 6 months of healing to plan implant insertion; J) periapical radiograph at placement of the 4 mm-diameter implant; K) clinical view of the provisional resin crown placed after 4 months of submerged healing; L) periapical radiograph at delivery of the definitive crown, 4 months after initial loading; M) clinical view of the definitive crown at its delivery.*

where aesthetics was of concern, for patients randomised to small diameter implant(s), a soft tissue connective tissue graft harvested from the palate or the maxillary retromolar area was to be inserted using a pouch technique at implant placement to improve aesthetics. However, no patients needing soft tissue graft to improve aesthetics were actually enrolled. To replace one single molar, two small diameter implants were used.

In patients having multiple horizontally resorbed areas, only one area was included in the study—the area which could be treated using up to three adjacent implants. Each patient could only be treated on one side of the jaw, in accordance with the parallel-group design.

Exclusion criteria were:

- General contraindications to implant surgery;
- Irradiation of the head and neck area;
- Immunosuppressed or immunocompromised status;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Untreated periodontitis;
- Poor oral hygiene and motivation;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;

- Substance misuse;
- Psychiatric problems;
- Unrealistic expectations;
- Lack of opposing occluding dentition in the area intended for implant placement;
- Acute or chronic infection/inflammation in the area intended for implant placement;
- Participation in other studies, if precluding proper adherence to the present protocol;
- Referral for implant placement alone, i.e., not having the prosthesis or maintenance procedures performed at the study treatment centres;
- Extraction sites with less than 3 months of healing time;
- Inability to participate in 5-year follow-up.

Patients were categorised into three groups according to their declarations: non-smokers, moderate smokers (up to 10 cigarettes per day), and heavy smokers (more than 10 cigarettes per day). Patients were recruited and treated in different centres by two different operators. One operator (Pietro Felice, PF) treated patients in the Bologna University clinic, whereas the other operator (Roberto Pistilli, RP) treated patients in his private practice. Both followed similar standardised protocols.

The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to. The study was approved by the Comitato Etico Interaziendale Bologna-Imola, Italy, ethics committee on 9th December 2015 (Cod. CE: 15036). All patients received thorough explanation and signed an informed written consent form prior to being enrolled in the trial.

Augmentation and implant placement procedures

Patients received prophylactic antibiotic therapy with 2 g of amoxicillin (or clindamycin 600 mg if allergic to penicillin) one hour prior to augmentation, and rinsed for one minute with chlorhexidine 0.2% before the procedure. Patients were treated under local anaesthesia (articaine with 1:100,000 adrenaline). After crestal and releasing incisions and flap raising, patients were randomly allocated, by opening a sequentially numbered envelope corresponding to the patient recruitment number, to either the horizontal augmentation procedure to allow placement of one to three implants of 4 mm-diameter (control procedure) or to receive one to three 3.0 mm-wide implants (test procedure).

In the case of augmentation procedure, the crestal bone was, when possible, perforated with a bur. In the maxilla, a lamina of cortical bone was then positioned and fixed vestibularly or palatally, depending on the defect location, with one or more titanium miniscrews of width 1.2 mm (Minitek-Microtek, Global D). The site was then grafted with mp3 granular bone substitute, and the lamina was bent and fixed palatally or vestibularly with other miniscrews. In mandibles, the lamina was first fixed lingually. The lamina extended for at least 2 mm over the grafted area on sound bone. Incisions were made in the vestibular periosteum to release flaps as coronally as required, and the simple pressure of the fingers (the digitoclastic technique)[4] was used to better release the flaps. Flaps were sutured with horizontal mattress sutures and single simple sutures, using Vicryl 4.0 sutures (Ethicon FS-2, St-Stevens-Woluwe, Belgium), until the incisions were perfectly sealed. Ice packs were provided, and 1 g amoxicillin (or 300 mg clindamycin) was prescribed to be taken three times a day for 7 days. Ibuprofen 400 mg (or 1 g paracetamol in case of allergy to non-steroidal anti-inflammatory drugs) was prescribed 2 to 4 times a day to be taken during meals, as long as required. Patients were instructed to use chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks, to eat a soft diet for one week, and to avoid brushing or trauma to the surgical sites. Patients were

advised not to wear any removable prostheses. Patients were seen after 3 days, and sutures were removed after 10 days. Patients were recalled for additional postoperative check-ups at 1 and 2 months after the augmentation procedure. Grafted areas were left to heal for 6 months before placing the implants.

In the case of patients randomised to receive the 3 mm-wide implants, one to three titanium-alloy grade 5 tapered implants (In-Kone Universal, Global D), having a diameter of 3.0 mm, internal connection and a sand-blasted and double acid-etched roughened surface, were inserted under guidance of surgical stents to optimise implant positioning. Each missing tooth was replaced by one dental implant. In the case that a single molar had been randomised to be replaced by 3 mm-diameter implants, two implants were used instead, and three implants were used to replace two adjacent missing molars. The standard placement procedure was used, as recommended by the manufacturer. Drills of increasing diameters were used to prepare the implant sites. Bone quality (density) was subjectively assessed at drilling and divided into "hard", "medium" and "soft". Implant sites were slightly underprepared, and the surgical unit motor was set with a torque of 35 Ncm during implant insertion. Implants inserted with a torque of greater than 35 Ncm were loaded immediately, while those inserted with a torque of up to 35 Ncm were submerged and left to heal for 4 months before being functionally loaded. Implants were placed 2 mm subcrestally. Healing abutments were placed, and flap closure around the abutments was achieved using single Vicryl 4.0 sutures. In the case of aesthetic concerns, patients randomised to receive 3-mm diameter implants were to be given a soft tissue connective tissue graft harvested from the maxillary retromolar area or the palate, inserted using the pouch technique, at implant placement to improve aesthetics. Baseline periapical radiographs were taken of the study implants. If the peri-implant marginal bone levels were not measurable, a new radiograph was taken. Patients were instructed to take ibuprofen 400 mg (or 1 g paracetamol in case of allergy) two to four times a day during meals, except in the absence of pain, and to use chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks. Patients were seen after 1 week for suture removal, occlusion check and oral hygiene instructions.

In the horizontally augmented group, implants were placed following the same procedures, the differences being that they were 4 mm rather than 3 mm in diameter, that only one implant was used to replace one missing tooth (intermediate pontics were allowed), and that they were submerged unloaded for 4 months.

Prosthetic procedures

For the 3 mm-wide implants that were placed using a torque greater than 35 Ncm, the prosthetic procedures were begun immediately after suturing. All other implants were submerged for 4 months of unloaded healing. Impressions with the pick-up copings were taken using a polyether material (Impregum 3M/ESPE, Neuss, Germany) and customised resin impression trays. Definitive metal-composite cemented crowns rigidly joining the implants were delivered within the 24 hours after impressions. Prostheses were made avoiding cuspid guidance, and lateral and protrusive loading, trying to reach a balanced and mutually protected occlusion.

Periapical radiographs were taken using the paralleling technique. If the bone adjacent to the study implant was not properly visible, a second radiograph was made.

Patients from the 4 mm-diameter group were rehabilitated after 4 months of submerged healing using reinforced provisional screw-retained or cemented prostheses rigidly joining the implants. The occlusal scheme was the same as in the test group.

Four months after loading, implants were manually tested for stability and, in the control group, definitive metal-composite, metal-ceramic or zirconia prostheses, rigidly joining the

implants, were either screw-retained or cemented with provisional cement (Implacem, Dentalica, Milan, Italy, at PF's centre, or TempBond, Kerr Italia, Scafati, Italy, at RP's centre) on titanium abutments, and oral hygiene instructions were reinforced, if necessary.
Patients were enrolled in an oral hygiene programme with recall visits every 6 months for the entire duration of the study. Follow-ups were conducted by independent outcome assessors (Dr. Berti at PF's centre and Dr. Cassoni at RP's centre). This report presents preliminary outcome data at 4 months after prosthetic loading.

Outcome measures

This study tested the null hypothesis that there would be no differences in clinical outcomes between the two procedures against the alternative hypothesis of a difference. Outcome measures were the following.

- Prosthesis failure: planned prosthesis which could not be placed due to implant failure(s), loss of the prosthesis secondary to implant failure(s), or replacement of a definitive prosthesis for any reasons.
- Implant failure: implant mobility, removal of stable implants dictated by progressive marginal bone loss or infection, or any mechanical complications rendering the implant unusable (e.g., implant fracture). The stability of each individual submerged implant was measured at abutment connection (4 months after implant placement) and all implants 4 months after loading by tightening the abutment screws with the removed prostheses using a manual wrench with a force of 20 Ncm.
- Any biological or prosthetic complications.
- Peri-implant marginal bone levels changes, as evaluated on digital periapical radiographs taken using the paralleling technique at implant placement, and 4 months after loading. Radiographs were stored in TIFF format with a 600 dpi resolution 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 length. Measurements of the mesial and distal bone crest levels adjacent to each implant were made to the nearest 0.01 mm and averaged for implants, patients and groups. The measurements were made parallel to the implant axis. Reference points for the linear measurements were the apical margin of the implant collar and the most coronal point of bone-to-implant contact.
- Aesthetic evaluation of clinical vestibular and occlusal pictures of each individual experimental tooth and its adjacent tooth/implant, taken at 4 months after loading (after delivery of the definitive prostheses in the 4 mm-diameter group), on a computer screen by a blinded independent dentist. The aesthetic evaluation was to be performed using the pink aesthetics score (PES)[5] and the white aesthetics score (WES)[6]. Aesthetics scores were to be evaluated at single teeth, and then averaged for patients and groups. Unfortunately only pictures of five patients were taken, so no aesthetic evaluation could be performed.
- Patient satisfaction: four months after loading, the independent outcome assessor at each centre asked to the patient the following questions:
  1) "Are you satisfied with the function of your implant-supported prostheses?" Possible answers were: "yes, absolutely", "yes, partially", "not sure", "not really", or "absolutely not";
  2) "Are you satisfied with the aesthetic outcome of your implant-supported prostheses?" Possible answers were: "yes, absolutely", "yes, partially", "not sure", "not really", or "absolutely not";
  3) "Would you undergo the same treatment again?" Possible answers were: "yes" or "no".

Methodological aspects

The study was designed to be conducted at four centres, but only two recruited patients: the University of Bologna dental clinic (PF) and a private practice in Rome of (RP). Two dentists (Dr. Berti at PF's centre and Dr. Cassoni at RP's centre), not involved in the treatment of the patients, performed the implant stability assessment and took the periapical radiographs without knowing group allocation; however, augmented sites could be easily identified due to their anatomy. Complications were dealt with directly and reported by the treating clinicians, who were not blinded. One experienced assessor (Dr. Barausse), not involved in the treatment of the patients, performed all radiographic assessments without knowing group allocation; however, augmented sites could be easily identified on radiographs due to the different implant diameters and the presence of a more radio-opaque bone substitute.

No sample size calculation was performed since no data on 3.0 mm-diameter implants was available when this trial was conceived. It was agreed to run the trial at four different centres. Each centre had to include 28 patients, 14 having thin ridges in mandibles and 14 in maxillae, to be randomly allocated in equal numbers to each treatment group. In total, 112 patients were to be recruited, 56 receiving 3 mm-wide implants and 56 having conventional 4 mm-diameter implants after horizontal bone augmentation. However, two centres did not recruit one single patient, and one centre treated seven partially edentulous patients in mandibles and 10 in maxillae.

