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DENTAL IMPLANTS WITH INTERNAL *VERSUS* EXTERNAL CONNECTIONS: 10-YEAR POST-LOADING RESULTS OF A PRAGMATIC MULTICENTRE RANDOMISED CONTROLLED TRIAL

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PURPOSE. To compare the effectiveness of identical implants with internal or external connections.

MATERIALS AND METHODS. One hundred and twenty patients with any type of edentulism (single tooth, partial or total edentulism) requiring one implant-supported prosthesis were randomly allocated at four centres to two equal groups to receive either implants with external connection (EC) or implants of the same type but with internal connection (IC) (EZ Plus, MegaGen Implant, Gyeongbuk, South Korea). Due to slight differences in implant design/components, IC implants were platform-switched while ECs were not. Patients were followed up for 10 years after initial loading. Outcome measures were: any prosthesis/implant failures, complications, and marginal bone level changes, as assessed by blinded outcome assessors whenever possible.

RESULTS. Sixty patients received 96 EC implants and 60 patients 107 IC implants. Eight patients from the EC group and nine from the IC group dropped out, but all remaining patients were followed up to 10 years post-loading. Two EC patients experienced implant and prosthesis failures *versus* three IC patients (P = 0.631, diff = 0.02, 95% CI: -0.07 to 0.11). Fifteen complications occurred in 13 EC patients *versus* 13 complications in 11 IC patients (P = 0.720, diff. = -0.03, 95% CI: -0.19 to 0.13). There were no statistically significant differences for prosthesis and implant failures and complications between the different connection types. Ten years after loading, both groups had lost a significant amount of bone (1.01 mm at EC implants and 1.27 mm at IC implants), but there was no statistically significant difference in estimated marginal bone levels between the two groups (diff. = 0.07 mm, 95% CI: -0.41 to 0.54 mm, P (ANCOVA) = 0.782).

CONCLUSIONS. Acknowledging the difference between EC and IC implants in terms of neck design and platform-switching, 10-year post-loading data revealed no statistically significant differences between the two connection types, and clinicians can therefore choose which they prefer.

CONFLICT OF INTEREST STATEMENT. This trial was partially funded by MegaGen Implant, Gyeongbuk, South Korea, the manufacturer of the implants evaluated in this investigation. However, the resulting data belonged to the authors and by no means did the manufacturer interfere with the conduct of the trial or the publication of the results.

INTRODUCTION

Implant-supported prostheses are an effective and reliable treatment for replacing missing dentition. The success of implant-supported prostheses is mainly based on the "integration" of dental implants into newly formed bone[1]. This process is generally known as osseointegration. Literally thousands of new dental implant designs, materials and surface technologies are continuously being developed to further improve the outcome of implant therapy, many of them claiming superiority over competitors. This has led to many randomised controlled trials (RCTs) comparing different dental implants made of various materials and having different designs and/or and surface characteristics[2].

Most of the dental implants used nowadays have a connection which allows a stable and more or less rigid connection to an abutment or directly to the dental prosthesis. There are connections allowing the retention of the abutment/prosthesis via a screw, and others in which the abutment is permanently cemented into the implant. Connections usually have various shapes (triangles, hexagons, octagons, etc.) and other mechanisms to minimise the risk of movements and screw loosening. The connections most commonly used are the screw-retained ones, since abutments can be removed, if needed. Screw-retained connections can be divided into two major groups, depending on whether they have external or internal connections.

External connection implants are characterised by a mechanism on the top of the implant to block rotation movements, which allows the prosthesis/abutment to be screwed off. The most widely used external connection is the "external hexagon" originally used on the Brånemark implant system[1]. The hexagonal external connection can be considered the "gold-standard", and has been adopted by many manufacturers, though there are several other types of external connections. Internal connection implants, on the other hand, are characterised by the presence of the connection mechanism inside the implant body. There are many different types of internal connections, with and without anti-rotation mechanisms, and a gold standard is not easy to identify, though the so-called "conometric" connections are favoured by many authors.

The implant–abutment connection is believed to play an important role in the outcome of implant therapy, and almost every dental implant manufacturer has developed its own unique connection. These connections are often the subject of aggressive marketing campaigns, with many manufactures and clinicians claiming the superiority of one connection over the others. However, despite the fact that osseointegrated dental implants have been in use for almost half a century, not a single well designed and conducted RCT has been performed with a view to specifically investigating the role, if any, of different implant connections, by comparing implants in which the only difference is their connections[2]. Since there is not yet any valid evidence-based clinical data evaluating whether one implant connection could be superior to the others, and whether and how the different connection types could influence the clinical outcome of implant-supported rehabilitations in terms of complications, peri-implant marginal bone loss, aesthetics and ease of use, RCTs evaluating these aspects are long overdue. It would also be interesting to determine whether the best connection type could differ depending on the numbers of implants supporting the same prosthesis (single crown, two to three implants, or more than three implants supporting the same prosthesis).

The aim of this pragmatic multicentre RCT of parallel-group design was to compare the outcomes of identical implants with internal *versus* external connection. This is the third report on this trial, presenting clinical outcomes at 10 years post-loading; data at one[3] and 5[4] years have previously been published. This article has been drafted according to the CONSORT

statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/).

MATERIALS AND METHODS

The study was designed as a multicentre randomised controlled trial of parallel-group design with two arms and blind outcome assessments. Any patient requiring one implant-supported prosthesis, supported by one or more implants, being 18 years or older, and able to understand and sign an informed written consent form was eligible for this trial. Only one prosthesis per patient was to be considered for this trial, which could only be supported by the type of implants dictated by the randomisation procedure. This trial was designed as a pragmatic trial in order to mirror clinical reality as closely as possible. Broad inclusion criteria were used, including, for instance, any type of bone quality, any jaw location, and whether or not patients were heavy smokers.

