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The Influence of Repeated Abutment Changes on Peri-Implant Tissue Stability and Keratinised Tissue on Peri-Implant Health: 12-Year Post-Loading Results From a Multicentre Randomised Controlled Trial

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ABSTRACT

Aims: To evaluate the influence of at least three abutment disconnections in conventionally loaded implants against placement of a definitive abutment in immediately non-occlusal loaded implants on hard and soft tissue changes. A secondary aim was to evaluate whether the presence of less than 2 mm of keratinised mucosa is associated with increased peri-implant marginal bone loss and soft tissue recessions.

Methods: Sixty patients requiring one single crown or one fixed partial prosthesis supported by a maximum of three implants were randomised, after implants were placed with a torque superior to 35 Ncm, according to a parallel group design to receive definitive abutments which were loaded immediately (definitive abutment group) or transmucosal abutments which were delayed loaded after 3 months and were removed at least three times (repeated disconnection group). Patients were treated in three centres, and each patient contributed to the study with only one prosthesis followed for 12 years after initial loading. Outcome measures were: prosthesis failures, implant failures, complications, pink esthetic score (PES), buccal recessions, patient satisfaction, peri-implant marginal bone level changes, and height of the keratinised mucosa.

Results: Thirty patients were randomly allocated to each group according to a parallel group design. Six patients dropped out or died from the definitive abutment group and seven from the repeated disconnection group. At 12 years post-loading, no patient in the definitive abutment group had implant failures versus three patients who lost five implants in the repeated disconnection group (difference = 13.04%; 95% CI: −6.7 to 26.8 to; $p = 0.109$; Fisher's exact test). No patient in the definitive abutment group had a prosthesis failure versus four patients of the repeated disconnection group. The difference was statistically significant (difference = 17.39%; 95% CI: 1.9 to 32.9; $p = 0.049$; Fisher's exact test). Four patients from the definitive abutment group versus seven patients from the repeated disconnection group were affected by complications (difference = 13.77%; 95% CI: −37.8 to 10.2; $p = 0.318$; Fisher's exact test), the difference not being statistically significant. PES scores did not show any statistically significant differences between the two groups: 10.84 ± 1.95 for the definitive abutment group and 10.31 ± 2.57 for the repeated abutment

changes group (difference = −0.53; 95% CI: −1.14 to 2.20; $p = 0.505$). Buccal recessions amounted to 0.30 ± 0.98 mm for the definitive abutment group and 0.15 ± 0.54 mm for the repeated abutment changes group with no statistically significant differences between the two groups (difference = −0.14; 95% CI: −0.69 to 0.41; $p = 0.592$). All patients were declared to be very satisfied with the function and aesthetics of the prostheses and would undergo the same procedure again. Mean peri-implant marginal bone loss was 0.25 ± 0.49 mm for the definitive abutment group and 0.70 ± 1.04 mm for the repeated abutment changes group (difference = 0.45; 95% CI: −0.16 to 1.05; $p = 0.135$), the difference not being statistically significant. Height of keratinised mucosa was 2.56 ± 1.75 for the definitive abutment group and 2.77 ± 2.07 for the repeated abutment changes group (difference = 0.21 mm; 95% CI: −1.06 to 1.49; $p = 0.746$). There was no significantly increased marginal bone loss (difference = 0.20; 95% CI: −0.06 to 0.33; $p = 0.268$) or buccal recessions (difference = 0.10; 95% CI: −0.05 to 0.33; $p = 0.203$) at implants having less than 2 mm of keratinised mucosa at loading.

Conclusion: More prosthesis failures were observed at 12 years after loading when comparing implants that underwent at least three repeated abutment disconnections to implants subjected to no disconnection. Immediate non-occlusal loading is a viable alternative to conventional loading. No increased bone loss or buccal recessions were noticed at implants with less than 2 mm of keratinised mucosa compared to those having more than 2 mm of keratinised mucosa.

1 | Introduction

Implant supported prostheses are an effective and reliable treatment for replacing missing teeth. Their success is mainly based on the ability of the bone to integrate and stabilise dental implants [1]. This process is known as 'osseointegration' and implants can be submerged unloaded for the duration of the healing period. After several months implants are exposed and healing or provisional abutments are connected on them for the period necessary to complete the restorative procedures. Depending on the procedures used, healing or temporary abutments may have to be disconnected and reconnected several times, and it was concluded, based on the results of an experimental study performed on five dogs [2], in which five abutment disconnection-reconnections were made, that 0.7 mm more marginal peri-apical bone loss occurred at implant subjected to repeated abutment disconnection. If this observation is correct then it would be better in clinical practice to minimise the number of abutment disconnections, by placing a definitive abutment immediately which preferably should not be removed thereafter. On the other hand, there might be clinical situations where it could be a disadvantage to place immediately a definitive abutment since it is not always possible to predict the amount of soft tissue shrinkage. Therefore, it would be nice to retain the possibility of changing abutments, when necessary, without causing too much disruption of the peri-implant tissues.

One randomised controlled trial (RCT) [3] reported 0.2 mm higher peri-implant marginal bone levels by not removing definitive abutments at immediate post-extractive implants, 3 years after loading, which was statistically significant. Such procedure was therefore termed as 'one abutment at one time concept'. From a clinical point of view, a statistically significant mean difference of 0.2 mm may not be clinically noticeable and should not discourage clinicians to change abutments if needed or even to use healing and/or provisional abutments. Another controlled but non-randomised study tested the same hypothesis [4] in posterior edentulous mandibles and found no statistically significant difference in marginal bone loss 3 years after implant placement, at implants treated according to the 'one abutment at one time' concept compared to abutments disconnected four times. Two RCTs by the same group [5, 6] reported 0.3 and 0.5 mm of more bone loss after 1 year for implants whose abutments were disconnected multiple times, both differences being statistically significant, while no significant differences were observed in another RCT [7].