One computer-generated restricted randomisation list was created for each centre. Only one of the investigators (Dr. Esposito), not involved in the selection and treatment of patients, was aware of the random sequence and could have access to the randomisation list stored on his password-protected laptop computer. The information on how to treat each patient was enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially after flap raising. 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. A dentist with expertise in statistics (Dr. Buti) analysed the data, without knowing the group codes. The patient was the statistical unit of the analyses. Differences in the proportion of patients with prosthesis failure, implant failure and complications (dichotomous outcomes) were compared using the chi-squared test or Fisher's exact probability test (when 20% of cells with expected count <5). Differences in patient means for continuous outcomes (radiographic bone levels) were compared between groups using a t-test for independent samples. Comparisons between each time point and the baseline measurements were made using paired t-tests, to detect any changes in marginal peri-implant bone levels. The chi-squared test or Fisher's exact probability test were used to compare the number of prosthesis failures, implant failures and complications, and a t-test for independent samples was used to compare the marginal bone level changes in at the two centres. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Sixty-one patients were screened for eligibility, but 16 patients were not included in the trial for the following reasons: 13 patients (nine of PF's and four of RP's) requested horizontal bone augmentation in aesthetic areas, and three patients (RP) refused any surgical intervention and asked for an adhesive prosthesis instead. Forty-five patients were considered eligible and were consecutively enrolled in the trial. All patients were treated according to the allocated interventions. No patient dropped-out before 4-month post-loading follow-up, and data from

all patients could be evaluated in the statistical analyses, with the exception of the clinical photographs to be used for evaluating aesthetics 4 months after loading.

Apart from the reduced number of patients than planned, treated by only two of the four planned centres, and the inconsistencies in taking clinical photographs for the aesthetic evaluation at 4 months after loading, the following deviations from the protocol were reported.

- Three mm-diameter implants (test group):
  - In one patient there was insufficient space to place two implants to replace a molar, so only one implant was inserted;
  - In two patients, in which a torque superior 35 Ncm was not achieved, healing abutments were placed instead of fully submerging the implants.
- Augmentation group (control):
  - Two patients had one 6 mm-long implant inserted and their implant submerged time prolonged by 2 months due to the augmented bone being too soft;
  - Two patients had a soft tissue graft from the palate at their mandibular implants due to total lack of keratinised mucosa and pain on brushing;
  - One patient asked to have the definitive prosthesis directly, eschewing the provisional prosthesis, for financial reasons;
  - One patient received the final prosthesis after 1 year, instead of 4 months, for personal reasons.

Patients were recruited and treated from January 2016 to February 2018. The follow-up was 4 months after initial loading.

The main baseline patient and intervention characteristics, divided by study group and location, are presented in **TABLE 1**. Thirty-five implants were placed in the augmentation group (control) and 49 in the 3 mm-wide implant group (test). This difference was due to the fact that two 3 mm-wide implants were used to replace single molars *versus* only one 4 mm-diameter implant. There were no baseline differences between the two groups, with the exception of twice the number of smokers in the 3 mm-diameter group, and that all 3 mm-diameter implants were rehabilitated with cemented metal-resin prostheses. Five implants in three patients from the 3 mm-diameter group were inserted with a torque lower than 35 Ncm, and were loaded after 4 months of unloaded healing. Among the 4 mm-diameter implants, none could be placed with torque of at least 35 Ncm, indicative of a generalised softer bone quality at horizontally augmented sites.

- Prosthetic and implant failures: no patient from the 3 mm-diameter group lost any implant *versus* two patients from the augmentation group, who lost one implant each (P (Fisher's exact probability test) = 0.2333; difference in proportion = -0.09; CI 95% -0.24 to 0.07). One mandibular 6 mm-long implant in a premolar position was found to be mobile at abutment connection in a non-smoking female whose graft was characterized by poor integration, despite the implant healing having been prolonged by two months. This patient also experienced temporary post-augmentation paraesthesia. Another mandibular 8.5 mm-long implant in a premolar position was found to be mobile at abutment connection in a female moderate smoker whose graft was characterized by poor integration. Both patients had their failed implants replaced, but have not yet received their definitive prostheses.
- Complications: significantly more complications occurred at augmented sites: three patients from the 3 mm-diameter group were affected by three complications *versus* 10 complications in nine patients from the augmented group (P (chi-square test) = 0.0346; difference in proportion = -0.28; CI 95% -0.50 to -0.01). A detailed description of the complications and treatment is presented in **TABLE 2**.

TABLE 1 PATIENT AND INTERVENTION CHARACTERISTICS

	3 mm-wide implants (n = 23)	Augmentation + 4 mm-wide implants (n = 22)
Females	11 (48%)	13 (59%)
Mean age at recruitment (range)	50.26 (27-71)	48.82 (22-72)
Moderate smokers (up to 10 cig/day)	6 (26%)	4 (18%)
Heavy smokers (more than 10 cig/day)	4 (17%)	1 (5%)
Baseline average bone thickness 3 mm below the crest (SD)	4.78 mm (0.13)	4.70 mm (0.23)
Patients treated in mandibles	11 (48%)	10 (45%)
Number of implants	49	35
Number of implants placed in mandibles	22 (45%)	17 (49%)
Number of 6.0 mm-long implants	0 (0%)	2 (6%)
Number of 8.5 mm-long implants	19 (39%)	15 (43%)
Number of 10.0 mm-long implants	7 (14%)	9 (26%)
Number of 11.5 mm-long implants	22 (45%)	6 (17%)
Number of 13.0 mm-long implants	1 (2%)	3 (8%)
Number of implants in upper molar sites	7 (14%)	4 (11%)
Number of implants in lower molar sites	20 (41%)	9 (26%)
Number of implants in upper premolar sites	17 (35%)	12 (34%)
Number of implants in lower premolar sites	2 (4%)	6 (17%)
Number of implants in upper canine sites	3 (6%)	1 (3%)
Number of implants in lower canine sites	0 (0%)	0 (0%)
Number of implants in upper incisor sites	0 (0%)	1 (3%)
Number of implants in lower incisor sites	0 (0%)	2 (6%)
Number of implants placed with at least 35 Ncm torque	44 (90%)	0 (0%)
Number of patients receiving 1 implant	0 (0%)	9 (41%)
Number of patients receiving 2 implants	20 (87%)	13 (59%)
Number of patients receiving 3 implants	3 (13%)	0 (0%)
Number of screw-retained zirconia definitive prostheses	0 (0%)	5 (23%)
Number of screw-retained metal/composite definitive prostheses	0 (0%)	9 (41%)
Number of cemented metal-ceramic definitive prostheses	0 (0%)	4 (18%)
Number of cemented zirconia definitive prostheses	0 (0%)	2 (9%)
Number of cemented metal-composite definitive prostheses	23 (100%)	0 (0%)
Number of patients treated with soft tissue grafts	0	2 (9.1%)*

** Soft tissue grafting was only allowed to improve the aesthetics at small-diameter implants placed in aesthetic areas, but no procedure was actually implemented with the exception of 2 protocol deviations, justified by lack of keratinised mucosa. On 3-mm implants only cemented prostheses could be manufactured since the abutment is of press-fit type.*

— Peri-implant marginal bone levels: at implant placement, there were no differences in bone levels between 3 and 4 mm-diameter implants **(TABLE 3)**. There were, however, significant differences in bone levels between the two groups at 4 months post-loading (P [t-test] = 0.0319; **TABLE 3**). Both groups lost a statistically significant amount of bone: at 4

TABLE 2 DESCRIPTION OF COMPLICATIONS AND THEIR OUTCOMES UP TO 4 MONTHS

Patient number	Time	Complications	Treatment and outcome
Patients allocated to 3 mm-diameter implants			
2 Mand (PF)	4w.pi	Cover screw loosening and inflammation of the peri-implant tissues	Chlorhexidine flushing and gel application, and retightening of the cover screw. Chlorhexidine gel twice/day for 14 days. Problem solved
1 Mand (PF)	2m.pl	Prosthesis de-cementation	Recemented
19 Mand (RP)	3m.pl	Prosthesis de-cementation	Recemented
Patients allocated horizontal augmentation and 4 mm-diameter Implants			
5 Mand (PF)	0d.pg	Temporary paraesthesia	Resolved after 2 weeks
15 Mand (RP)	0d.pg 4m.pl	Temporary paraesthesia Loosening of the prosthesis screw at 36	Resolved after 2 weeks Retightened
8 Mand (PF)	0d.pg	Temporary paraesthesia	Resolved after 3 weeks
1 Max (PF)	3d.pg	Large ecchymosis from 13 **(Fig. 4)**	Totally resorbed after 14 days
17 Max (RP)	6d.pg	Central and occlusal wound dehiscence	Flushing with chlorhexidine and applications of chlorhexidine gel twice a day for 21 days, and thereafter water and salt mouthwash twice/day until implant placement
18 Max (RP)	7d.pg	Central and occlusal wound dehiscence	Flushing with chlorhexidine and application of chlorhexidine gel twice a day for 21 days, and thereafter water and salt mouthwash twice/day until implant placement
5 Max (PF)	11d.pg	Central and occlusal wound dehiscence	Flushing with chlorhexidine and application of chlorhexidine gel twice a day for 21 days, and thereafter water and salt mouthwash twice/day until implant placement
8 Max (PF)	30d.pg	Small central and occlusal wound dehiscence	Flushing with chlorhexidine and application of chlorhexidine gel twice a day for 21 days, and thereafter water and salt mouthwash twice/day until implant placement
4 Mand (PF)	4m.pl	Prosthesis loosening with chipping on 36	Retightened at 20 Ncm and chipping fixed chairside using composite

Max = maxilla; Mand = mandible; d.pg = days post-grafting; w.pi = weeks post-implantation; m.pl = months post-loading; (PF) = Dr. Pietro Felice; (RP) = Dr. Roberto Pistilli.

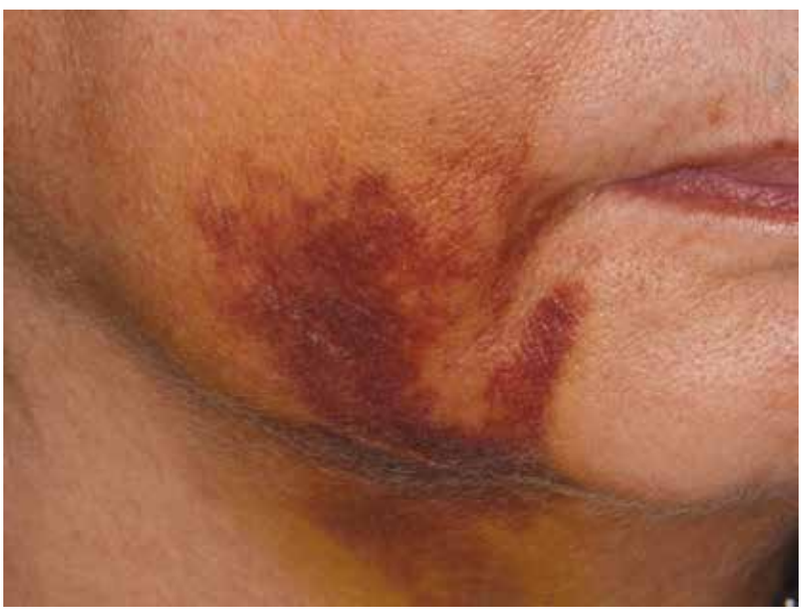

Fig. 4: *Picture taken 8 days post-operatively of a large ecchymosis that occurred in one of the patients treated with horizontal augmentation at the upper canine. It totally resorbed spontaneously 14 days after augmentation.*

months post-loading, 3 mm-diameter implants were associated with 0.09 mm bone loss, and 4 mm-diameter implants with 0.26 mm. The difference was statistically significant (mean difference 0.17 mm, 95% CI 0.02 to 0.31, P = 0.0235; **TABLE 3**).