Clinicians were free to choose the treatment option they considered optimal for the patient to be rehabilitated (for instance flapless implant placement; immediate post-extraction implants; minor augmentation procedures at implant placement; immediate, early or delayed loading; submerged or non-submerged techniques, etc.) at their discretion.

Pre-operative radiographs (intra-oral, panoramic, CT scans or other radiographic exams, at the discretion of the operators) together with clinical inspection were used to determine bone volumes.

Exclusion criteria were:

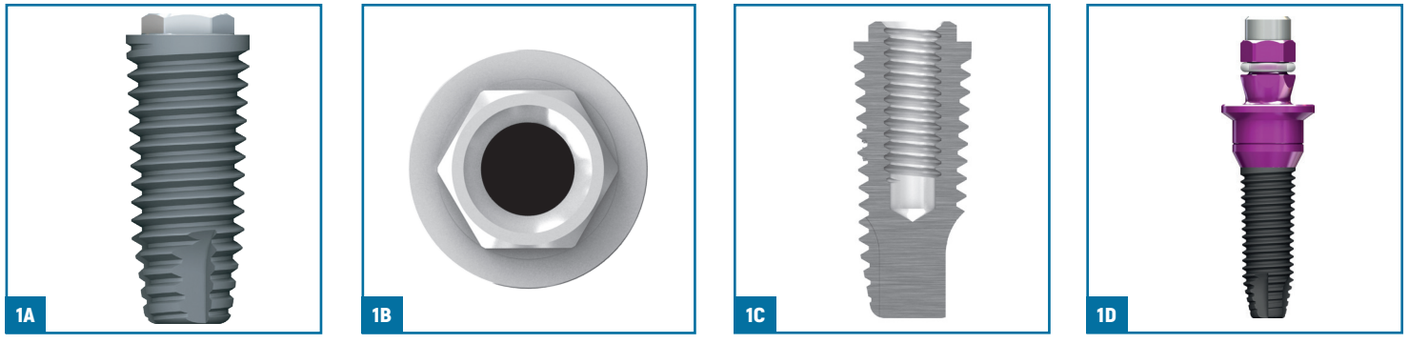
- General contraindications to implant surgery;
- Irradiation to the head and neck area;
- Immunosuppression or immunocompromised;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Untreated periodontitis;
- Poor oral hygiene and motivation;
- Uncontrolled diabetes;
- Pregnancy or lactation;
- Substance abuse;
- Psychiatric problems or unrealistic expectations;
- Lack of antagonistic occlusal surfaces for the implant-supported prosthesis at implant loading;
- Acute/purulent infection in the area intended for implant placement;
- Unrestorable with a removable prosthesis to allow individual implant stability assessment (with exceptions of single implants);
- Participation in other studies if the present protocol could not be properly adhered to;
- Referral solely for implant placement;
- Inability to commit to 10 years of follow-up.

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); they were given the opportunity to ask questions pertaining to this study, and were apprised of treatment alternatives. The study was open to qualifying patients without regard to sex or race.

Patients were categorised into three groups according to how much they declared smoking: non-smokers, moderate smokers (up to 10 cigarettes per day), and heavy smokers (more

than 10 cigarettes per day). For patients needing more than one implant-supported prosthesis, the operator was free to choose which one to include in the study at the screening visit. Originally ten centres agreed to participate in the study, but two centres did not provide any data and one centre provided data not compatible with the random allocation procedure and no periapical radiographs, and their data was therefore not considered. The remaining seven centres provided the 1 year post-loading data, but two centres never supplied the intraoral radiographs[3]. Only four centres delivered the 5- and 10-year post-loading data, and only data from these latter four centres is therefore presented below. Three of these four practices were located in Italy (Drs. Grusovin, Gualini and Pistilli) and the other in South Korea (Dr. Lee). Each dentist treated 30 patients. All follow-up appointments were held at the respective treatment centres.

The devices investigated were commercially available tapered titanium screw-shaped EZ Plus dental implants (MegaGen Implant, Gyeongbuk, South Korea) with sand-blasted acid-etched surface up to the neck and either external (EC, **FIGS. 1A-D**) or internal (IC, **FIGS. 2A-C**) connection. The external connection was the standard external hexagon of the Brånemark System (**FIGS. 1A-C**), whereas the internal connection was an 11° morse-taper connection (**FIGS. 2A-C**), which produces a conical seal via cold welding between the abutment and implant. The only differences between the two implants apart from the connection were the presence of a bevel at the implant neck of the IC (designed to allow platform mismatching) which is not present in the EC design (**FIGS. 1A** and **2A**), and a different neck design in implants with external connection of 3.3 mm diameter (**FIG. 1D)**. In this case the neck was designed



FIGS. 1A-D: *EZ Plus implant with external connection: sagittal view (A); occlusal view of the external connection (B); sagittal section showing the external connection (C); the 3.3 mm diameter has a different neck design to have the same connection and it is represented here with the implant mount (D)*