Another interesting aspect of the rehabilitation with implant supported prostheses is the possibility to load implants immediately without waiting for bone healing around the implants. This procedure has important advantages, especially for the patients, who can have fixed prostheses on the same day of implant placement, if the risk of implant failures is not increased. There is substantial evidence that immediate loading can be as effective as delayed loading [8], if implants are inserted with a sufficient insertion torque [9, 10], the efficacy of immediate loading procedures still needs to be fully evaluated, especially in partially edentulous patients.

The aims of this multicentre RCT of parallel group design were to compare hard and soft tissue changes between immediately non-occlusal loaded implants which had definitive abutments placed at implant placement and never removed versus conventionally loaded implants which had provisional abutments changed at least three times: at impression making, 3 months after implant placement; when checking the zirconium core on titanium abutments for single crowns or the fitting of the prostheses metal structure; and at delivery of the definitive crowns/prostheses.

A secondary aim was to explore whether the presence of less than 2 mm of buccal keratinised peri-implant mucosa could be associated with increased buccal recessions and peri-implant marginal bone loss.

This is the fifth report in a series presenting the clinical outcome at 12 years post-loading. Data at 4 months [11], 1 year [12], 3 years [13] and 5 years [14] post-loading were previously published. The present article is reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement for improving the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/). This clinical trial was not registered prior to the study's initiation, as this was not mandatory at the time.

Summary

- Background
  - The main question was whether the procedure of changing abutments multiple times during the prosthetic rehabilitation phase could negatively affect the long-term clinical outcome.
- Added value of this study
  - This 12-year follow-up randomised controlled trial is so far the largest trial with the longest follow-up ever published. In addition, it was specifically designed and reported, using a robust methodology, to contribute to future systematic reviews on this topic.
- Clinical implications
  - Clinicians can remove abutments, as they commonly did historically, during the prosthetic rehabilitation phase. However, they should try to minimise these procedures since they may induce overtime additional prosthetic failures.
  - Immediate loading on definitive abutments, which were never removed, can be a reliable procedure.

2 | Methods

The trial was designed as a multicentre RCT of parallel group design with two arms. One arm consisted of patients who received definitive abutments immediately after implant placement, which were immediately loaded with a provisional acrylic fixed temporary prosthesis, without removing the abutments (Figure 1a–g). Patients of the other arm received abutments that were removed at least three times and were conventionally loaded after 3 months of unloaded healing (Figure 2a–g).

Any partially edentulous patient requiring one fixed implant-supported prosthesis, supported by a maximum of three implants, being 18 years old or older, and able to understand and sign a written informed consent form was eligible to be included in this trial. Only one prosthesis per patient was considered in the study, supported by implants inserted with an initial insertion torque of at least 35 Ncm, as assessed with a manual ratchet. Implants not achieving such torque were not included in the study.

Preoperative radiographs (periapical, panoramic, computerised tomography (CT) scans or other radiographic examinations at discretion of the operators) together with clinical inspections were used to determine bone volumes and anatomic landmarks. Patients were not included in the study if any of the following exclusion criteria were present: general contraindications to implant surgery; subjected to irradiation in the head and neck area; immunosuppressed or immunocompromised patients; treated or under treatment with intravenous amino-bisphosphonates; untreated periodontitis; poor oral hygiene and poor motivation; uncontrolled diabetes; pregnant or nursing; substance abusers; psychiatric problems; full edentulism; post-extractive sites with a buccal bone loss of more than 3 mm in relation to the palatal wall; need for any bone augmentation at implant placement, with the exception of using a bone substitute between the socket and the implants at immediate post-extractive sites; lack of opposite occluding dentition/prosthesis in the area intended for implant placement; acute infection in the area intended for implant placement; when immediate non-occlusal loading was not possible; patients who could not be restored with a retrievable prosthesis to allow individual implant stability assessment (with exceptions of single implants); implants that did not achieve an insertion torque of at least 35 Ncm; implants that could not be restored with standard straight or angulated titanium Ankylos (Dentsply Sirona Implants, Manheim, Germany) abutments; patients participating in other studies if the present protocol could not be properly followed; patients unable to commit to a 10-year follow-up.

For patients who had more than one eligible implant site, the operator was free to choose the site to be included in the study at the screening visit, to be randomised after implant placement.

Patients were recruited and treated in three Italian private practices by experienced operators (Drs. Bressan, Grusovin and Luongo); each dentist treated 20 patients. Originally, six centres agreed to participate in the study, but two centres had to be excluded from the study because one centre never recruited any patient and the other centre supplied incomplete data without any evidence in the case report forms that the planned abutment removal procedures were ever implemented. The third centre supplied data up to 5 years after loading [14], but refused to provide the 12-year data since Dentsply did not respect the original agreement.