- Patient satisfaction: almost all patients were fully satisfied with both function and aesthetics, with two exceptions: one patient from the 3-mm group was only partially satisfied with both aesthetics and function, and one patient from the augmentation group was only partially satisfied with the aesthetics. That being said, all patients declared that they would undergo the same procedure again.

No significant differences in outcomes were found between the two operators **(TABLE 4)**.

DISCUSSION

This trial was designed to evaluate whether or not 3-mm narrow-diameter implants could be a treatment option for the rehabilitation of 4 to 5-mm thin ridges with implant-supported partial fixed prostheses. The control procedure was horizontal augmentation using a granular bone substitute covered by a 1 mm-thin bone lamina of porcine origin. Both tested interventions provided satisfactory outcomes, but 3 mm-diameter implants were associated with fewer complications and failures, and could be loaded immediately. In contrast, control-group patients had to wait for at least 10 months, and bone augmentation surgeries were more invasive and caused more discomfort.

TABLE 3 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS AND CHANGES BY GROUP AND TIME PERIOD

	Implant placement/loading	4 months post-loading	Baseline – 4 months post-loading
	N Mean (SD) [95% CI]	**N Mean (SD) [95% CI]**	**N Mean (SE) [95% CI]**
3-mm implants	23 0.02 (0.03) [0.01, 0.03]	23 0.11 (0.10) [0.07, 0.15]	23 0.09 (0.02) [0.05, 0.13]
4-mm implants	22 0.02 (0.03) [0.01, 0.03]	20 0.27 (0.29) [0.13, 0.40]	20 0.26 (0.07) [0.12, 0.39]
Difference	0 [-0.02, 0.02]	0.16 [0.01, 0.30]	0.17 [0.02, 0.31]
P-value	0.8304	0.0319*	0.0235*

**Statistically significant difference. All changes from baseline were statistically different (P [paired t-test] < 0.001).*

TABLE 4 COMPARISON OF THE OUTCOMES AT THE TWO STUDY CENTRES UP TO 4 MONTHS AFTER LOADING

	Dr. Felice 28 patients	Dr. Pistilli 17 patients	Difference	95% CI	P-value
Patients with implant failures (# of implants)	2 (2)	0 (0)	0.07	-0.10, 0.19	0.5192
Patients with complications (# of complications)	8 (8)	4 (5)	0.05	-0.22, 0.29	0.7108
	N Mean (SE) [95% CI]	**N Mean (SE) [95% CI]**	**Difference**	**95% CI**	**P-value**
Peri-implant bone loss	26 0.16 (0.04) [0.07, 0.24]	17 0.19 (0.06) [0.05, 0.32]	0.03	-0.12, 0.18	0.6792

Although these results come from a limited number of patients, who were followed for only 4 months after loading, some important observations can be made. First and foremost, it was interesting to note that sometimes horizontal bone augmentation procedures, after a healing period of 6 months, were associated with occlusal dehiscence of the soft tissues, and resulted in bone of poor consistency. This seems to suggest that such procedures should be improved if possible.

Furthermore, regarding peri-implant marginal bone level changes, using implant placement as baseline, four months after loading 3 mm-diameter implants lost on average 0.09 mm bone, and 4 mm-diameter implants about 0.26 mm. The 0.17 mm difference between groups was statistically significant, thought may not be of clinical significance. Such a minor difference may not be unexpected since recently augmented and not fully mineralised bone might be, at least initially, more prone to bone loss.

It is difficult to compare the results of the present trial with those from similar trials, as these could not be found in the published literature. That being said, our results do show interesting similarities to those of other RCTs investigating vertical atrophy cases, comparing 4- to 6.6-mm short implants *versus* augmentation procedures to place 10 mm or longer implants[7-12]. Such results, obtained in vertically atrophic mandibles, were also summarised in a recent systematic review[13]; together they suggest that augmentation procedures to create new supporting bone are more technically demanding than placing small-diameter or short implants, and are generally associated with higher post-operative morbidity, complications, longer treatment periods and an increased number of surgeries. Therefore, the less invasive technique could be the preferable choice. Nevertheless, more RCTs with larger sample sizes and longer follow-ups are needed; in it would also be interesting to test other horizontal bone augmentation techniques.

Indeed, there are several limitations to the present investigation, including the small number of patients included in the trial, especially those treated in the aesthetic areas. Other features that may affect results are the use of different prosthesis design in the two groups, the lack of the aesthetic evaluation, and the short follow-up duration.

Regarding the small number of patients included, there were two issues: 1) the trial was originally supposed to include 112 patients at four different centres, but two centres did not recruit a single patient and one centre did not manage to treat their full allocated quota; 2) thirteen potentially eligible patients who were edentulous in "aesthetic" areas refused to participate in the trial, opting instead for the augmentation procedure. Probably the most likely reason to explain this attitude is that all those patients were referred to the treatment centres for bone augmentation, and had therefore already been convinced by their referring dentists that bone augmentation was the best option for them, even though this might not, in fact, have been the case. In addition, the original protocol allowed for soft tissue grafting at implant placement for those patients whose aesthetics could have been compromised by using 3 mm-diameter implants without horizontal augmentation; however, no soft tissue augmentation was, in fact, implemented. That being said, in order to better understand how things work in reality, it is important to be open-minded, and to bear in mind that many of the procedures commonly implemented nowadays may not be the best options for a patient's individual treatment.

There was a systematic difference between the two groups in prosthesis design; the immediately loaded small-diameter implant group had to be rehabilitated with cemented prostheses because the abutments that could be used were of press-fit type only. As the small-diameter implants and the related prosthetic components are structurally weaker

than normal-diameter implants, we elected to minimise the risk of fractures by making all prostheses out of cemented metal composite. Although the same type of prostheses should have been used in the augmentation group, clinicians elected to use a variety of prosthesis types, the majority being screw-retained. This is an unfortunate protocol deviation that could have been avoided, but it is often difficult to make clinicians follow strict research protocols specifically designed to minimise possible confounding factors. It is also very difficult to speculate to what extent these differences in prosthesis type may have impacted the results.

The lack of aesthetic evaluation 4 months after loading (i.e., at delivery of the definitive prostheses in the control group) was due to the fact that both assessors neglected to take the clinical photographs, except for of the first five patients treated. It is our intention, however, to take pictures of all patients at the 1-year post-loading follow-up, to be reported in due course. Indeed, we consider aesthetics to be of great interest in a proper comparison of the two groups, especially because it has the potential to shift the findings in favour of the augmentation procedure. It is interesting to observe, however, that the aesthetic assessment performed by the patients themselves did not reveal any trend in favour of either procedure, bearing in mind, however, that the great majority of patients were treated in "non-aesthetic" areas. In terms of future research, it would be interesting to run a similar trial focussing on the anterior portion of the mouth, which is actually the area that small-diameter implants were actually designed for to be used.

The present 4-month post-loading follow-up is, of course, short, but it was planned to follow these cohorts of patients up to 5 years after loading, so these findings should be considered as preliminary.

Both operators were experienced with the bone augmentation procedures evaluated in this trial and this might limit extrapolations of the present results; however, all interventions were tested in real clinical conditions and the inclusion criteria were sufficiently broad, therefore the results of the present trial can be generalised with confidence to a wider population with similar characteristics.

In terms of future research it would be interesting to run another similar trial focussing on the anterior portion of the mouth, which actually is the area for which small-diameter implants were actually designed to be used for.

CONCLUSIONS

Bearing in mind the limitations at this stage of the trial, in particular the lack of aesthetic evaluation, it is apparent that better results were achieved at 4 months after loading in patients treated with 3 mm-wide implants than those horizontally augmented to receive 4 mm-wide implants. As the former treatment is less invasive, faster, cheaper, and associated with less morbidity, it may be the preferable option, although 5- to 10-year post-loading data will be necessary before reliable conclusions on this issue can be drawn.

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KEY WORDS
atrophic maxilla, sinus lift, patient morbidity, patient preference

Randomised controlled trial

CRESTAL *VERSUS* LATERAL SINUS LIFT: ONE-YEAR RESULTS FROM A WITHIN-PATIENT RANDOMISED CONTROLLED TRIAL

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PURPOSE. To compare the effectiveness of and patient preference for crestal *versus* lateral sinus lift.

MATERIALS AND METHODS. Fifteen partially edentulous patients missing bilateral maxillary molars and/or premolars and having 2 to 6 mm of residual crestal height below the maxillary sinuses were randomised to receive one to three implants placed in sinuses crestally or laterally lifted with bone substitutes according to a split-mouth design. Implants were submerged and loaded after 6 months with definitive screw-retained metal-ceramic prostheses, and patients were followed-up to 1 year after loading.

RESULTS. Twenty crestal implants were placed *versus* 23 lateral ones. One patient dropped out and one lateral implant failed (n = 14; difference = 0.07, 95% CI from -0.28 to 0.13; P = 0.99). No prosthesis failed. Three patients were affected by three complications at crestal *versus* three patients by four complications at lateral sites. The difference was not statistically significant (n = 14; Diff = 0.07; 95% CI -0.24 to 0.38; P-value = 0.99). Statistically significantly less time was required to place crestal implants (28.2 *versus* 62.2 minutes on average; Diff = 33.4; SD = 12.1; 95% CI -40.4 to 26.4; P = 0.001). Eight patients preferred the crestal procedure and six had no preference. Crestal implants lost 0.99 mm (SD = 0.55) of peri-implant bone height *versus* 1.02 mm (SD = 0.57) for lateral ones, the difference being not statistically significant (0.03 mm; 95% CI of difference -0.52 to 0.59; P = 0.89)

CONCLUSIONS. Both techniques produced successful outcomes, but the crestal technique required less surgical time and was preferred by patients.

CONFLICTS OF INTEREST STATEMENT. This trial was partially supported by Maxillent (Herzliya, Israel), the manufacturer of the implants employed in this investigation; however, data belonged to the authors and the manufacturer by no means interfered with the conduct of the trial or the publication of the results.

INTRODUCTION

Reduced bone volumes below the maxillary sinuses limit the possibility of placing dental implants for supporting fixed prostheses. However, the bone inside the maxillary sinus can be augmented using sinus lift procedures to solve this problem. The first of these sinus lift procedures was described in 1980[1]; a lateral window is opened into the maxillary sinus, the sinus epithelium is carefully lifted up, and autogenous bone (or bone substitute) is placed into the sinus and allowed to heal for about 6 months or more before placing the implants. The lateral window sinus lift technique is one of the most commonly performed augmentation procedures and is considered one of the most reliable, particularly when autogenous bone is used[2,3].

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While patients with extremely atrophic subantral bone could be good candidates for major sinus lift procedures[4], there is some controversy on how to treat patients with "intermediate" amounts of bone below the maxillary sinuses. A less invasive technique for sinus augmentation was described by Tatum[5] in 1986 and modified by Summers[6] in 1994. The main difference with the lateral window technique is that the sinus membrane is lifted through the crestal bone using osteotomes of increasing diameters, and implants are inserted directly into the prepared sites[7]. The crestal approach technique has since been modified by Cosci[8] who introduced a series of atraumatic lifting drills of varying lengths to reduce the risk of perforation of the sinus lining during drilling of the implant site**.** These are only two of the numerous techniques currently used to augment the sinus through a crestal approach[9]. Another of these crestal sinus lift techniques consists of the elevation of the sinus membrane, via hydraulic pressure, using the implant itself, which, in addition, enables the insertion of bone graft material via the implant body (iRaise, Maxillent, Herzliya, Israel)[10].