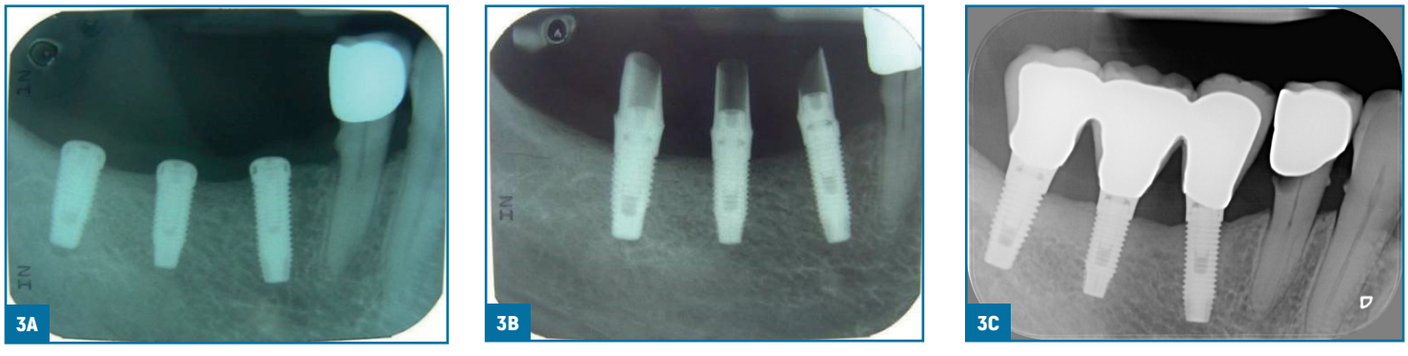
FIGS. 2A-C: *EZ Plus implant with internal connection: sagittal view (A); occlusal view of the internal connection (B); sagittal section showing the internal connection (C)*

differently in order to adapt the standard external hexagon to a small diameter implant. The other difference involved the abutment shape, since those designed for the IC group had to be platform-switched (**FIGS. 3A-C, 4A-C**). Operators were free to choose implant lengths (7, 8.5, 10, 11.5, 13 or 15 mm) and diameters (3.3, 4, 4.5 or 5.5 mm) according to clinical indications and their preference.

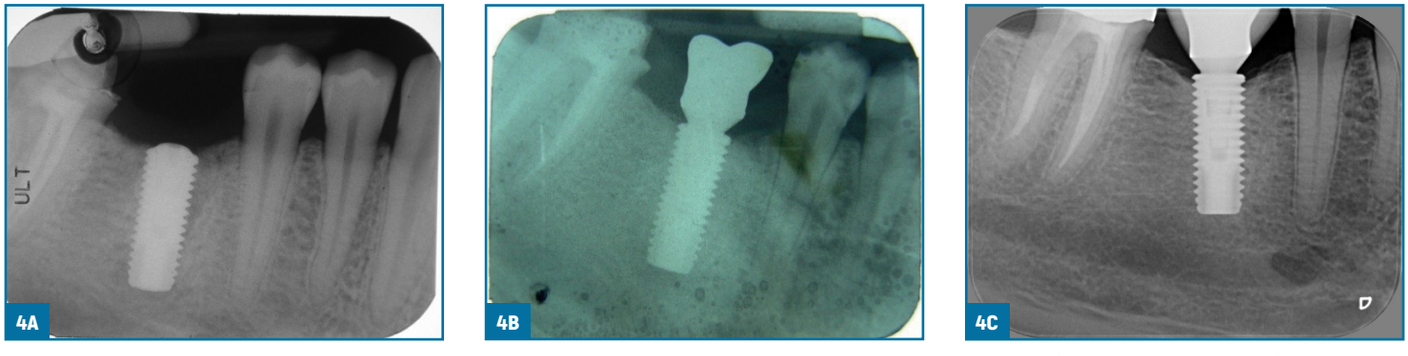
Clinical procedures

Patients received prophylactic antibiotic therapy, specifically 2 g of amoxicillin (or 600 mg of clindamycin if allergic to penicillin), one hour prior to surgery, and rinsed for one minute with 0.2% chlorhexidine. All patients were treated under local anaesthesia. Tooth extractions, when needed, were performed as atraumatically as possible, attempting to preserve the buccal alveolar bone. Extraction sockets were carefully cleaned of any granulation tissue residue. The decision to raise the flap or not was left to the individual clinician. The standard implant site preparation procedure, as recommended by the implant manufacturer, was used. During implant site preparation, bone quality was subjectively assessed and divided into hard, medium and soft. In soft bone, a final drill of one size smaller than the conventional procedure was used to underprepare the implant site.

Once the implant site preparation was complete, the operator was informed whether the implant to be placed had to be with external or internal connection, according to a paral-



FIGS. 3A-C: *Sequence of periapical radiographs of one of the patients treated with Ez Plus implants with external connection (EC) included in this study (courtesy of Dr. Pistilli): implant placement (A); initial loading (B); 10-year after loading; while peri-implant bone levers are maintained, a distal caries and calculus can be noticed at tooth 44 (C)*



FIGS. 4A-C: *Sequence of periapical radiographs of one of the patients treated with Ez Plus implant with internal connection (IC) included in this study (courtesy of Dr. Pistilli): implant placement (A); initial loading (B); 10-year after loading (C). Please note that IC implants had to be platform-switched due to the implant design.*

lel-group study design with two arms, by opening a sequentially numbered sealed envelope corresponding to the patient recruitment number. Implants were placed with the neck flush to the crestal bone level, with the exception of post-extraction implants, which were placed more palatally, about two mm below the palatal bone level.

Clinicians were free to decide whether to load the implants immediately, early or conventionally, and whether to submerge them or not for the healing period, but had to ensure that both groups were treated in a similar way, with similar healing times, etc. Just after implant placement, intraoral 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 was prescribed to be taken 2 to 4 times a day during meals for as long as required. Patients were instructed to use 0.2% chlorhexidine mouthwash for one minute twice a day for two weeks, and to avoid brushing or trauma to the surgical sites. Post-operative antibiotics were only prescribed to patients subjected to bone augmentation procedures, specifically 1 g of amoxicillin twice a day for six days. Patients allergic to penicillin were prescribed 300 mg of clindamycin twice a day for six days. Within one week all patients were recalled and checked.

Clinicians were also free to choose screw-retained restorations or those cemented with provisional cement, to load the implants directly with definitive prostheses, and whether to use metal-ceramic or metal-composite restorations (single crowns could be also in full ceramic). Overdentures could also be used. Patients were enrolled in an oral hygiene programme, with recall visits planned at least every 6 months for the entire duration of the study.