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

The investigational devices used were Ankylos C/X titanium dental implants with internal connection (Dentsply Sirona Implants). Operators were free to choose implant lengths (8, 9.5, 11 and 14 mm) and diameters (3.5, 4.5 or 5.5 mm) according to clinical indications and their preferences to be restored with standard straight or angulated Ankylos C non-indexed titanium abutments. Soon it was apparent that the selection of non-indexed abutments for an indexed implant was not the ideal choice, given that while removing and reconnecting the abutment, it could be repositioned in a slightly different position, which would require adjustments or even the remaking of the prosthesis. As soon as the problem was brought to the attention of the study advisor, it was proposed to modify the research protocol by using indexed abutments, but the proposal was rejected by the sponsor.

2.1 | Clinical Procedures

Patients received prophylactic antibiotic therapy: 2 g of amoxicillin (or clindamycin 600 mg if allergic to penicillin) 1 h prior to surgery and rinsed for 1 min with chlorhexidine 0.2%. All patients were treated under local anaesthesia using 1% Alfacaina 40 mg/mL with Epinephrine 1:200 000 (Dentsply Sirona Implants). Tooth extractions, when needed, were performed as

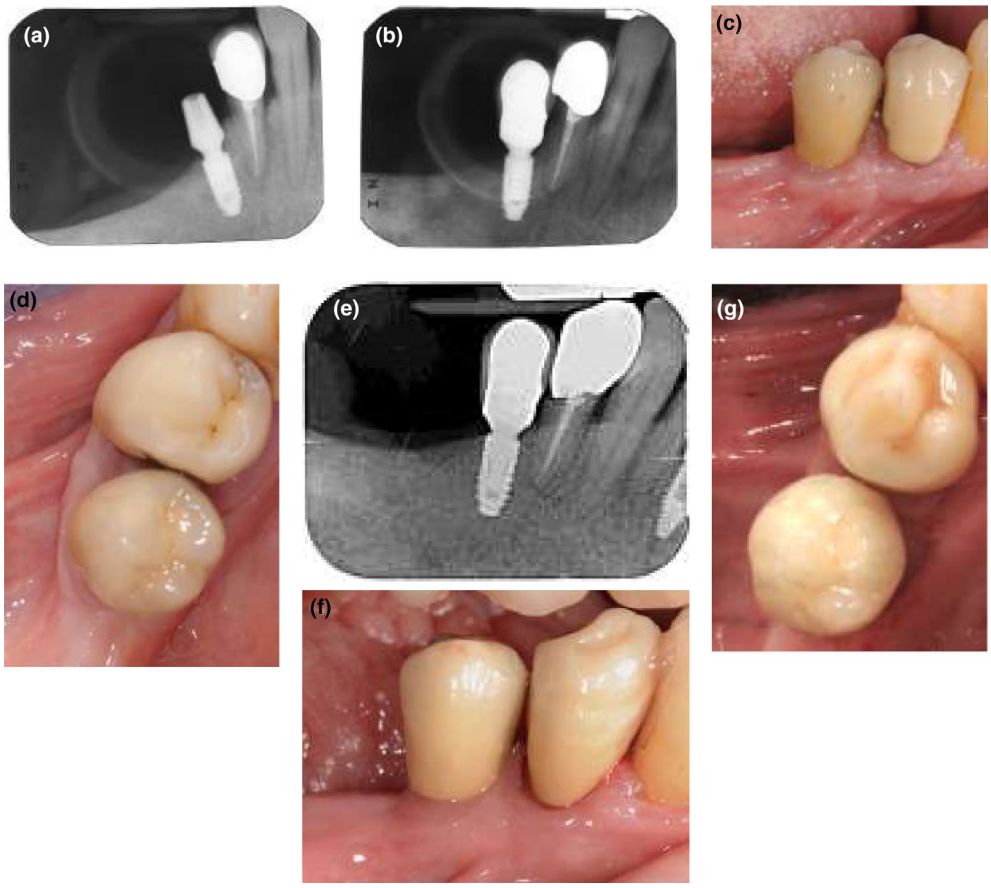

FIGURE 1 | (a–g) Treatment sequence of a patient randomly allocated to the definitive abutment group (Dr Maria Gabriella Grusovin): (a) periapical radiograph at placement of implant in position 45; (b) periapical radiograph, (c) vestibular and (d) occlusal clinical view 4-month after loading at delivery of the definitive crown; (e) periapical radiograph; (f) vestibular and (g) occlusal clinical views at 10-year post-loading. Please note the cuspid abrasion which occurred over 12 years.