While the crestal approach is less invasive, there are some potential disadvantages associated with this technique, such as the limited amount of bone that can be gained vertically, and the minimal amount of crestal bone height (about 3 mm) that is recommended to stabilise the implant at placement[8], even though absolute figures are still questionable. Hence, clinical research is now focussing on evaluating simpler and less invasive sinus lift procedures.

It is unclear whether any of the various crestal sinus lift procedures currently used is advantageous or superior to the others[11]. It would be interesting, therefore, to investigate whether a potentially less invasive technique for crestally lifting maxillary sinuses with residual bone heights between 2 to 5 mm could provide as good results or even better than the lateral window technique. The aim of this randomised controlled trial (RCT) of split-mouth design was therefore to compare the patient preference for and effectiveness of two different techniques for lifting the maxillary sinus: the crestal approach *versus* the lateral window approach. The present article is reported according to the CONSORT statement (http://www.consort-statement.org/) and its extension checklist for reporting within-person randomised trials (http://www.consort-statement.org/extensions/overview/withinperson) to improve the quality of reports of within-person randomised controlled trials.

MATERIALS AND METHODS

Trial design

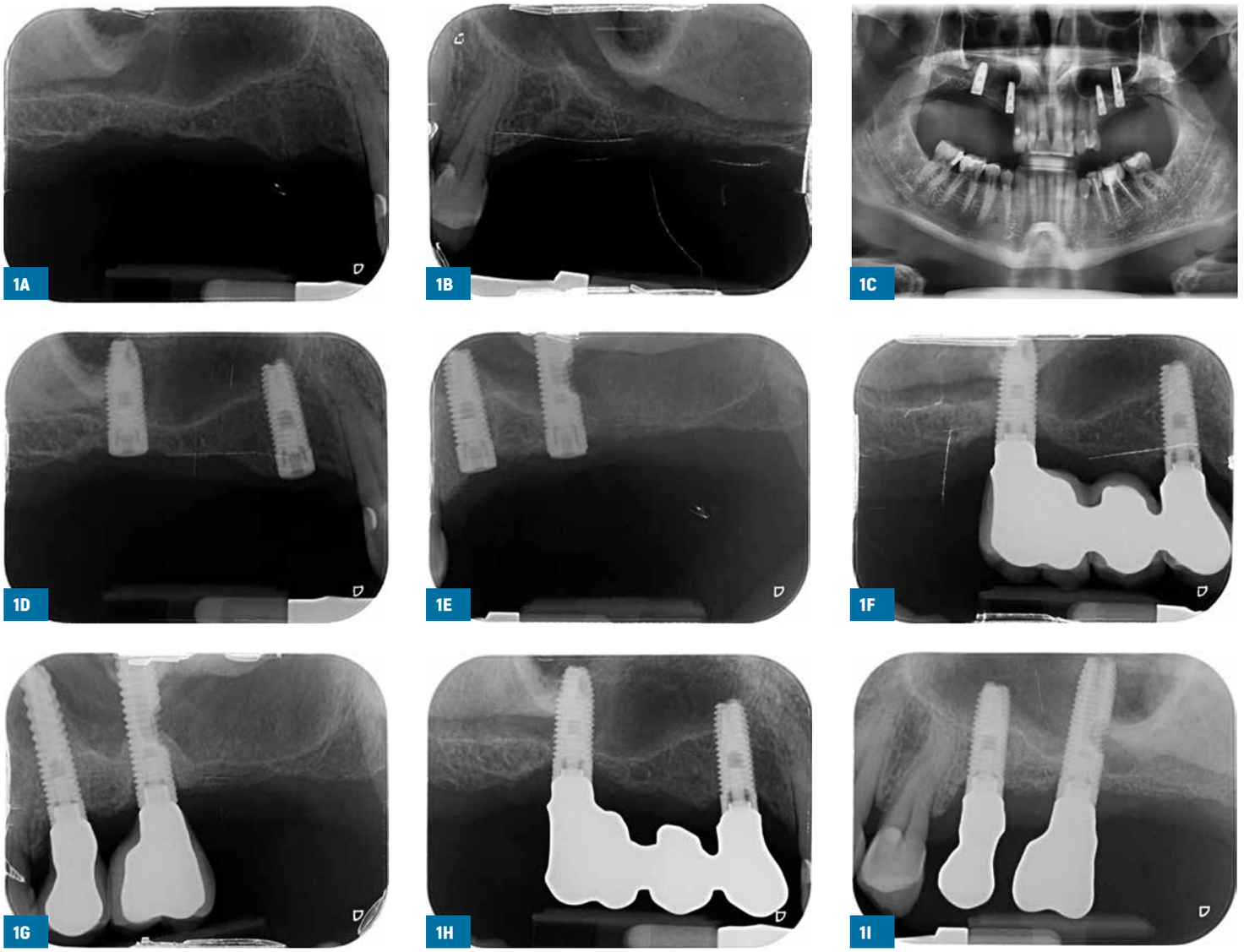
This was a single centre RCT of within-person design evaluating two different interventions with blind assessment. Each patient had both sides of the posterior maxilla randomised to receive one partial fixed prosthesis supported by one to three implants placed either with a crestal or with lateral window sinus lift procedure **(FIGS. 1A-I)**.

Eligibility criteria for participants

Any partially edentulous patient having bilateral edentulism in the posterior maxillae (premolars and/or molars) with a similar degree of bone resorption requiring one to three implants, being 18 years or older, and able to understand and sign informed consent was considered eligible. Only healed implant sites were considered (at least 3 months after tooth extraction). The vertical bone height at the implant sites to be included had to be between 2 to 6 mm, alongside bone thickness of at least 6 mm, as measured on cone-bean computed tomography (CBCT) scans.

Patients were not included in the study if any of the following exclusion criteria was present:

- General contraindications to implant surgery;
- Any irradiation of the head and neck area;



Figs. 1A-I: *Preoperative periapical radiographs of one patient treated in the study: A) the right quadrant was randomly allocated to the lateral sinus lift and, consequently, B) the left quadrant to the crestal sinus lift procedure; C) postoperative panoramic radiograph showing two study implants (the distal ones) and two additional implants. This patient represents a protocol deviation since the study implant at the lateral window treated side should not have been connected to the additional implant under the same prosthesis; D) and E) baseline periapical radiographs; F and G) periapical radiographs at initial loading with the definitive prostheses; H) and I) periapical radiographs at 1 year after loading.*

- Immunosuppression or immunocompromised;
- Past or ongoing treatment with intravenous aminobisphosphonates;
- Poor oral hygiene and motivation;
- Untreated periodontal disease;
- Uncontrolled diabetes;
- Pregnancy or breast-feeding;
- Substance misuse;
- Psychiatric problems;
- Unrealistic expectations;

- Lack of opposing occluding dentition, or prosthesis in the area intended for implant placement;
- Acute or chronic infection/inflammation in the area intended for sinus augmentation/implant placement;
- Referrals for implant placement alone (unavailability for rehabilitation and follow-up at the study treatment centre);
- Inability to attend a 5-year post-loading follow-up.

Smokers were included, and patients were categorised into three groups according to their declarations: 1) non-smokers; 2) moderate smokers, if smoking up to 10 cigarettes/day; 3) heavy smokers, if smoking more than 10 cigarettes/day.
Patients were recruited and treated in one private practice in Tirana, Albania by two operators: Marco Tallarico (MT), who performed all surgical interventions, and Erta Xhanari (EX), who performed all prosthetic and maintenance procedures.
The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to. The study protocol was approved by the Ethics Committee of Our Lady of Good Counsel University in Tirana on 26th July 2016 (Protocol n° 1/2016). All patients received thorough explanation and signed an informed written consent form prior to their enrolment in the trial. After informed consent was signed, the operator selected one maxilla side of their choice as side number 1.

Surgical procedures

Intranasal spray antibiotic (thiamphenicol glycinate acetylcysteinate, TGA, 810 mg/4 mL) and cortisone (betamethasone 1 mg) was administered twice a day starting the day before surgery. Patients received further prophylactic antibiotics: 2 g of amoxicillin (875 mg) + clavulanic acid (125 mg), or clyndamicin 600 mg if allergic to penicillin, one hour before the intervention. Patients rinsed for one minute with chlorhexidine mouthwash 0.2% prior to any clinical procedures, and were treated under local anaesthesia using articaine with 1:100,000 adrenaline. Both sinuses were to be treated during the same surgical session.

Opening of the sealed envelopes and group allocation

The sealed envelope containing the group allocation code corresponding to the recruitment number of the patient was opened, and the surgeon treated site number one with the technique (crestal or lateral sinus lift) indicated. After the procedure was completed, the contralateral side was treated with the other technique, during the same session.
A crestal incision coupled to one or two buccal releasing incisions was made to expose the alveolar ridge, and a full-thickness flap was raised. Implant position and inclination were guided by surgical templates.

Crestal sinus lift

Only one iRaise Sinus Lift implant (Maxillent, Herzliya, Israel) was used in each augmented side. iRaise implants have a tapered body with a specific internal l-shaped channel allowing the hydraulic lifting of the sinus membrane and the delivery of bone substitute gel. The channel has a diameter of 1.5 mm, and is isolated from the prosthetic connection and the oral cavity. These implants, made of titanium-6 aluminum-4 vanadium alloy, have a surface treated via grit-blasting using an apatitic calcium phosphate media, followed by acid etching, and have an internal hexagonal connection. Additional conventional iSure implants (Maxillent) were also placed in the same quadrant, and those placed in 2 to 6 mm of subantral bone height were included in the study.

Implant sites were marked with the marking drill at 800 rpm. To begin the osteotomy, an Initial drill was used at 800 rpm up to 3 mm deep, until it stopped or reached the cortical bone. When necessary, iRaise Drill Stoppers were used to limit the drilling depth. The flat drill was then used until the sinus floor cortex was reached. A flat depth guide was used to check the osteotomy depth and angulation. Finally, the cortex drill was used to abrade the remaining sinus cortex at 2000 rpm. The integrity of the sinus lining was assessed visually, using a blunt instrument and the Valsalva manoeuvre. Any laceration or perforation of the Schneiderian membrane was to be recorded, and the intervention aborted. The length of the iRaise implants (14.5 and 16 mm, the latter used only in the presence of 5 to 6 mm subantral bone height) had previously been selected based on the residual bone height at the planned implant sites from the bone crest to the floor of the sinus; residual bone heights were measured on the preoperative CBCT scans along the planned implant axis.

iRaise implants were inserted into the osteotomy site up to their entire working lengths, leaving the lateral tubing port outside the bone. The single-use tube connector was screwed to the implant tubing port **(FIG. 2)**. With the exception of the silicone ring, the connector did not touch the implant. Two to 3 cm^3 of saline solution was gently injected into the sinus through the internal L-shaped channel, and then aspirated back into the syringe; next, a syringe filled with a flowable bone graft material (Micro-Macroporous Biphasic Calcium phosphate, MBCP Gel, Biomatlante, Vigneux-de-Bretagne, France) was connected to the same port. Two syringefuls, each of 1 ml (2 cm^3 total volume), of bone graft material with a granulometry ranging from 80–200 μm were slowly injected through the implant channel into the sinus, after mixing with 0.2 cc of 0.9% sterile saline solution; this graft material is a 100% synthetic injectable bone substitute composed of 60% biphasic calcium phosphate and 40% of hydroxyapatite, suspended in a soluble polymer. After completing the grafting procedure, the hydraulic system was disconnected from the implant, and the full length of the implant was inserted until the coronal portion was flush with the surrounding crestal bone. After having placed the iRaise implants, additional iSure implants (Maxillent) were placed; those inserted in subantral bone heights of greater 6 mm were not considered in the present investigation.