Outcome measures

This study tested the null hypothesis that there would be no difference in clinical outcomes between the two connection types, *versus* the alternative hypothesis of a difference.

Outcome measures were the following.

- *Prosthesis failure* (primary outcome measure): impossibility of placing prosthesis due to implant failures or secondary to implant losses, and definitive prosthesis that had to be remade for any reason.
- *Implant failure* (primary outcome measure): 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 with a wrench delivering a torque of 20 Ncm, or by assessing the stability of single crowns using the handles of two instruments, at initial loading, and at 1, 5 and 10 years after loading.
- *Any complications or adverse events* (primary outcome measure) were recorded and reported by connection type directly by the operators.
- *Peri-implant marginal bone level changes* (secondary outcome measure) evaluated on intraoral radiographs taken using the paralleling technique at implant placement, initial loading, and at 1, 5 and 10 years after loading. Non-digital radiographs were scanned in TIFF format with a 600 dpi resolution, and stored on a personal computer. Peri-implant marginal bone levels were measured using the UTHSCSA Image Tool 3.0 software (The University of Texas Health Science Center, San Antonio, USA). The software was calibrated for each image using the known implant neck diameter. Measurements of the mesial and distal bone crest levels adjacent to each implant, parallel to the implant axis, were made to the nearest 0.01 mm, and averaged per implant, then patient and finally by group. Reference points for the linear measurements were: the most coronal margin of the implant collar and the most coronal point of bone-to-implant contact.

At each centre a local outcome assessor evaluated implant stability blind. The implant type was not recognizable when assessing implant stability of single crowns. One dentist (Dr. Maghaireh), not involved in the treatment of the patients, performed all radiographic assessments without knowing group allocation, but IC implants could be identified on radiographs due to the presence of the neck bevel and platform-switched abutments.

Methodological aspects

No sample size calculation was attempted. It was originally decided to include 30 patients at each of the 10 planned centres for a total of 300 patients, i.e., 150 patients to be randomised to each group. Ten computer generated restricted random lists were created. Only one investigator (Dr. Esposito), who was not involved in the selection and treatment of the patients, knew the random sequence and had access to the randomisation list, which was stored on a password-protected laptop computer. The randomisation codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Only after the implant sites were prepared was the envelope corresponding to the patient recruitment number opened, informing the clinician whether to place an implant with internal or external connection. Therefore, treatment allocation was concealed to the investigators in charge of enrolling and treating the patients.

All data analyses were carried out according to a pre-established analysis plan. A dentist with expertise in statistics (Dr. Buti) analysed the data. Differences in the proportions of patients with prosthesis failures, implant failures and complications (dichotomous outcomes) were compared between groups using the Chi-squared test or Fishers Exact test (when cell count was <5). Differences in patient means for continuous outcomes (bone levels) between groups were compared using t-tests. 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. Covariance analysis was used to compare the mean radiographic values at loading and at 1, 5 and 10 years, with the baseline value as a covariate. Differences in dichotomous outcomes among centres were calculated using the Chi-squared test or the Freeman-Halton extension of Fishers Exact test (when cell count <5). Between-centre differences in mean radiographic values at 10-years were calculated using covariance analysis with the baseline value as covariate. The Tukey's Test for Post-Hoc Analysis was used. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

The four centres screened 221 patients for eligibility, but 101 patients were not included for the following reasons: 57 patients did not want to participate in a clinical trial, 26 patients were referred just for implant placement; seven patients were unable to commit to a 10-year follow-up; five patients had been or were being treated with oral bisphosphonates; four patients' implants were to be connected to other implant types; and two patients had poor oral hygiene/motivation. All remaining 120 patients had their sites treated according to the allocated interventions. Seventeen patients with 30 implants dropped out before completion of the 10-year post-loading follow-up, eight from the EC group (11 implants) and nine from the IC group (19 implants).

Drop-outs from the EC group were the following.

- Patient #10 with one implant was severely depressed and unable to attend both 5- and 10-year appointments, but reported that everything was fine (Dr. Pistilli).
- Patient #7 with two implants was sick and unable to attend both 5- and 10-year appointments (Dr. Gualini).

- Patient #21 with one implant had a serious accident and was unable to attend the 5-and 10-year appointments; last seen at 3-year follow-up (Dr. Lee).
- Patient #2 with one implant did not want to attend the 10-year follow-up, but reported no problems; last seen at 5 years post-loading (Dr. Pistilli).
- Patient #27 with two implants moved away and has a different dentist. No problems reported up to 10 years after loading; last seen at 5-year follow-up (Dr Gualini).
- Patient #10 with one implant became uncontactable; last seen at 5-year follow-up (Dr. Lee).
- Patient #23 with one implant died of lung cancer 6 years after loading (Dr. Lee).
- Patient #20 with two implants died of a stroke 6 years and 4 months after loading (Dr. Gualini).

Drop-outs from the IC group were the following.

- Patient #25 with two implants had financial problems and was depressed, and did not attend any follow-up after prosthesis delivery, but reported no problems with the implant-supported prosthesis (Dr. Grusovin).
- Patient #16 with one implant died of lung carcinoma just after the 1-year follow-up (Dr. Gualini).
- Patient #1 with two implants did not want to attend the 5- and 10-year appointments (Dr. Gualini).
- Patient #6 with two implants was very sick and unable to attend the 5- and 10-year appointments (Dr. Gualini).
- Patient #4 with four implants became severely ill and was last seen at 5-year follow-up, sent panoramic radiograph at 10 years and reported no complications (Dr. Pistilli).
- Patient #21 with one implant did not attend for health reasons; last seen at 5-year follow-up (Dr. Pistilli).
- Patient #25 with three implants became uncontactable; last seen at 5-year follow-up (Dr. Pistilli).
- Patient #8 with one implant was unable to attend the 10-years appointment; last seen at 5 years. Reported no problems (Dr. Grusovin).
- Patient #24 with three implants promised to come to the 10-year follow-up but did not; last seen at 5 years (Dr. Gualini).