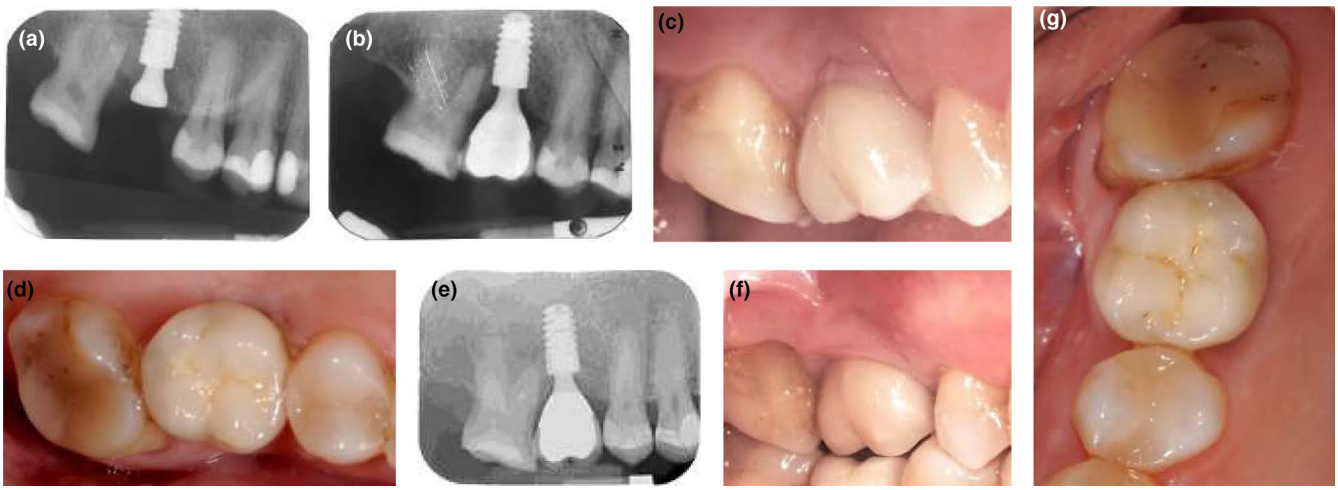

FIGURE 2 | (a–g) Treatment sequence of a patient randomly allocated to the repeated abutment disconnection group (Dr. Maria Gabriella Grusovin): (a) periapical radiograph at placement of implants in position 16; (b) periapical radiograph, (c) vestibular and (d) occlusal clinical view 4-month after loading at delivery of the definitive crown; (e) periapical radiograph; (f) vestibular and (g) occlusal clinical views at 12-year post-loading. Please note the creeping attachment of the vestibular mucosa which occurred at implant 16 over 12 years.

atraumatically as possible in order to preserve the buccal alveolar bone. Extraction sockets were carefully cleaned from any remains of granulation tissue. Flapless implant placement was also allowed and the decision to elevate or not the flap was left to the individual clinician. The standard implant site preparation procedure as recommended by the implant manufacturer was used. In brief, the round bur or lance drill was used to prepare the cortical entrance, followed by the drills of increasing

diameters. Bone quality was subjectively recorded as hard, medium, or soft. Tapping was done only in the presence of hard bone. Implants were placed 1 mm subcrestally to the palatal wall. The insertion torque was assessed manually using the Ankylos ratchet. Implants not achieving an insertion torque of at least 35 Ncm or placed at angles that did not allow the use of standard straight or angulated Ankylos titanium abutments were not included in the study. Implants that were not properly seated using a manual force of 35 Ncm were removed, and the site was tapped. In the case of post-extractive implants having a buccal wall loss of up to 3 mm when compared to the palatal wall and in the presence of an implant-bone gap, a bone substitute (Symbios Algipore, Dentsply Sirona Implants) could be used to fill the gap. After implants were placed, the sealed envelope containing the group allocation code was opened, and the surgeon knew whether to place definitive abutment(s) that were not removed or to place transmucosal healing abutment(s) to be removed at least three times. Flaps were repositioned and sutured around the abutments. Healing abutments had their coronal portion at the level of the soft tissues or 1 mm above the soft tissues. Fixed full acrylic non-occluding provisional prostheses were prepared and connected on the definitive abutments of the definitive abutment group within 24 h. The immediate provisional prostheses were not in contact, either in static occlusion or during movements with the opposite dentition (non-occluding loading). Just after implant placement, periapical radiographs (baseline) were made with the paralleling technique. The amount of keratinised mucosa was measured at buccal sites of each implant. Four hundred milligrams of ibuprofen were prescribed to be taken two to four times a day during meals, as long as required. Patients were instructed to use 0.2% chlorhexidine mouthwash for 1 min, twice a day for 2 weeks, and to avoid brushing and trauma on the surgical sites. Postoperative amoxicillin 1 g twice a day for 6 days was prescribed to patients treated with a bone substitute or in case of a long and complicated surgery. Patients allergic to penicillin were prescribed Clindamycin 300 mg twice a day for 6 days. Within 1 week, all patients were recalled and checked.

Implants of the repeated abutment disconnection group were left to heal unloaded for 3 months. During the healing period, operators were allowed to use different types of provisional dentures or prostheses. Possible options were no use of provisional prosthesis; removable provisional prostheses not pressing on soft tissues, or provisional prostheses fixed to the adjacent dentition. At the end of the healing period, the healing abutments were removed, the copy transfer inserted, impressions (Aquasil Ultra, Dentsply Sirona Implants) were taken at implant level, and the healing abutments were repositioned. The stability of individual implants was also tested by applying a 20 Ncm rotational force.

Healing abutments were removed three times as described below:

1. When taking the impression at the implant level.
2. When testing the fit of the metal core for single crowns or the titanium framework for fixed prostheses, the healing abutments were placed back after checking the suitability of the prosthetic components.
3. During the delivery of the definitive metal-ceramic prostheses, the stability of individual implants was checked again by applying a 20 Ncm rotational force.

After 3 months with provisional prostheses, the stability of individual implants of the definitive abutment group was tested by applying a 20 Ncm rotational force, and an impression at abutment level was taken using Aquasil Ultra without removing the definitive abutments. Within 1 month after the definitive impression, implants of both groups were tested for stability by applying a 20 Ncm torque force, retrievable metal-ceramic prostheses were delivered (with the exception of crowns) and intraoral radiographs of the study implants were taken. Patients were enrolled in an oral hygiene program, with recall visits planned at least every 6 months for the entire duration of the study.