Fig. 2: *Example on how i-Raise implants were used at crestally lifted sites, The tube connector was screwed to the implant tubing port to allow the passage into the sinus, through the internal L-shaped channel of saline solution first and then of the flowable bone graft.*

Lateral window sinus lift

A window was delineated on the lateral wall of the sinus with a bur, under abundant saline irrigation. The bone was gently removed, layer by layer, using a piezo-surgical device (Piezotome 2 Acteon, Novaxa SPA, Milan, Italy), until a bluish line, indicating the sinus membrane, appeared around the entire outline of the window **(FIG. 3)**. The bone in the window was gently tapped with a blunt instrument until it fractured completely, and was then internally displaced after having carefully detached the maxillary membrane from the sinus bone using proper curettes, starting from the borders of the window and then proceeding towards the floor of the sinus. The sinus membrane was lifted, allowing the placement of implants of length at least 10 mm.

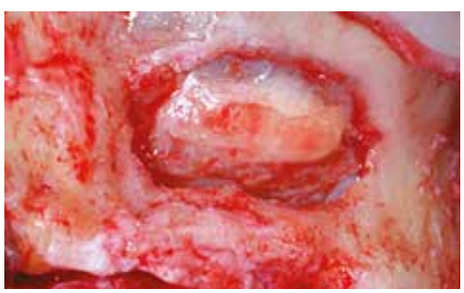


Fig. 3: *Preparation of the lateral sinus window.*

Once the implant sites had been prepared, the sinus lining was examined for any perforations, as discussed above. In the presence of laceration of the Schneiderian membrane, the established protocol required placement of a resorbable collagen barrier (Bio-Gide, Geistlich Pharmaceutical, Wolhusen, Switzerland) in order to contain the graft. If this was not possible, the operation was to be aborted and repeated after a healing period of at least 2 months. The space between the base of the sinus bone and the sinus membrane was filled with granules of anorganic bovine bone (Bio-Oss, small granules, 0.25 to 1 mm, Geistlich Pharmaceutical). One to three 10 to 13 mm-long iSure (Maxillent) implants were inserted, until the coronal portion was flush with the surrounding crestal bone; these implants are similar to the iRaise

implants but do not have the specific internal L-shaped channel. After having completely seated the iSure study implants, additional implants were placed in sites with subantral bone height greater than 6 mm, but these were not be considered in the present investigation. The remaining empty spaces in the sinus cavity were gently packed with Bio-Oss, and resorbable collagen membranes (BioGide) were used to seal the lateral windows.

Cover screws were placed, and all implants were submerged. Flap closure was achieved using Vicryl 4.0 (Ethicon, Padua, Italy). Periapical radiographs and clinical photographs of the study implants were taken. If the peri-implant marginal bone levels were distorted or not clearly visible, a second radiograph was to be taken.

Patients were instructed to continue the prophylactic antibiotic therapy, 875 mg amoxicillin + 125 mg clavulanic acid or 300 mg clindamycin if allergic to penicillin, twice a day for 6 days. Ibuprofen 400 mg analgesic tablets (or 1 g paracetamol if allergic to ibuprofen) were prescribed, to be taken 2 to 4 times a day during meals as long as required. Patients were also prescribed intranasal spray (thiamphenicol glycinate acetylcysteinate 810 mg/4 mL) and cortisone (betamethasone 1 mg) for 10 days after the sinus lift procedure, and instructed to avoid blowing the nose and using drinking straws, and to try to keep the mouth open when sneezing in order to decrease intra-sinus pressure. Patients were also instructed to use 0.2% chlorhexidine mouthwash for one minute twice a day for 2 weeks, to avoid brushing or trauma at surgical sites, and not to wear any removable dentures that could press on the areas operated on for 1 month.

Patients were seen after 1 week for suture removal, and were asked about their preference regarding the two procedures. One month after implant placement, patients were checked again, and were again asked which of the two procedures they preferred.

After 6 months of submerged healing, local anaesthesia was given and implants were exposed via a crestal incision 2 mm palatal to the centre of the implants, and manually tested for stability. Healing abutments and, if needed, sutures were placed. Patients were instructed to rinse with chlorhexidine mouthwash 0.2% for 1 minute twice a day for 2 weeks, and to take 400 mg ibuprofen, or 1 g paracetamol if allergic to ibuprofen, 2 to 4 times a day during meals if they experienced pain. After 2 weeks, occlusion was registered, and impressions with the pick-up impression copings at implant level were taken using a polyether material (Impregum 3M/ESPE, Neuss, Germany) and customised resin impression trays. Models were made with grade 4 precision plaster and mounted in a standard articulator. Within 1 week, definitive screw-retained metal-ceramic crowns or partial fixed prostheses rigidly joining the two or three study implants were delivered. Additional implants in more than 6 mm of bone height were not to be joined under the same fixed prosthesis together with the study implants, and were not evaluated in the present study. The occlusal ceramic surface was in slight contact with the opposing dentition. Periapical radiographs and clinical pictures of the study implants were taken, and oral hygiene instructions delivered as required. One week after, the prostheses were checked, and patients were given additional oral hygiene instructions. Patients were enrolled in an oral hygiene maintenance programme with recall visits every 4 months.

Outcome measures

This study tested the null hypothesis that there would be no differences between the two procedures against the alternative hypothesis of a difference. Outcome measures are listed below.

- Prosthesis failure: planned prosthesis which could not be placed due to implant failure(s), loss of the prosthesis secondary to implant failure(s), or a prosthesis that had to be remade for any reason.

- Implant failure: implant mobility, removal of stable implants dictated by progressive marginal bone loss or infection, implant fracture, or any other mechanical complication rendering the implant unusable. The stability of each individual implant was measured with the prosthesis removed at the abutment junction at delivery of the permanent prostheses and at 1 year after loading, by tightening the implant abutment screws with a torque of 20 Ncm or by assessing the stability of individual crowns using the handles of two metallic instruments.
- Any biological or prosthetic complications occurring during the entire follow-up period. Complications were assessed and treated by EX, who was not masked to group allocation.
- Patient preference, as assessed 1 week and 1 month after surgery, and 1 year after loading, by a blinded independent assessor asking patients which treatment they preferred; possible answers were: 1) the side treated with the crestal technique, 2) the side treated with the lateral technique, 3) none, both treatments were equally good, 4) none, both treatments were equally bad.
- Time necessary to complete the augmentation procedures (expressed in minutes) starting from the surgical incision to application of the last suture, including the additional implants.
- Peri-implant marginal bone level changes, as assessed on digital periapical radiographs taken using the paralleling technique at implant placement **(FIGS. 1D-E)**, prosthesis delivery **(FIGS. 1F-G)** and 1 year after loading **(FIGS 1H-I)** using a digital appliance (CS 2100, Carestream Dental, Rochester, NY, US). In the event of a radiograph not being properly readable, the radiograph was to be taken again. Radiographs were stored in TIFF format with 600-dpi resolution in a personal computer. Peri-implant marginal bone levels were measured using DFW 2.8 software for Windows (Soredex, Tuusula, Finland). The software was calibrated for each single image using the known implant diameter. The distance between marginal bone level and implant/abutment junction was measured to the nearest 0.01 mm at both mesial and distal sides and averaged. Bone level changes at single implants were averaged at both sinus and group level. Reference points for the linear measurements were: the coronal margin of the implant collar, and the most coronal point of bone-to-implant contact.

Two dentists (Edlira Dedaj and Onani Xhanari) not involved in the treatment of the patients made all clinical and radiographic measurements, respectively, without knowing group allocation; both outcome assessors were therefore masked.

Sample size calculation and randomisation

Sample size was calculated to detect a preference of one group over another against the alternative hypothesis that the treatments would be equally preferred. This reduces to a simple one-sample proportion scenario. A single-group chi-square test with a 0.050 two-sided significance level has 80% power to detect the difference between the null hypothesis proportion of 0.500 and the alternative proportion of 0.900 when the sample size is 10. Fifteen partially edentulous subjects with bilateral posterior maxillary atrophy were included in this study to compensate for possible drop-outs. A restricted randomisation list was computer generated. Only one of the investigators (Marco 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 in his password-protected laptop. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. The sealed envelope containing the random code was opened after having anaesthetised the patient at site number 1. Site number 1 was treated as indicated in the envelope. The contralateral site was to be treated

with the other intervention during the same session; treatment allocation was therefore concealed from the investigators in charge of enrolling and treating the patients.

Statistical analyses

All data analysis was carried out according to a pre-established analysis plan. A dentist (Zamira Kalemaj) experienced in dental statistics analysed the data without knowing the group codes. Differences in the proportion of patients with prosthesis failures, implant failures, and complications (dichotomous outcomes) were compared between groups using the McNemar chi-square test (one implant failure or complication counted as a failure for that group within that patient). Differences between continuous outcomes such as operation time or marginal bone levels were evaluated using a paired t-test. A single-sample test of proportions was used to estimate differences in intervention preferences at 1 week, 1 month and 1 year post-intervention. Comparative tests were estimated at a 0.05 level of significance. All statistical analyses were conducted using Stata 13 (Stata Statistical Software, release 13.0, StataCorp).

RESULTS

Sixteen patients were screened for eligibility, but one patient could not be enrolled in the trial because he declared he was unable to attend the follow-ups regularly. Fifteen patients were considered eligible and were consecutively enrolled in the trial. Patients were recruited and subjected to the sinus lift procedures from October 2016 to September 2017. The follow-up of all patients was 1 year after initial prosthetic loading.

All patients were treated according to the allocated interventions. One patient dropped out having moved to Asia just after prosthesis delivery, and failed to attend the 1-year follow-up; however, that patient was contacted by phone and reported that everything was fine. Data from all remaining patients were evaluated in the statistical analyses. The following deviations from the protocol were observed: originally, only patients with sites having subantral bone heights of 2 to 5 mm were to be included, but clinicians decided to include also patients having up to 6 mm bone height (seven crestal and five lateral sides); due to this increase in bone height, 16 mm-long iRaise implants were also used, while it was originally planned to use only 13 and 14.5 mm-long implants. In addition, the actual residual subantral bone height of the study implants to be included in the study should have been measured clinically at implant placement, but this was not performed, and instead bone heights were estimated on preoperative CBCT. At crestal sides, five patients had study implants joined under the same prosthesis with additional implants. For one patient, panoramic radiographs instead of periapical radiographs were taken at loading and 1 year after loading. Measurements were not made on the panoramic radiographs. At lateral window sites, only 13 mm-long implants should have been used; however only one 13 mm-long implant was placed, all the others being 10 and 11.5 mm long. Five patients had study implants joined under the same prosthesis with additional implants (for four patients this protocol deviation was bilateral). Two patients in the lateral window sinus lift group did not receive implants at the same time as sinus floor augmentation due to the lack of primary implant stability; one implant in each patient was unstable and therefore removed. These patients received their implants 6 months later than planned. For one patient in this group, panoramic radiographs instead of periapical radiographs were taken at loading and 1 year after loading.