One of the patients from the IC group (Dr. Pistilli) who was uncontactable at the 5-year follow-up attended the 10-year follow-up. The data from all remaining patients were included in the statistical analyses. The main protocol deviations are summarised in **TABLE 1.** An additional protocol deviation was that Dr. Lee did not record the number of patients who were screened as potential candidates for the trial but did not match the inclusion criteria, or the reasons they were excluded; "elderly" patients were also excluded from that sample.
Patients were recruited and implants were inserted from February 2009 to June 2010. The follow-up for all patients was 10-year post-loading. The main baseline patient and intervention characteristics, divided by study group, are presented in **TABLE 2**. There were no apparent significant baseline imbalances between the two groups. There were 60 patients in each group, and 96 EC and 107 IC implants were placed.

Prosthesis failures

Two prostheses failed in the EC group (one of the two supporting implants failed due to peri-implantitis one year and half after loading; a single implant failed for peri-implantitis at 8

TABLE 1 SUMMARY OF PROTOCOL DEVIATIONS BY CENTRE UP TO 10 YEARS AFTER LOADING (N = NUMBER OF PATIENTS)

	EC (n = 60)	IC (n = 60)
Pistilli (n = 30)	0	2 (took panoramic instead of periapical x-ray at 1 year) 1 (took panoramic instead of periapical x-ray at 10 years)
Grusovin (n = 30)	2 (used Ex-Feel implants) 1 (patient refused to have 5-year x-ray) 1 (patient refused to have 10-year x-ray) 1 (took readable panoramic instead of periapical x-ray at 10 years)	2 (used 3 Ex-Feel implants) 1 (still wearing provisional resin crown at 5 years due to financial reasons) 1 (patient refused to have 10-year x-ray) 1 (10-year x-ray not taken in patient with frank peri-implantitis and Alzheimer's)
Gualini (n = 30)	2 (missing periapical x-ray at 1 year after loading) 1 (took unreadable panoramic instead of periapical x-ray at 1 year)	1 (missing periapical x-ray at loading and at 1 year)
Lee (n = 30)	3 (prosthesis attached to other implant types having the same connection) 2 (used Ex-Feel implants with correct connection instead)	1 (prosthesis attached to other implant types having the same connection)
Total (n = 120)	13	10

years after loading) *versus* three prostheses (one not delivered due to implant failures and the other failed 5 and 8 years after loading due to peri-implantitis) of the IC group. There was no statistically significant difference between groups in patients experiencing prosthesis failures (P = 0.631, diff = 0.02, 95% CI: -0.07 to 0.11).

Implant failures

Two implants failed in two patients from the EC group *versus* four implants in three patients from the IC group. This difference was not statistically significant (P = 0.631, diff = 0.02, 95% CI: -0.07 to 0.11).

The following implant failures occurred in the EC implant group:

- One male non-smoker (Dr. Gualini's #22) had one of the two implants affected by peri-implantitis 1 year after loading. The implant in position 35 (10 x 4 mm) was treated via open flap debridement but failed 5 months after;
- One male non-smoker (Dr. Grusovin's #18) presented with mobility of the implant replacing 36 (11.5 x 4 mm) 8 years after loading. It was lost, apparently due to peri-implantitis.

The following implant failures occurred at IC implants:

- One female patient smoking more than 10 cigarettes per day (Dr. Gualini's #8), received two implants (10 x 4 mm and 11.5 x 4 mm) in positions 46 and 47. Bone was hard and the surgery was painful, and pain persisted postoperatively. After 2 weeks, the bone was exposed and necrotic at both implants, which were removed. These implants replaced two implants which had previously failed, and were not replaced again;
- One female non-smoker (Dr. Gualini's #19) had one of her two implants affected by peri-implantitis 3 years after loading. The implant in position 16 (13 x 4 mm) was treated via open flap debridement but failed 2 years after. The implant was successfully replaced;
- One male smoker (Dr. Grusovin's #13) presented with mobility of the implant replacing 21 (13 x 4 mm) 8 years after loading with no apparent signs of inflammation. The patient had

TABLE 2 PATIENT AND INTERVENTION CHARACTERISTICS

	EC (n = 60)	IC (n = 60)
Females (%)	37 (61.7%)	36 (60%)
Mean age at implant insertion (range)	50.4 ± 13.8 (25-74)	54 ± 13.4 (20-79)
Smoking up to 10 cigarettes/day (%)	6 (10%)	10 (16.7%)
Smoking more than 10 cigarettes/day (%)	9 (15%)	9 (15%)
Number of implants placed	96	107
Implants in upper jaws (%)	38 (39.6% implants)	40 (37.4% implants)
Implants in lower jaws (%)	58 (60.4% implants)	67 (62.6% implants)
Implants in incisor position	2 (2.1% implants)	6 (5.6% implants)
Implants in canine position	0	8 (7.5% implants)
Implants in premolar position	36 (37.5% implants)	34 (31.8% implants)
Implants in molar position	58 (60.4% implants)	59 (55.1% implants)
Implants in hard bone	20 (20.8% implants)	25 (23.4% implants)
Implants in medium bone	61 (63.5% implants)	70 (65.4% implants)
Implants in soft bone	15 (15.6% implants)	12 (11.2% implants)
Implants of diameter 3.3 mm	13 (13.5% implants)	8 (7.5% implants)
Implants of diameter 4 mm	44 (45.8% implants)	63 (58.9% implants)
Implants of diameter 4.5 mm	1 (1% implants)	0
Implants of diameter 5 mm	38 (39.6% implants)	36 (33.6% implants)
Implants of length 7 mm	0	0
Implants of length 8.5 mm	18 (18.8% implants)	16 (15% implants)
Implants of length 10 mm	23 (24% implants)	35 (32.7% implants)
Implants of length 11.5 mm	34 (35.4% implants)	35 (32.7% implants)
Implants of length 13 mm	21 (21.9% implants)	21 (19.6% implants)
Post-extraction implants (%)	9 (15%)	7 (11.7%)
Implants in augmented sites (%)*	19 (31.7%)	23 (38.3%)
Implants inserted flapless (%)	0	0
Patients with submerged implants (%)	44 (73.3%)	51 (85%)
Single crowns (%)	30 (50%)	26 (43.3%)**
Partial fixed prostheses (%)	30 (50%)	31 (51.7%)**
Cross-arch fixed prostheses (%)	0	0**
Overdentures (%)	0	2 (2.3%)**
Patients with immediately loaded implants (within 1 week) (%)	0 (0%)	1 (1.7%)
Patients with early loaded implants (between 1 week and 2 months) (%)	2 (2.3%)	0 (0%)
Patients with conventionally loaded implants (after 2 months) (%)	58 (96.7%)	58 (96.7%)**