2.2 | Outcome Measures

This study tested the null hypothesis that there were no differences in the clinical outcomes between immediately placing definitive abutments supporting non-occluding provisional restorations versus connecting healing abutments that were disconnected three times before definitive prosthesis delivery and loaded after 3 months, against the alternative hypothesis of a difference. Primary outcome measures were:

Prosthesis failure: Whether it was not possible to place the prosthesis due to implant failures or secondary to implant losses, or replacement of a prosthesis for any reasons.

Implant failure: Implant failure was defined as implant mobility and/or any infection dictating implant removal or any mechanical failure rendering the implant unusable, such as implant fracture or deformation of the implant-abutment connection. The stability of each implant was measured manually by tightening the abutment screw at delivery of the definitive prostheses. One, 3, 5, and 12 years after loading, partial prostheses were removed to assess implant stability, whereas single crowns were rocked with the metallic handles of two dental instruments.

Any complication and adverse event was recorded and reported with the exception of the crown misfits determined by the use of non-indexed abutments, which were accounted as prosthetic failures when the crown had to be remade. These were assessed and treated by the operators.

Secondary outcome measures were:

Buccal peri-implant tissue recessions were assessed by a blinded outcome assessor (Dr. Sbricoli) on plaster models created from alginate impressions taken at delivery of the definitive prostheses (baseline) and 1, 3, 5, and 12 years after initial loading. Measurements were done vestibularly from an occlusal reference point perpendicular to the marginal gingiva. For incisors, the reference point was the middle of the incisal margin; for canines and premolars, it was the tip of the cuspid; and for molars, the deepest occlusal vestibular margin between the two

cusps. Values were averaged at the patient level and then at the group level.

Aesthetic evaluation of the vestibular and occlusal clinical pictures, including the two adjacent teeth at 4 months, 1, 3, 5, and 12 years after loading (Figures 1c,d,f,g and 2c,d,f,g), and performed on a computer screen. The aesthetic evaluation was carried out by a blinded outcome assessor (Dr. Sbricoli) using the pink esthetic score (PES) [15]. 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 was assessed at definitive prostheses delivery, and at 1, 3, 5, and 12 years after initial loading by the independent outcome assessors at each centre who asked patients the following questions:

1. Are you satisfied with the function of your implant supported prosthesis? Possible answers: 'yes absolutely', 'yes partly', 'not sure', 'not really', 'absolutely not'.
2. Are you satisfied with the aesthetic outcome of your implant supported prosthesis? Possible answers: 'yes absolutely', 'yes partly', 'not sure', 'not really', 'absolutely not'.
3. Would you undergo the same therapy again? Possible answers: 'yes' or 'no'. Patients comments were also recorded.

Peri-implant marginal bone level changes were assessed on periapical radiographs taken with the paralleling technique at implant placement (Figures 1a and 2a), 4 months after loading (Figures 1b and 2b), at delivery of definitive prostheses, at 1, 3, 5, and 12 (Figures 1e and 2e) years after initial loading. In the case of unreadable radiographs, new radiographs were made. A blind outcome assessor (Dr. Sbricoli) scanned the non-digital radiographs in TIFF format with a 600 dpi resolution and stored the radiograph files in a personal computer. The blind assessor measured the peri-implant marginal bone levels using the Scion Image (Scion Corporation, Frederick, MD, USA) software. The software was calibrated for every single image using the known distance of two consecutive threads. 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. Implants with bone up to the coronal margin of the implant collar were given a value of zero. Mesial and distal measurements of each implant were averaged, and a mean calculated at patient level and then at group level.

The height of the keratinised mucosa was measured with a periodontal probe rounded off to 0.5 mm in the middle of the buccal side of each study implant at loading of definitive prostheses, at 1, 3, 5, and 12 years after initial loading by the local blind outcome assessors.

At each centre there was a local blind outcome assessor who recorded implant stability, height of the keratinised mucosa, and patient satisfaction. The local assessors were not calibrated.

2.3 | Methodological Aspects

2.3.1 | Sample Size Calculation

The sample size was calculated for the radiographic peri-implant marginal bone level changes. A sample size of 55 in each group had 90% power to detect a difference in means of peri-implant marginal bone level changes of 0.300 mm, assuming that the common standard deviation is 0.480, using a two-group *t*-test with a 0.05 two-sided significance level. For $n = 40$ patients in each group, the power is still at 78.8%. We planned to recruit 60 patients per arm, but unfortunately only data from 40 patients per arm were initially available since two centres did not contribute any data.

2.3.2 | Randomisation and Allocation Concealment Procedures

Six 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 random list stored in a password protected portable computer. The random codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Only after the implants were placed, the envelope corresponding to the patient recruitment number was to be opened and the clinician knew whether to place a definitive or a healing abutment. Therefore, treatment allocation was concealed from the investigators in charge of enrolling and treating the patients.

2.3.3 | Data Analyses

All data analysis was carried out according to a pre-established analysis plan and was made at the patient's level otherwise specified. A biostatistician (Dr. Neumann) with expertise in dentistry and a dentist (Dr. Buti) with expertise in statistics analysed the data up to 5-year. Thereafter, analyses were made by a dental student (Riccardo Visconti), specifically trained in statistics, who analysed the data without knowing group allocation. Differences in the proportion of patients with prosthesis failure, implant failures, and complications (dichotomous outcomes), as well as patient satisfaction were compared using the Chi-square test or Fisher's exact test (for small cell sizes with expected values less than 5), where appropriate. The differences between the two study groups for mean PES scores, peri-implant radiographic marginal bone level changes, buccal recessions, and the amount of keratinised mucosa were compared using the *t*-test.