The mean patient age at the time of the augmentation procedure was 51.5 years (range 36 to 76), and there were five females and 10 males. Three patients declared they smoked up to 10 cigarettes per day, two more than 10, and 10 declared themselves to be non-smokers. The implant sites characteristics are summarised in **TABLE 1**. In total, 29 implants were placed in

crestal sites and 30 at lateral sites (two additional implants were removed at placement, being unstable); however, there were 20 and 23, study implants, meaning those placed in 2 to 6 mm subantral bone height, respectively, and these were the only implants assessed in the present study. The residual mean bone height at the study implant sites, estimated on preoperative CBCT scans, was 4.8 mm (SD = 1.15) at crestal sites and 4.2 mm (SD = 1.14) at lateral sites, with no significant difference between sites (P = 0.13). However, implants placed at crestally lifted sites were longer that those placed in sinuses lifted with the lateral window technique (n = 15, Diff. = 4.32 mm, CI 3.4 to 5.2; P-value = 0.001).

- Implant and prosthesis failures: one implant from the lateral group, in position 26, failed. It was found to be painful and mobile at second-stage surgery and was therefore removed. It was replaced 2 months later. There were no difference in implant failures between the two groups (n = 14; difference = 0.07, 95% CI from -0.28 to 0.13; P = 0.99). No prosthesis failed.
- Complications: three patients were affected by three complications at crestal *versus* three patients by four complications at lateral sites. The difference was not statistically significant (n = 14; Diff. = 0.07; 95% CI -0.24 to 0.38; P-value = 0.99). In addition to the pain reported at the failed implant in the lateral group, two patients experienced the same bilateral complication: pain for 4 weeks after implant placement. They were merely treated with analgesics and were checked every 3 to 4 days until spontaneous resolution of the symptoms. Moreover, one patient in each group showed a minor cusp chipping noticed 1 year after loading; these were treated with chairside polishing. The chip noted at the lateral side affected one of the patients who had previously experienced prolonged bilateral pain after sinus lift. Only one complication occurred at implants not examined in the study. One prosthesis screw loosened 7 months after prosthesis delivery (crestal group). It was replaced with a new screw.

TABLE 1 BASELINE INTERVENTION CHARACTERISTICS OF THE 15 PATIENTS INCLUDED

	Crestal sinus lift	Lateral window
Total number of inserted implants	29	30 + 2 removed since unstable at insertion
Total number of implants inserted in 2 to 6 mm of subantral bone height (study implants)	15 iRaise + 5 iSure	23 iSure
Sites receiving 1 study implant	10	8
Sites receiving 2 study implants	5	6
Sites receiving 3 study implants	0	1
Number of 14.5 mm-long iRaise implants	7	0
Number of 16 mm-long iRaise implants	8	0
Number of 10 mm-long iSure implants	4	19
Number of 11.5 mm-long iSure implants	0	3
Number of 13 mm-long iSure implants	1	1
Number of 3.75 mm-diameter implants	1	2
Number of 4.2 mm-diameter implants	14	20
Number of 5 mm-diameter implants	5	1
Mean residual bone height (mm) at implant sites (SD) on preoperative CBCT scans	4.8 (1.15)	4.2 (1.14)

SD = standard deviation.

- Patient preference: one week after surgery, eight out of 15 patients reported preferring the side treated with the crestal technique and seven had no preference (two patients disliking both interventions). One month after surgery, seven out of 14 patients preferred the side treated with the crestal technique, and seven had no preference (two patients disliking both interventions). One year after loading, eight out of 14 patients preferred the side treated using the crestal technique and six had no preference (one patient disliking both interventions). A single-sample proportion test indicated the crestal technique as the preferred intervention at all time-points (1-week P-value=0.004, 1-month P-value=0.008, 1-year P-value=0.004).
- Time necessary to complete the augmentation procedures: the operating time was on average 28.8 minutes (SD = 5.1) for the crestal technique and 62.2 minutes (SD = 12.3) for the lateral technique, the difference of an average 33.4 minutes (SD = 12.1) being statistically significant in favour of the crestal technique (P = 0.001; 95% CI -40.4 to 26.4).
- Peri-implant marginal bone level changes: at implant placement, baseline peri-implant bone levels were 0.42 mm (SD = 0.61) for crestal and 0.31 mm (SD = 0.41) for lateral window sites **(TABLE 2)**. The difference between baseline values was not significant (t-test P-value = 0.49). Both groups lost significant peri-implant marginal bone up to 1 year in function (0.99 mm; SD=0.55 for crestal and 1.02 mm; SD = 0.57 for lateral) with no statistically significant differences between the groups (difference 0.03 mm; 95% CI of difference -0.52 to 0.59; P = 0.89; **TABLE 3**).

TABLE 2 MEAN PERI-IMPLANT BONE LEVELS BETWEEN GROUPS AND TIME POINTS

	Placement	Loading	1-year
	N Mean (SD)	N Mean (SD)	N Mean (SD)
Crestal lift	15 0.42 (0.61)	13 1.18 (0.64)	13 1.41 (0.59)
Lateral window	15 0.31 (0.41)	13 1.18 (0.49)	13 1.33 (0.56)
Mean difference (SD)	0.11 (0.16)	0 (0.14)	0.08 (0.2)
95% CI of difference	-0.47 to 0.24	-0.32 to 0.31	-0.53 to 0.38
P values	0.498	0.991	0.723

TABLE 3 MEAN PERI-IMPLANT CHANGES BETWEEN GROUPS AND TIME POINTS

	Placement-loading	Placement-1 year
	N Mean (SD)	N Mean (SD)
Crestal lift	13 0.77 (0.53)	13 0.99 (0.55)
Lateral window	13 0.88 (0.59)	13 1.02 (0.57)
Mean difference (SD)	0.11 (0.21)	0.33 (0.26)
95% CI of difference	-0.34 to 0.56	-0.52 to 0.59
P values	0.597	0.894

DISCUSSION

This split-mouth RCT was designed to evaluate which sinus lift technique, crestal or lateral window, would be more effective and preferred by patients. The split-mouth design made it possible for patients to express their preference, since they could experience both procedures. Both techniques were clinically successful, and able to achieve the planned goals, with no major complications occurring in either case. However, the crestal technique required half an hour less to be completed on average, and was preferred by patients. From a clinical point of view, to reduce the surgical component of the intervention by half an hour is surely appreciated by patient, as reflected by the patient preference.

Patient preference remained substantially stable over the entire follow-up period, with slightly more than half of the patients preferring the crestal approach and none preferring the lateral approach. The remaining patients showed no preference for either of the techniques. Clinicians should take into serious consideration patient preference when opting for alternative techniques providing similar clinical outcomes. Indeed, taking all these factors in consideration, we would choose to treat patients requiring a sinus lift with the faster procedure that gives patients the least discomfort, as the final clinical outcome appears to be similar. Interestingly there is one 5-year follow-up RCT[12] that compared a modified Cosci crestal sinus lift procedure with a 1-stage lateral window sinus lift procedure. The results of this trial also suggested that the less invasive crestal sinus procedure and 8 mm-long implants can achieve similar, if not better, results than a more invasive procedure involving the placement of longer implants, even when implants were loaded early, 6 weeks after their placement.

The main limitations of the present trial are some of the deviations from protocol, especially the inclusion of sites based on preoperative CBCT scans instead of intrasurgical measurement, and the inclusion of subantral bone heights up to 6 mm, etc., which could have been treated with less invasive procedures like short implants[13-18]. Another limitation was the small number of patients included. All that being said, both sinus lift techniques, as well as the implants used in the present investigation, had good clinical outcomes with few complications and failures. Both techniques were tested under real clinical conditions, and patient inclusion criteria were rather broad, meaning that the results of the present trial are likely generalisable to patients having similar characteristics. However, the operating surgeon was very experienced in both techniques, and this factor might limit generalisation of the findings.

CONCLUSIONS

Within the limits of this trial, both sinus lift procedures produced successful results over a 1-year follow-up period, but the crestal technique required less surgical time and was preferred by patients.

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KEY WORDS
oral hygiene, tooth brushing, motivational interviewing, counseling, pamphlet, video, motivation

Randomised controlled trial

EFFICACY OF FOUR MOTIVATIONAL TECHNIQUES FOR IMPROVING ORAL HYGIENE. ONE-YEAR FOLLOW-UP OF A RANDOMISED CONTROLLED TRIAL

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PURPOSE. The aim of this randomised controlled trial with blinded examiner was to compare the efficacy of four different methods of enhancing oral hygiene motivation in: 1) modifying patient behaviour, 2) reducing the full-mouth plaque score (FMPS) and full-mouth bleeding score (FMBS), 3) amount of the intervention time required, 4) the degree of patient satisfaction at one-year follow-up.

MATERIALS AND METHODS. In a private practice, 100 subjects aged 18–75 years with at least 20 teeth/implants present and a FMPS ≥40% were consecutively recruited. From baseline up to one-year of follow-up, the subjects randomly underwent one of four different oral hygiene motivational techniques, namely (i) standard instructions on oral hygiene (SIOH); ii) reading a pamphlet (P); iii) watching a video (V); or iv) Brief Motivational interviewing (BMI). The outcome variables considered were reduction in FMPS, reduction in FMBS, frequency of daily tooth brushing, frequency of daily flossing, motivational intervention time, degree of patient satisfaction, patient perception of oral health (by means of a questionnaire), and number of teeth lost for each method. A sole operator carried out all motivational sessions and/or professional oral hygiene procedures at baseline and at 1, 3, 6 and 12 months. Another operator, blinded to the methods used, recorded the variables at baseline, and at 6 and 12 months.

RESULTS. At 12-month follow-up, there were no significant differences between the four tested methods in either FMPS (-16.7 for SIOH, -18.8 for V, -20.1 for P, and -27.7 for BMI; P = 0.0730), FMBS (-3.0 for SIOH, -2.3 for V, -4.2 for P, and -2.9 for BMI; P=0.5776), degree of patient satisfaction (P = 0.2410), improvement in perception of oral health (P = 0.2067), frequency of daily flossing (P = 0.2500), or number of teeth lost (P = 0.5296). Although the total time required for motivation was significantly greater for the BMI than the other techniques (P <0.0001), the frequency of daily tooth brushing significantly increased after BMI as compared to SIOH and V (the difference between BMI and SIOH was 0.6; 95%CI from 0.2 to 1.0, and the difference between BMI and V was 0.5 95%CI from 0.1 to 0.9; P = 0.0011).

CONCLUSIONS. All tested methods improved FMPS and FMBS, and were appreciated by all subjects. The change in patient behaviour was more pronounced in the BMI group, but the intervention time required was greater than in the other techniques; nevertheless it was compatible with a professional oral hygiene session of one-hour duration.

CONFLICTS OF INTEREST STATEMENT. The authors declare that they have completely self-funded the study, and that there are no conflicts of interest.

INTRODUCTION

Periodontal disease can be slowed or stabilised by reducing bacterial biofilm deposition. Professional periodontal therapy is crucial for control of this disease, but the quality of oral hygiene at home and patient compliance with an individualised periodontal care programme is fundamental in the long-term prevention and treatment of periodontal disease[1-8]. However, some studies[9,10] on the effectiveness of oral hygiene motivation have shown that patient adherence to a programme of home and professional periodontal maintenance remains generally poor. Often, periodontal treatment support sessions are cancelled, resulting in reduced periodontal health, decreased motivation and attention to oral hygiene at home, and the possibility of recurrence of periodontal disease[10-12].