**Including post-extraction sites augmented at implant placement*
***Two implants on the same patient (Dr. Gualini) were removed 2 weeks after placement due to infection, so the patient could not be rehabilitated; therefore the prosthesis is not accounted for in this Table*

previously lost another implant in the same position and then had a cystic formation treated one year before placing the failed study implant.

Complications

Thirteen EC patients were affected by 15 complications *versus* 11 IC patients affected by 13 complications, the difference not being statistically significant (P = 0.720, diff. = -0.03, 95% CI: -0.19 to 0.13). The following complications occurred in patients who received EC implants (different complications that occurred in the same patient are numbered):

- 1) Loosening of one healing abutment after one week, which was retightened; 2) Loosening of the abutment at 6 years after loading, which was retightened;
- The abutment screw become loose once at single implants carrying provisional crowns in three patients. Crowns were drilled and screws retightened;
- 1) The abutment screw become loose once at a single implant one month after fitting a definitive screw-retained crown. The screw was retightened at 30 Ncm; 2) It loosened again at 7 years post-loading and was retightened;
- Contact points between implant-supported crowns and adjacent natural teeth were lacking in three patients at crown delivery. Crowns were unscrewed and reshaped by the dental technician;
- One implant, replacing 35, out of two in the same patient was affected by peri-implantitis at 1-year post-loading. It was surgically treated but subsequently failed;
- Peri-implantitis at 3 years post-loading at an implant replacing 46 was treated via prosthesis removal and surgical debridement plus systemic antibiotics. It recurred at 6 years and was retreated surgically;
- Peri-implantitis at implant replacing 15 at 8 years post-loading was treated surgically;
- Peri-implantitis at implant replacing 36 at 8 years post-loading. The patient did not come to regular check-ups, the implant was mobile and was therefore removed;
- Peri-implantitis at implant replacing 26 at 9 years post-loading was reated via non-surgical debridement and a chemical desiccant (HybenX, EPIEN Medical, St. Paul, MN, USA); now stable.

Patients with IC implants were affected by the following complications:

- Post-operative infection with bone exposure leading to failure of two implants in one patient;
- An abutment screw become loose once at a single implant carrying a provisional crown. The crown was drilled and the screw retightened;
- Loosening of one definitive crown after three months. The screw was retightened at 30 Ncm;
- Loosening of one partial fixed prosthesis after 3 months. Screwed again using the manual torque wrench at 30 Ncm;
- Peri-implantitis at implant replacing 16 at 3 years post-loading; treated via surgical debridement but the implant failed at 5 years post-loading;
- Peri-implantitis at both mandibular implants supporting one overdenture 4 years post-loading. The patient had previously been hospitalized and did not come to check-ups. Since she refused surgical cleaning, a non-surgical debridement was performed and systemic antibiotics prescribed. The problem was temporarily resolved, but the patient did not manage to attend regular maintenance visits. Recurrence at 10 years post-loading, and the patient is now also affected by Alzheimer's and continuous inflammation; the problem is ongoing;

- Peri-implantitis at single implant replacing 43 at 4 years and 6 months after loading; treated via flap surgery and maintenance and local antibiotics. Implant still in function at 10 years but with purulent secretion;
- 1) Peri-implantitis at two implants replacing 37 and 47 at 5 years post-loading; treated via debridement and local antibiotics; 2) Screw loosening at implant replacing 45 ten years post-loading; retightened;
- Peri-implant mucositis at two implants replacing 34 and 36 noted at 5 years post-loading; successfully treated using local antibiotics and antiseptic;
- Loosening of the contact point with the adjacent natural tooth causing food impaction noted at 5 years post-loading. The crown was unscrewed and reshaped in a dental laboratory;
- Peri-implantitis at a single implant replacing 26 at 10 years post-loading; treated non-surgically, the inflammation resolved.