The differences between the different study centres were compared using ANOVA for metrical variables and a chi-square test for count data. Changes in bone levels in both groups were tested by *t*-tests for paired samples. Mean buccal recession and peri-implant bone loss at 12-year post-loading for implants with buccal keratinised mucosa height less than and more than 2 mm were compared using mixed effects models (with implants clustered within patients) where baseline values were the covariate and the keratinised mucosa was the factor.

The level of significance was $\alpha = 0.05$. The statistical analyses were carried out using IBM SPSS Statistics Version 25 until the 5-year report, while for the 12-year report, R version 4.4.2 was used instead.

During the revision phase of this manuscript and upon reviewers' request, further post hoc analyses of 12-year data were conducted using the implant as the unit of analysis and accounting for the hierarchical data structure. Between-group differences for mean buccal recession, peri-implant bone loss, and total PES scores at 12-year post-loading were estimated using mixed effects models (with implants clustered within patients and patients within centres), accounting for baseline values as covariates and including treatment group as the factor. Analysis of binary outcomes (implant failures) was not conducted at the implant level due to rare events (only 5 total failures) and model instability/convergence issues of complex hierarchical structure. JMP Pro (Version 18.0.2) software was used for the above additional analyses.

3 | Results

Three of the six centres had to be excluded from the study: one because it never treated any patient; another because it supplied incomplete data without any evidence in the case report forms that the planned abutment removal procedures were ever implemented; and the third centre because it refused to continue to participate in the study after the fifth year of follow-up. The three remaining centres treated 20 patients each (in total 60 patients) with 104 implants supporting 25 single crowns and 35 fixed partial prostheses.

Originally, 121 patients were screened for eligibility by the three centres, but 61 patients were not included in the trial for the following reasons: insufficient bone to place 8.0 × 3.5 mm implants (18 patients); not available for a 10-year follow-up (15 patients); specifically requested an immediate loading procedure (12 patients); in need of a bone augmentation procedure at implant placement with the exception of using a bone substitute in post-extractive sites (eight patients); need to use other implants in addition to implants already placed (four patients); implants placed with a torque inferior to 35 Ncm (two patients); insufficient oral hygiene (one patient); not possible to perform immediate non-occlusal loading (one patient).

All patients had their sites treated according to the allocated interventions. No implant was placed flapless, or in an immediate post-extractive alveolus; therefore, no socket was grafted with a bone substitute.

3.1 | Drop-Outs

Thirteen patients dropped out at the 12-year follow-up. Six patients from the definitive abutment group: one patient died of a heart attack just before the 1-year follow-up (Dr. Luongo); one patient died of cancer 2 years after loading (Dr. Bressan); one patient died of cancer between Years 3 and 5 of follow-up (Dr. Bressan); one patient moved to another town after the 4th-year follow-up (Dr. Grusovin); one patient became ill and was unable to come; last seen at the 5-year follow-up (Dr. Grusovin); one patient moved to another town after the 6th-year follow-up (Dr. Grusovin).

Seven patients from the repeated disconnection group: one patient moved to another town and was seen last time at the 2-year follow-up (Dr. Bressan); one very old female patient with walking problems was unable to attend and was seen last time at the 3-year follow-up (Dr. Luongo); one patient moved to another town and was seen last time at the 3-year follow-up (Dr. Grusovin); one patient died of a heart attack between years 3 and 5 of follow-up (Dr. Grusovin); one patient died for unknown reasons between years 3 and 5 of follow-up (Dr. Luongo); unable to contact one patient, last seen at the 6-year follow-up (Dr. Grusovin); one patient died, last seen at the 7-year follow-up (Dr. Grusovin).

3.2 | Protocol Deviations

Protocol deviations and reasons for missing data are explained in a previous paper [13]. Additional protocol deviations occurring after the 5-year follow-up were: the planned 7- and 10-year data collection and publications were not implemented. One patient of the definitive abutment group (Dr. Grusovin) withdrew consent to take clinical pictures of her prosthesis.

3.3 | Main Results

Patients were recruited and implants were inserted from April 2010 to September 2012. The follow-up for all patients was 12 years post-loading.

The main baseline patient and intervention characteristics, divided by study group, are presented in Table 1. There were no apparent significant baseline imbalances between the two groups.

Prosthesis failures: No patient of the definitive abutment group had a prosthesis failure versus four patients of the repeated disconnection group. The difference was statistically significant (difference = 17.39%; 95% CI: 1.9 to 32.9; $p = 0.049$; Fisher's exact test). More specifically, one definitive crown had to be remade because it fractured 6 months after its delivery (Dr. Bressan). Another definitive prosthesis had to be remade because one of its three supporting implants fractured after almost 3 years in function (Dr. Bressan). Another partial prosthesis supported by three implants failed 3 years and 4 months after loading (Dr. Bressan) because of the fracture of implants in position 45. At the 5-year follow-up, also an implant in position 46 was lost for peri-implantitis. Finally, another prosthesis (Dr. Bressan) was lost because peri-implantitis affected both the supporting implants in position 42 and 32 about 4 years after loading.

Implant failures: No patients of the definitive abutment group lost any implant versus three patients of the repeated disconnection group who lost five implants. There were no differences for patients experiencing implant failures between the two groups (difference = 13.04%; 95% CI: −6.7 to 26.8; $p = 0.109$; Fisher's exact test). More specifically:

TABLE 1 | Patient and intervention characteristics.