The observation that patient compliance tends to decrease over time has led to the hypothesis that the traditional methods of motivation to oral hygiene at home might not be effective in all subjects. This consideration was the stimulus for research to identify and test many new tools and various methods of more patient-centred motivation for behavioural change[13]. For example, new technologies have facilitated the spread of affordable DVDs and videos accessible online on diseases of the oral cavity and oral hygiene techniques. The internet also provides webpages where issues related to oral diseases and their prevention and treatment are discussed. However, there is little evidence in the dentistry and periodontal health literature on the effectiveness of these new tools in increasing the motivation and quality of oral hygiene techniques practiced at home[14].

Patient-centred counseling techniques[15,16] can be used as a replacement for traditional methods of motivation to induce behavioural change. In fact, the results of one study showed that an individually tailored oral health education programme, based on a behavioural-medicine approach, was preferable to a standard education programme as an intervention for improving oral hygiene behaviours in patients with periodontal issues[17]. Advancements in cognitive psychology also enable healthcare providers to motivate patients to be more responsible for managing their own health through behavioural change[18-24]. Changing health behaviours through motivation is the focus of Motivational Interviewing (MI). Motivational interviewing (MI)[21,25] is a "collaborative, person-centred form of guiding to elicit and strengthen motivation for change". This directive method enhances intrinsic motivation by exploring and resolving a person's ambivalence about change[23,24]. MI has been shown to be effective for achieving behaviour change related to obesity, drug rehabilitation, physical fitness, mental health, glycaemic control (in diabetics), smoking cessation, treatment for alcoholism, HIV/AIDS, drug abuse, medication adherence, gambling and eating disorders[21,23,24,26-30].

That being said, there is currently insufficient and controversial information on the use of MI in dentistry and periodontal health support[31-34], and a specific method of using MI needs to be developed for oral health professionals[35,36]. The Brief Motivational Interviewing (BMI) [21,25] can be used in the field of prevention and health education and, more generally, in all those situations where it is desirable or necessary to promote adherence to treatment regimes, reduce risk behaviours and promote healthy habits. Due to the small number of sessions and the specific tools provided, dentistry practitioners too may be able to use the BMI[21,25] without incurring additional costs and without the intervention of a psychologist.

We set out to test the efficacy of this instrument, in comparison to three other methods of patient motivation, on oral hygiene in a randomised controlled trial with blinded examiner and one-year follow-up. Outcome measures were: the full mouth plaque score (FMPS), the full mouth bleeding score (FMBS), patient behaviour (frequency of daily tooth brushing), the intervention time required for each technique, and the degree of patient satisfaction with each method.

MATERIALS AND METHODS

Trial design

This single-centre, parallel randomised controlled trial had 4 arms, with an allocation ratio of 1:1:1:1 to the four motivational technique groups, and a blinded examiner. It was conducted according to the recommendations of the CONSORT Statement for the quality of randomised controlled trials[37].

Eligibility criteria for participants

Study participants were recruited among patients undergoing recall sessions for professional oral hygiene. All had already been provided with instruction on how to maintain oral hygiene at home, but nevertheless presented high dental plaque index (FMPS greater than 40%).
Inclusion criteria were:

- Age between 18 and 75 years;
- At least 20 teeth and/or implants present (pontics were not considered);
- More than 40% of FMPS.

The exclusion criteria were:

- Subjects with disabilities that could compromise their understanding of the motivational technique tested;
- Patients receiving chemotherapy for cancer;
- Women with ongoing pregnancy at baseline;
- Subjects suffering from diseases that could affect the frequency of their attendance.

Setting and location

The subjects were consecutively recruited from patients attending a private dental practice in Campi Bisenzio, Italy, from 5th September to 2nd December 2011. The investigators explained the nature of the trial and its aims and methods to the patients fully, anticipating the benefits, potential risks, and any form of discomfort that participation might entail. The patients read and asked questions inherent to the study prior to signing their informed consent.

Interventions

The four methods of oral hygiene motivation tested were the following.
Standard instruction on oral hygiene (SIOH): chairside instruction on toothbrushing and interproximal cleaning techniques.
Pamphlet (P): home reading of a 20-page printed pamphlet (text and images) with the same content as the abovementioned video.
Video (V): home viewing of a 20-minute video. A DVD containing the educational video was given to the patients. The video illustrated the risks of undisturbed accumulation of plaque in the oral cavity, and the proper techniques for both tooth brushing (roll technique) and the use of dental floss and/or toothpicks.
Brief Motivational Interviewing (BMI): this method was based on both the *key concepts* (i.e., the importance of changing behaviour, the confidence to be able to do so [self-efficacy], and the willingness to change) and the *primary activities* (i.e. open questions, active listening, clarifying and summarizing, and negotiating goals and strategies) of motivational interviewing (MI). The BMI consisted of administering *primary activities* by *appropriate tools* [a) questionnaire on "importance" and "trust"; b) diary of the objectives, strategies to achieve them and goals; and c) home oral hygiene diary][22,25].

At baseline, a single operator, a dental hygienist with over 10 years of experience (MG), assessed whether participants met the inclusion criteria. The same dental hygienist carried out all motivational sessions and professional oral hygiene procedures required at baseline and at the scheduled recalls (one, two, three, six and twelve months). Patients were all given (by MG) a questionnaire to be filled out at baseline, and were randomised to one of the four groups: 1 (SIOH), 2 (P), 3 (V), 4 (BMI), contained within a sealed envelope. At each session, the time required to perform the randomly allocated motivational procedure was recorded with a chronometer. Patients were re-assessed at 1, 3, 6, and 12 months, repeating the motivational technique each time.

During each follow-up session, the instructions delivered to the patient at baseline were discussed; at all scheduled recalls, the dental hygienist (MG) reinforced the previously delivered motivational techniques. For patients allocated to the SIOH group, the dental hygienist reinforced the notions on cleaning techniques; with P and V group patients, the dental hygienist conducted an interview on the content of the two methods; and with the BMI group the dental hygienist reinforced the relevant strategies. Professional cleaning was performed according to individual need at months 6 and 12.

Outcome measures

An assessor blinded to the treatment selected (UP) recorded all outcome measures. The examiner conducted a plaque test for calibration purposes, and was then subjected to an intra-rater agreement test, which resulted in a kappa score of 0.85, considered almost perfect agreement[38].

At the scheduled 6- and 12-month appointments, the examiner (UP), blinded to the motivation technique administered, recorded the following clinical variables.

- Plaque accumulation at six sites per tooth/implant[39] evaluated as Full-Mouth Plaque Score (FMPS). The examiner used a 3.2x magnification system and a staining liquid to detect the presence or absence of plaque at each site assessed.
- Bleeding on probing at six sites per tooth/implant[40] evaluated as Full-Mouth Bleeding Score (FMBS); the examiner used a 3.2x magnification system to detect the presence or absence of bleeding at each site assessed.
- Frequency of daily tooth brushing, as reported in the questionnaire.
- Frequency of daily flossing, as reported in the questionnaire.
- Patient satisfaction score (assessed using a score of 0 to 10) for the given technique, as reported in the questionnaire.
- Patient perception of their own oral health level (assessed on a VAS from 0 to 10), as reported in the questionnaire.
- Number of teeth lost.

Sample size

Considering $\alpha = 0.05$, a power of 80%, a standard deviation of 10 in FMPS[17] and 10 as a clinically significant difference, 17 patients per group were required. This number was increased to 25 per group, making a total of 100 subjects, due to the possibility of drop-outs and in order to make multiple comparisons.

Randomisation and blinding

A computer-generated list of random numbers was used for participant allocation. A blocked randomisation was applied to allocate 25 patients to each of the four treatment groups.

The allocation sequence was concealed from the researcher (MN) enrolling and assessing

participants in sequentially numbered, opaque, sealed and stapled envelopes. Only after the patient was examined at baseline did the operator (MG) open the envelope.
Even though the operator and the patient were aware of the allocated arm, the outcome assessor was kept blinded to the allocation.

Statistical analysis

Descriptive statistics were performed using mean and standard deviation for quantitative data and frequency and percentage for qualitative data. The statistical unit of the analysis was the patient.
Analysis of variance (ANOVA) was performed for the outcome variables: patient satisfaction, number of teeth lost and total motivation time, while analysis of covariance (ANCOVA) was performed for the outcome variables: change in FMPS, change in FMBS, change in daily flossing frequency, change in daily brushing frequency, and change in perceived periodontal health. Value at baseline was the covariate. The interaction term (treatment x covariate) was added to the model only if significant.
In the event of statistical significance (ANOVA or ANCOVA), Tukey's HSD test for multiple comparisons was carried out with a 95% confidence interval of the differences between treatments.
Intention-to-treat analysis was performed, and the statistical software used was JMP v. 13 (SAS Institute, Cary, NC).

RESULTS

One hundred patients were consecutively enrolled in the trial and randomly allocated to the four experimental groups. As a consequence, 25 patients per group underwent the four different motivational approaches: standard instructions on oral hygiene (SIOH), pamphlet (P), video (V), and Brief Motivational Interviewing (BMI). Patients were recruited and treated at a private practice from September to December 2011. The final (12-month) follow-up was performed in December 2012.
Baseline patient characteristics are shown in **TABLE 1**. There were no apparent imbalances between the four groups at baseline, except that more females were allocated to the BMI group.

TABLE 1 CHARACTERISTICS OF THE FOUR GROUPS AT BASELINE

Variable	SIOH group n = 25	P group n = 25	V group n = 25	BMI group n = 25
Age [years]	45.1 (12.7) [18; 64]	44.7 (14.0) [19; 66]	42.3 (12.2) [20; 65]	48.8 (13.7) [24; 73]
Gender [Females]	15 (60%)	10 (40%)	16 (64%)	20 (80%)
Smokers	8 (32%)	8 (32%)	6 (24%)	8 (32%)
FMPS	65.6 (11.2)	66.4 (11.6)	64.8 (11.3)	68.5 (10.0)
FMBS	5.7 (4.6)	7.4 (5.2)	5.1 (3.5)	7.4 (4.2)
Tooth brushing (times per day)	2.1 (0.5)	2.1 (0.6)	2.5 (0.6)	2.0 (0.5)
Flossing (times per day)	0.8 (0.6)	0.7 (0.7)	0.5 (0.5)	0.7 (0.6)
Health perception (VAS)	4.9 (1.3)	5.0 (1.0)	4.8 (1.2)	4.9 (1.6)

Legend *SIOH: Standard instructions on oral hygiene; P: Reading a pamphlet; V: Watching a video; BMI: Brief Motivational Interviewing; FMPS: Full-Mouth Plaque Score; FMBS: Full-Mouth Bleeding Score. VAS: Visual Analogue Scale.*
Standard deviations for quantitative variables and percentages for qualitative variables are in round brackets, while minimums and maximums are in square brackets.

One patient belonging to the SIOH group dropped out at six months and declined to return for the follow-up visits. One patient belonging to the P group dropped out at one month, declining to return for follow-up visits. Seven patients belonging to the V group dropped out (two at 1-month follow-up, four at 3-month follow-up and one at 6 months) and declined to return for follow-up visits). Two patients belonging to the BMI group dropped out at 1 and 6 months, respectively, and declined to return for follow-up visits.

There were no deviations from the protocol.

Results recorded at 6 and 12 months are shown in **TABLES 2** and **3**, respectively. As very similar responses were found at 6 and 12 months, only the latter data will be considered. Of note, at 12-month follow-up the improvement from baseline in terms of FMPS was substantial (16.7 for SIOH, 20.1 for P, 18.8 for V, and 22.7 for BMI), and the within-group changes from baseline were significant (P <0.0001 for all groups). However, no statistically significant differences in FMPS were detected between the four tested methods (P = 0.0730).