Peri-implant marginal bone levels

At baseline (implant placement), there was no statistically significant difference (P = 0.092; diff. = -0.11 mm; 95% CI: -0.24 to 0.02). Both groups gradually lost a highly statistically significant amount of marginal peri-implant bone up to 10 years after loading (P <0.001; **TABLE 3**),

TABLE 3 IMPLANT PLACEMENT, LOADING, 1-, 5- AND 10-YEAR MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVELS AND THEIR WITHIN-GROUP CHANGES IN MM

	EC Implants			IC Implants		
	N	**Mean (SD)**	**95% CI**	**N**	**Mean (SD)**	**95% CI**
Implant Placement	60	0.21 (0.45)	[0.10; 0.33]	60	0.1 (0.24)	[0.04; 0.16]
Loading	60	0.79 (0.62)	[0.63; 0.95]	58	0.65 (0.73)	[0.46; 0.84]
Change	60	0.58 (0.66)	[0.41; 0.75]	58	0.56 (0.67)	[0.38; 0.74]
P-value	<0.001*			<0.001*		
	N	**Mean (SD)**	**95% CI**	**N**	**Mean (SD)**	**95% CI**
Implant placement	60	0.21 (0.45)	[0.10; 0.33]	60	0.1 (0.24)	[0.04; 0.16]
1-year	57	1.23 (0.93)	[0.98; 1.48]	58	1.03 (0.87)	[0.80; 1.26]
Change	57	1.00 (1.03)	[0.73; 1.28]	58	0.94 (0.84)	[0.72; 1.16]
P-value	<0.001*			<0.001*		
	N	**Mean (SD)**	**95% CI**	**N**	**Mean (SD)**	**95% CI**
Implant placement	60	0.21 (0.45)	[0.10; 0.33]	60	0.1 (0.24)	[0.04; 0.16]
5-year	56	1.36 (1.04)	[1.08; 1.64]	54	1.28 (1.11)	[0.98; 1.58]
Change	56	1.13 (1.24)	[0.80; 1.46]	54	1.21 (1.09)	[0.92; 1.51]
P-value	<0.001*			<0.001*		
	N	**Mean (SD)**	**95% CI**	**N**	**Mean (SD)**	**95% CI**
Implant placement	60	0.21 (0.45)	[0.10; 0.33]	60	0.1 (0.24)	[0.04; 0.16]
10-year	48	1.26 (0.95)	[0.98; 1.53]	48	1.35 (1.30)	[0.98; 1.73]
Change	48	1.01 (1.15)	[0.67; 1.34]	48	1.27 (1.30)	[0.89; 1.64]
P-value	<0.001*			<0.001*		

**All changes from baseline (paired t-test) statistically different (P<0.001); SD = Standard deviation; CI = Confidence interval*

when patients with EC implants had lost an average of 1.01 mm peri-implant bone *versus* 1.27 mm in patients with IC implants (**TABLE 3**). When considering baseline bone level as a covariate, no statistically significant differences were found between the two groups in terms of estimated peri-implant bone levels at loading (diff. = 0.07 mm, 95% CI: -0.17 to 0.31 mm, P (ANCOVA) = 0.566; **TABLE 4**), or 10 years after loading (diff. = 0.07 mm, 95% CI: -0.41 to 0.54 mm, P (ANCOVA) = 0.782; **TABLE 4**).

A comparison of the four centres is presented in **TABLES 5, 6**. There were no statistically significant differences between centres in terms of either complications (P = 0.567), implant failures (P=0.084) or prosthesis failures (P = 0.084) (**TABLE 5**). Regarding marginal bone loss, however, significantly more bone loss was observed at Dr. Gualini and Dr. Grusovin's centres compared to Dr. Lee (P = <0.001); and at Dr. Gualini compared to Dr. Pistilli (P = 0.037) (**TABLE 6**).

DISCUSSION

Ten years post-loading, no statistically significant differences or even trends could be discerned when comparing similar implants with internal and external connections. In order to perform a reliable comparison regarding the role of the type of connection, only the type of connection has to be different, all other implant characteristics (implant material, surface characteristics and implant shape) remaining exactly the same. The EZ Plus implant system was chosen because it had almost all the required characteristics (the main differences being the bevel present at the coronal portion of IC implants (**FIG. 2A**) and the different neck

TABLE 4 ADJUSTED MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVEL ESTIMATES WITH BASELINE BONE LEVEL AS COVARIATE PER GROUP AT DIFFERENT TIMES

	Baseline–loading*			Baseline-1 year*			Baseline-5 years*			Baseline-10 years*		
	N	Mean	(SE)	N	Mean	(SE)	N	Mean	(SE)	N	Mean	(SE)
EC implants	60	0.76	(0.09)	57	1.21	(0.12)	56	1.39	(0.15)	48	1.27	(0.17)
IC implants	58	0.69	(0.09)	58	1.05	(0.12)	54	1.25	(0.15)	48	1.34	(0.17)
Difference (SE); 95% CI	0.07	(0.12)	-0.17 to 0.31	0.17	(0.17)	-0.17 to 0.50	0.14	(0.21)	-0.28 to 0.56	0.07	(0.24)	-0.41 to 0.54
P-value (ANCOVA)	0.566			0.332			0.505			0.782		

**Analysis of covariance at loading, 1, 5 and 10 years after loading with baseline as a covariate*

TABLE 5 COMPARISON AMONG STUDY CENTRES FOR THE VARIOUS PATIENT LEVEL OUTCOME MEASURES (N = NUMBER OF PATIENTS) AT 10-YEAR POST-LOADING

	Pistilli	Grusovin	Gualini	Lee	Total (103)	P-value
Patients with prosthesis failures (N = 103)	0 out of 25	2 out 28	3 out 23	0 out of 27	5	0.084*
Patients with implant failures (N = 103)	0 out of 25	2 out 28	3 out 23	0 out of 27	5	0.084*
Patients with complications (N = 104)	5 out of 26	9 out 28	5 out 23	5 out of 27	24	0.567**

**Freeman-Halton extension of Fishers Exact test; **Chi-squared test*

TABLE 6 MEAN RADIOGRAPHIC PERI-IMPLANT MARGINAL BONE LEVEL ESTIMATES PER CENTRE WITH BASELINE BONE LEVEL AS COVARIATE AT 10 YEARS (N = NUMBER OF PATIENTS)

	Mean in mm (SE) 95% CI
Pistilli (N = 25) b c	1.12 (0.21) [0.71; 1.53]
Grusovin (N = 23) a b	1.74 (0.22) [1.31; 2.16]
Gualini (N = 21) a	1.95 (0.22) [1.51; 2.40]
Lee (N = 27) c	0.61 (0.20) [0.21; 1.00]