	Definitive abutment group $n = 30$	Abutment disconnection group $n = 30$
Females	17 (56.67%)	19 (63.33%)
Mean age at implant insertion (SD; range)	57.2 (13.2; 30–81)	60.2 (12.8; 38–85)
Smoking up to 10 cigarettes/day	5 (16.67%)	8 (26.67%)
Smoking more than 10 cigarettes/day	2 (6.67%)	1 (3.33%)
Implants in upper jaws	16/47 (34.04%)	28/57 (49.12%)
Implants in lower jaws	31/47 (65.96%)	29/57 (50.88%)
Implants in incisor position	9/47 (19.15%)	6/57 (10.53%)
Implants in canine position	1/47 (2.13%)	4/57 (7.02%)
Implants in premolar position	18/47 (38.3%)	23/57 (40.35%)
Implants in molar position	19/47 (40.43%)	24/57 (42.11%)
Implants in hard bone	11/47 (23.4%)	10/57 (17.54%)
Implants in medium bone	25/47 (53.19%)	33/57 (57.89%)
Implants in soft bone	11/47 (23.4%)	14/57 (24.56%)
Site previously augmented with bone substitute	0 (0%)	0 (0%)
Implants with 3.5 mm diameter	33/47 (70.21%)	46/57 (80.7%)
Implants with 4.5 mm diameter	14/47 (29.79%)	11/57 (19.3%)
Implants with 5.5 mm diameter	0 (0%)	0 (0%)
Implants 8 mm long	17/47 (36.17%)	27/57 (47.37%)
Implants 9.5 mm long	21/47 (44.68%)	20/57 (35.09%)
Implants 11 mm long	8/47 (17.02%)	8/57 (14.04%)
Implants 14 mm long	1/47 (2.13%)	2/57 (3.51%)
Implants inserted flapless	0 (0%)	0 (0%)
Post-extractive implants	0 (0%)	0 (0%)
Implants in simultaneously augmented sites	0 (0%)	0 (0%)
Single crowns	16 (53%)	9 (30%)
Prostheses supported by 2 to 3 implants	14 (47%)	21 (70%)

1. One implant in position 25 supporting a fixed partial prosthesis together with two other implants fractured after almost 3 years in function (Dr. Bressan). It was replaced by an implant in position 24, and a new prosthesis was made. The same implant was previously affected by multiple complications, including prosthesis debonding, which may be indicative of an overload aetiology.
2. One patient had the implant in position 45 that fractured at 3 years and 4 months after loading (Dr. Bressan). A new implant was placed in position 42 to stabilise the prosthesis. At 5 years after loading also the other implant in position 46 was lost for peri-implantitis.
3. One patient had the implant in position 42 affected by peri-implantitis at 3 years and 5 months after loading (Dr. Bressan). The second implant in position 32 was also affected by peri-implantitis at 3 years and 8 months after loading. Despite the attempted treatments, both implants failed and the patient was rehabilitated with a removable prosthesis.

Complications: four patients from the definitive abutment group versus seven patients from the repeated disconnection group were affected by complications (difference = 13.77%; 95% CI: −37.8 to 10.2; $p = 0.318$; Fisher's exact test), the difference being not statistically significant.

The following patients of the definitive abutment group had complications:

1. A definitive partial fixed prosthesis supported by implants in position 24 and 25 bonded with a provisional cement (TempBond, Kerr, Orange, CA, USA), de-bonded after 6 months (Dr. Bressan). It was bonded again with Harvard permanent cement.
2. A definitive prosthesis supported by implants in position 25 and 26 debonded 1 year and 10 months after delivery (Dr. Bressan). It was recemented with Harvard (Harvard Dental International, Hoppegarten, Germany).
3. A fracture of the porcelain was observed at a crown in position 47, 3 years and 1 week after loading (Dr. Grusovin). It was polished chairside.
4. Crown loosening at implant in position 36 at 4 years and 2 months (Dr. Grusovin), re-cemented again with temporary cement.
5. No number here and then please correct numbering below Complications at the repeated disconnection abutment group included:
6. A palatal wound dehiscence on implant 23 healed spontaneously (Dr. Bressan). The same patient had his provisionally cemented definitive prosthesis debonded 1 week after its delivery. It was bonded again with Harvard definitive cement and developed peri-implantitis at implant 25, 22 months after loading, which was surgically treated the following month with open flap debridement and anorganic bovine bone with added collagen. Finally, the implant fractured at the 3-year follow-up.

7. One definitive crown fractured 6 months after its delivery (Dr. Bressan) and was replaced by a new crown.
8. A fistula, which was present at definitive crown placement (Dr. Grusovin), disappeared within 1 week after disconnecting and cleaning the definitive abutment. In the same patient, the definitive abutment unscrewed 1 week after delivery and was re-screwed in place, and again the crown debonded 35 months after loading and was cemented with temporary cement.
9. Peri-implantitis was observed at 42 at 3 years and 5 months from loading and at 32 at 3 years and 8 months after loading (Dr. Bressan). Both implants were treated with scaling but failed, and a removable prosthesis was delivered.
10. Peri-implantitis was observed at 46 5 years after loading (Dr. Bressan). Implant failed.
11. Fracture of the resin prosthesis lining on 24–25 noticed at the 5-year follow-up (Dr. Grusovin). Repaired chairside.
12. A partial fixed prosthesis debonded at 5 years and 4 months from loading (Dr. Bressan) and was re-cemented with Harvard definitive cement.