In terms of FMBS, the changes were more moderate (3.0 for SIOH, 4.2 for P, 2.3 for V, and 2.9 for BMI), with no significant differences between the four methods (P = 0.5776). The within-group changes from baseline were significant for SIOH, P, and V (P <0.05) and not significant for BMI (P = 0.07).

The change in daily tooth brushing frequency was null for SIOH and V, while the BMI group showed an increase of 0.6. The frequency of daily tooth brushing increased significantly in the BMI group, as compared to SIOH and V (the difference between BMI and SIOH was 0.6; 95%CI from 0.2 to 1.0, and the difference between BMI and V was 0.5 95%CI from 0.1 to 0.9; P = 0.0011).

The improvement in daily flossing frequency was also null or very low in all four groups, and the difference was not statistically significant (P = 0.2500).

The patient satisfaction score (assessed on a scale of 0 to 10) for the given technique was high in all groups, and the differences between them were not significant (P = 0.2410). All groups reported an improvement in oral health perception, but the differences were not significant (P = 0.2067).

Eight teeth had been lost in six patients at 12-month follow-up. In the SIOH group two patients had lost one tooth each (one due to fracture and the other to periodontitis); in the P group two patients had lost two teeth each (two teeth in one patient due to periodontitis and two teeth in one patient to dysodontiasis); in the BMI group, two patients lost one tooth each (one due to fracture and the other to periodontitis). The difference between groups was not significant (P = 0.5296).

As for the total time spent on motivation, BMI took significantly longer than the other techniques (difference between BMI and SIOH was 24.2 minutes [95%CI from 18.2 to 30.2]; difference between BMI and P was 26.3 minutes [95%CI from 20.3 to 32.4]; difference between BMI and V was 30.3 minutes [95%CI from 23.8 to 36.8], P <0.0001).

DISCUSSION

This investigation reveals that the four different methods of motivating oral hygiene examined, consisting, respectively, of standard instructions, pamphlets, educational video, and Brief Motivational Interviewing (BMI), are all effective. All tested methods were appreciated by enrolled subjects, and all improved FMPS and FMBS up to 1 year of follow-up.

No statistically significant differences were observed between the four methods of motivation in terms of FMPS, FMBS, frequency of daily flossing, mean number of teeth lost, degree of patient satisfaction or perception of oral health. However, BMI induced a statistically significantly greater increase in the frequency of daily brushing with respect to standard instructions and video motivation (P = 0.0011). Although the BMI motivation required a significantly greater total

TABLE 2 RESULTS AT 6-MONTH FOLLOW-UP

Variable	SIOH group n = 24	P group n = 24	V group n = 18	BMI group n = 23	P-value
FMPS	53.4 (13.7)	52.6 (15.1)	48.6 (16.7)	45.9 (15.4)	0.2220
Difference in FMPS between baseline and 6 months	12.6 (16.1)	14.7 (16.2)	15.7 (16.4)	22.1 (14.4)	0.2220
FMBS	3.9 (2.7)	4.1 (2.8)	4.2 (3.6)	3.8 (3.6)	0.7276
Difference in FMBS between baseline and 6 months	1.8 (3.9)	3.4 (4.4)	1.1 (5.2)	3.5 (3.7)	0.7276
Tooth brushing (times per day)	2.1 (0.5)	2.2 (0.5)	2.4 (0.7)	2.6 (0.5)	0.0021*
Difference in tooth brushing between baseline and 6 months	0.0 (0.4)	0.2 (0.6)	-0.1 (0.7)	0.6 (0.5)	0.0021*
Flossing (times per day)	0.8 (0.5)	0.8 (0.6)	0.7 (0.4)	1.0 (0.7)	0.3002
Difference in flossing between baseline and 6 months	-0.0 (0.5)	0.2 (0.7)	0.1 (0.4)	0.2 (0.4)	0.3002
Satisfaction score	8.6 (1.3)	8.7 (1.0)	8.5 (0.9)	8.2 (1.1)	0.4020
Health perception (VAS)	5.8 (1.3)	5.8 (1.2)	5.7 (1.3)	6.3 (1.3)	0.4156
Difference in health perception between baseline and 6 months	0.9 (1.0)	0.8 (1.2)	1.0 (1.6)	1.3 (1.7)	0.4156

Legend *SIOH: Standard instructions on oral hygiene; P: Reading a pamphlet; V: Watching a video; BMI: Brief Motivational Interviewing; FMPS: Full-Mouth Plaque Score; FMBS: Full-Mouth Bleeding Score; VAS: Visual Analogue Scale.*
Standard deviations are in round brackets.

** Statistically significant BMI values compared to SIOH and V (P = 0.0021).*

TABLE 3 RESULTS AT 12-MONTH FOLLOW-UP

Variable	SIOH group n = 24	P group n = 24	V group n = 18	BMI group n = 23	P-value
FMPS	49.2 (12.5)	47.2 (12.1)	45.4 (13.3)	40.3 (14.9)	0.0730
Difference between baseline and 12 months in FMPS	16.7 (14.1)	20.1 (13.2)	18.8 (14.9)	27.7 (15.9)	0.0730
FMBS	2.8 (3.0)	3.3 (3.7)	2.9 (3.1)	4.4 (5.0)	0.5776
Difference between baseline and 12 months in FMBS	3.0 (5.2)	4.2 (5.2)	2.3 (3.8)	2.9 (7.3)	0.5776
Tooth brushing (times per day)	2.0 (0.5)	2.3 (0.6)	2.3 (0.7)	2.5 (0.6)	0.0011*
Difference in tooth brushing between baseline and 12 months	-0.1 (0.5)	0.2 (0.6)	-0.2 (0.6)	0.5 (0.5)	0.0011*
Flossing (times per day)	0.7 (0.5)	0.9 (0.6)	0.7 (0.4)	0.9 (0.6)	0.2500
Difference in flossing between baseline and 12 months	-0.0 (0.5)	0.2 (0.7)	0.1 (0.4)	0.2 (0.4)	0.2500
Satisfaction score	8.6 (1.2)	8.8 (1.0)	8.7 (1.0)	8.1 (1.7)	0.2410
Health perception (VAS)	5.6 (0.9)	6.0 (1.3)	5.7 (1.5)	6.4 (1.3)	0.2067
Difference in health perception between baseline and 12 months	0.7 (1.1)	0.9 (1.4)	1.0 (1.9)	1.3 (1.8)	0.2067
Tooth loss	0.1 (0.3)	0.2 (0.6)	0.0 (0.0)	0.1 (0.3)	0.5296
Total time (minutes)	35.2 (6.6)	33.0 (7.8)	29.1 (6.8)	59.3 (9.7)	<0.0001**

Legend *SIOH: Standard instructions of oral hygiene; P: Reading of a pamphlet; V: Overview of a video; BMI: Brief Motivational Interviewing; FMPS: Full-Mouth Plaque Score; FMBS: Full-Mouth Bleeding Score; VAS: Visual Analogue Scale.*
Standard deviations are in round brackets.

** Statistically significant BMI values compared to SIOH and V (P = 0.0011).*

*** Statistically significant BMI values compared to all other methods (P <0.0001).*

time than all other tested methods (P <0.0001), this time was compatible with the operational requirements of a professional oral hygiene session of one hour duration.

Our results reflect the improvements reported by a meta-analysis on the effects of motivational interviewing *versus* education and/or information on *gingivitis* (bleeding on probing: -2.81 [95% CI: -11.54, 5.91]), differences which were, however, neither statistically nor clinically significant[33]. Like our results, significant improvements in oral health behaviours, and in self-efficacy regarding tooth brushing, were reported in favour of psychological interventions[33], even though the clinical relevance of these differences was difficult to estimate, and long-term effects were not investigated[33].

In our study, the improvement from the baseline over the course of a year in terms of FMPS was substantial, but there were no statistically significant differences between the four tested methods. Nevertheless, the within-group changes from baseline were significant for all groups. The Hawthorne effect could have played a role in this improvement; this is a type of reactivity in which individuals modify an aspect of their behaviour in response to their awareness of being observed[41]. In this context, it is possible that the patients improved their oral hygiene because they knew that they were being monitored[42]. Indeed, as a real control group, without any treatment, was not part of our study, it is difficult to ascribe the improvement to the various interventions. That being said, what really matters in an RCT is the difference between the techniques, rather than the difference within each group.

Another RCT evaluated whether inclusion of a single session of motivational interviewing, as an adjunct to periodontal therapy, might be beneficial for preventing relapse in oral hygiene behaviours among patients treated for chronic periodontitis[34]. Marginal bleeding index and plaque index were assessed at 6-month and 3-year follow-ups[34,43], with no differences being observed between the two groups; the conclusion of the authors was therefore that a single BMI session does not add beneficial effects to standard periodontal therapy for efficacious oral hygiene behaviour[34]. We repeated the BMI (and the other motivational techniques) at each session (baseline, 1-, 3-, 6-, and 12-month recall visits), with similar FMBS results. However, as already reported, and in agreement with the conclusions of a systematic review[33], in our study BMI did induce a significantly greater increase in the frequency of daily brushing vs. SIOH (or V). Furthermore, it should be noted that in our study a dental hygienist operator conducted the BMI, which enabled us to repeat the BMI (and the other motivational techniques) at each recall session with reduced costs.

Recently, a clustered randomised controlled trial at two public primary schools was performed[14]. About 220 schoolchildren aged 10-–11 years were included in that study and grouped into two clusters. Children in Leaflet cluster received oral health education through leaflets, while children in E-learning cluster received oral health education through an E-learning programme[14]. The E-learning programme was full of colourful images, videos, interactive quizzes and age-related developmental tasks in the quest to deliver the information in an interactive, entertaining and simple manner. The E-learning programme included the same information as the leaflet, and only the way in which the content was conveyed to the children was different[14]. Interestingly, children in Leaflet cluster had significantly less plaque and statistically significantly better gum health than the E-learning cluster at 6 weeks (P <0.05) and 12 weeks (P <0.05)[14]. In our study on adult subjects, however, differences between standard instructions, reading a pamphlet, and watching a video on oral hygiene were not observed after one year of follow-up. All three methods seemed to be equally effective in improving home oral hygiene in adult subjects. BMI, on the other hand, proved able to induce changes in behaviour and lifestyle, i.e., an increased frequency of daily tooth brushing, even though it was as effective as the other techniques in reducing FMPS and FMBS percentages.

In this study, we also recorded the number of teeth lost by each patient. The difference between groups was not significant. However, the sample size was not calculated with this variable in mind, and so the study could be underpowered in this respect. Nevertheless, this variable is of the utmost importance from a clinical standpoint, and will be tested in subsequent updates of this study; an important limitation of this study is the short duration of follow-up, but we plan to prolong the follow-up until at least 3 years in order to assess the patients' long-term adherence and quality of oral health.
As the interventions were designed for adults with high levels of dental plaque, our results cannot be extrapolated to children or adolescents, or to patients with low level of dental plaque, who are already sufficiently motivated to preserve their oral health.

CONCLUSIONS

All tested methods improved FMPS and FMBS and were appreciated by enrolled subjects. Nonetheless, BMI was able to change patient behaviour, significantly improving the frequency of daily tooth brushing with respect to SIOH and V, without, however, leading to a significantly greater difference in FMPS and FMBS than other oral hygiene methods over the course of a year. The time required for BMI was greater than the other methods, but still compatible with a 1-hour professional oral hygiene session.

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