Ordered Differences Report

Centre Comparison		Mean Diff.	(SE)	95% CI	P-Value
Gualini	Lee	1.35	(0.30)	0.57; 2.13	<0.001*
Grusovin	Lee	1.13	(0.29)	0.36; 1.90	<0.001*
Gualini	Pistilli	0.83	(0.31)	0.04; 1.63	0.037*
Grusovin	Pistilli	0.62	(0.30)	-0.17; 1.41	0.176
Pistilli	Lee	0.51	(0.28)	-0.23; 1.25	0.279
Gualini	Grusovin	0.22	(0.31)	-0.59; 1.03	0.897

Statistically significant difference between centres (P-value [ANCOVA] P<0.001)
Levels not connected by the same letters are statistically significantly different
Tukey's Test for Post-Hoc Analysis was used
**Statistically significant difference*

design of the 3.3-mm diameter EC implants (**FIG. 1D**). Another reason for choosing the EZ plus systems was that the implant manufacturer was glad to sponsor an independently conducted trial to evaluate the clinical outcomes of different implant connections.

Some complications that arose might be related specifically to the connection type. Specifically, five EC implants in five patients were affected by peri-implantitis *versus* seven IC implants in five patients (plus another patient having two implants treated for peri-implant mucositis). Although these numbers are too small to draw any conclusions, they fail to support the marketing myth that external connections are more prone to peri-implantitis because of a poorer seal allowing increased bacterial leakage. The four incidents of early abutment screw loosening (three in the EC and one in the IC group) reported by Dr. Pistilli at single implants with provisional crowns can be explained by the operator's habit of screwing in the abutment screws manually, holding provisional crowns, with torques below 10 Ncm. When placing definitive crowns, the surgeon applied a torque of 25 Ncm and no more screw loosening occurred.

No differences in marginal bone levels were found between the two groups, despite IC implants having been designed to allow platform-switching. In this study, no advantages to platform-switched IC implants can be inferred. Contradictory results on this issue have been presented by different authors: some RCTs showed significantly less bone loss (about 0.3 mm) at platform-switched implants at 1 year post-loading[5,6], whereas other RCTs did not show any difference[7,8].

Comparisons among the four centres yielded an intriguing observation, with three times more bone loss being recorded at two centres as compared to another centre. We do not have a convincing hypothesis or even a tentative explanation for this difference, but some differences between treatment protocols could have been present.

According to the present findings, operators can choose the connection type they prefer. Internal connections may be more user-friendly when single implants or prostheses supported by two or three implants are to be fitted. On the contrary, it may be that in the presence of multiple implants, as when rehabilitating an edentulous jaw, the external connection could be more forgiving at impression taking than an internal one. However, these are merely hypotheses that need to be verified.

It is also interesting to observe that despite clinicians being left the option to choose the time of implant loading, only one and two patients were subjected to immediate and early loading procedures, respectively. This may suggest that immediately loading procedures for single implants or short partial fixed prostheses are not commonly performed.

There have been no other published randomised controlled trials comparing internal *versus* external connections alone, without changing the collar design of the implants[2], so meaningful comparisons with similar RCTs cannot be made at the present stage.

The main limitations of the present trial are: i) the design of the two implants investigated was not precisely identical, with additional platform-switching features being present at IC implants which may have slightly worked in their favour; ii) a low number of patients was available at 10-year post-loading follow-up. However, regarding the generalisation of these results, due to the pragmatic nature of the study design, similar results should be obtained by other operators treating patients using similar procedures.

CONCLUSIONS

Acknowledging that implants with internal connection had a slightly modified neck due to the presence of a minor bevel, no statistically significant differences were observed in clinical outcomes between implants with internal or external connections. Therefore the choice of the type of connection can be simply based on clinician preference.

REFERENCES

1. Brånemark P-I, Hansson BO, Adell R, Breine U, Lindström J, Hallén O et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. Stockholm: Almqvist & Wiksell International, 1977.
2. Esposito M, Ardebili Y, Worthington HV. Interventions for replacing missing teeth: different types of dental implants. Cochrane Database of Systematic Reviews 2014: Chichester, UK: John Wiley & Sons, Ltd.
3. Esposito M, Maghaireh H, Pistilli R, Grusovin MG, Lee ST, Gualini F et al. Dental implants with internal *versus* external connections: 1-year post-loading results from a pragmatic multicenter randomised controlled trial. European Journal of Oral Implantology 2015;8:331-44.
4. Esposito M, Maghaireh H, Pistilli R, Grusovin MG, Lee ST, Trullenque-Eriksson A et al. Dental implants with internal *versus* external connections: 5-year post-loading results from a pragmatic multicenter randomised controlled trial. European Journal of Oral Implantology 2016;9:129-41.
5. Canullo L, Goglia G, Iurlaro G, Iannello G. Short-term bone level observations associated with platform switching in immediately placed and restored single maxillary implants: a preliminary report. International Journal of Prosthodontics 2009;22:277-82.
6. Guerra F, Wagner W, Wiltfang J, Rocha S, Moergel M, Behrens E et al. Platform switch *versus* platform match in the posterior mandible - 1-year results of a multicentre randomised clinical trial. Journal of Clinical Periodontology 2014;41:521-9.
7. Enkling N, Johren P, Klimberg V, Bayer S, Mericske-Stern R, Jepsen S. Effect of platform switching on peri-implant bone levels: a randomised clinical trial. Clinical Oral Implants Research 2011;22:1185-92.
8. Meloni SM, Jovanovic SA, Lolli FM, Pisano M, De Riu G, De Riu N et al. Platform switching *vs* regular platform implants: nine-month post-loading results from a randomised controlled trial. European Journal of Oral Implantology 2014;7:257-65.