PES (Table 2): 12 years after loading, the average PES score was 10.84 ± 1.95 for the definitive abutment group and 10.31 ± 2.57 for the repeated abutment changes group, the difference being not statistically significantly different (difference = −0.53; 95% CI: −1.14 to 2.20; $p = 0.505$, Table 2). When evaluating single aesthetic domains, no statistically significant difference was observed either.

Buccal recession (Table 3): Buccal recessions at 12-year post-loading amounted to 0.30 ± 0.98 mm for the definitive abutment group and 0.15 ± 0.54 mm for the repeated abutment changes group, with no statistically significant differences between the two groups (difference = −0.14; 95% CI: −0.69 to 0.41; $p = 0.592$).

Patient satisfaction: 12 years after loading, all patients were fully satisfied with both function and aesthetics of their implant-supported prostheses and would undergo the same procedure again if necessary.

Marginal bone level changes (Tables 4 and 5): At implant placement, there was a difference between the two groups of 0.08 mm, though not statistically significant; bone levels were 0.12 mm for the repeated abutment changes group and 0.40 mm for the definitive abutment group. Also, at 12 years, the difference was not statistically significant (mean difference = 0.46 mm; 95% CI: −0.19 to 1.10; $p = 0.152$, Table 4). At 12 years, both groups gradually lost statistically significant marginal peri-implant bone: 0.25 mm ($p = 0.036$) for definitive abutment and 0.70 mm ($p = 0.017$) for the repeated abutment changes group (Table 5), the difference between groups being not statistically significant (difference = 0.45; 95% CI: −0.16 to 1.05; $p = 0.135$).

Keratinised mucosa: The mean buccal keratinised mucosa at delivery of definitive prostheses (4 months after loading)

TABLE 2 | PES scores at 12 years after loading by groups and by different aesthetic domains; standard deviation is in parenthesis.

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Definitive abutment group ($N = 19$)	1.37 (0.50)	1.16 (0.60)	1.63 (0.50)	1.68 (0.58)	1.47 (0.61)	1.79 (0.42)	1.74 (0.45)	10.84 (1.95)
Abutment disconnection group ($N = 16$)	1.13 (0.62)	1.19 (0.66)	1.69 (0.48)	1.50 (0.52)	1.56 (0.51)	1.69 (0.48)	1.56 (0.51)	10.31 (2.57)
Difference	−0.24	0.03	0.06	−0.18	0.09	−0.10	−0.17	−0.53
p	0.215	0.891	0.737	0.329	0.643	0.511	0.299	0.505

TABLE 3 | Mean soft tissue buccal recessions in mm between groups and time periods.

	1-year after loading			3-year after loading			5-year after loading			12-year after loading		
	N	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**
Definitive abutment group	26	−0.11 (0.32)	−0.24 to 0.02	25	0.07 (0.68)	−0.21 to 0.36	23	0.14 (0.70)	−0.16 to 0.45	20	0.30 (0.98)	−0.16 to 0.75
Abutment disconnection group	30	−0.11 (0.58)	−0.33 to 0.11	28	0.01 (1.19)	−0.45 to 0.47	21	−0.09 (1.31)	−0.68 to 0.51	16	0.15 (0.54)	−0.13 to 0.44
Difference		0.00 (SE = 0.12)	−0.26 to 0.25		−0.06 (SE = 0.26)	−0.61 to 0.48		−0.23 (SE = 0.32)	−0.90 to 0.44		−0.14 (SE = 0.26)	−0.69 to 0.41
p		0.986			0.818			0.477			0.592	

TABLE 4 | Mean radiographic peri-implant marginal bone levels in mm between groups and time periods.

	Implant placement			4-month after loading			1-year after loading			3-year after loading			5-year after loading			12-year after loading		
	N	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**	***N***	**Mean (SD)**	**95% CI**
Definitive abutment group	30	0.40 (0.12)	0.00 to 0.09	30	0.13 (0.21)	0.05 to 0.20	29	0.11 (0.22)	0.03 to 0.20	27	0.13 (0.21)	0.05 to 0.21	26	0.19 (0.32)	0.06 to 0.32	19	0.32 (0.47)	0.09 to 0.54
Abutment disconnection group	30	0.12 (0.20)	0.05 to 0.20	30	0.22 (0.31)	0.11 to 0.34	30	0.40 (0.59)	0.17 to 0.61	29	0.68 (1.11)	0.26 to 1.10	21	0.63 (0.89)	0.23 to 1.03	16	0.77 (1.14)	0.17 to 1.38
Difference		0.08 (SE = 0.04)	0.00 to 0.17		0.10 (SE = 0.07)	−0.04 to 0.24		0.28 (SE = 0.11)	0.04 to 0.51		0.55 (SE = 0.21)	0.12 to 0.98		0.44 (SE = 0.20)	0.02 to 0.87		0.46 (SE = 0.30)	−0.19 to 1.10
p		0.062			0.167			0.022*			0.014*			0.041*			0.152	

*Statistically significant difference.

TABLE 5 | Mean radiographic peri-implant marginal bone level changes in mm between groups and time periods.

	Difference placement—4-month			Difference placement—1-year			Difference placement—3-year			Difference placement—5-year			Difference placement—12-year	
	N	Mean (SD)	95% CI	*N*	Mean (SD)	95% CI	*N*	Mean (SD)	95% CI	*N*	Mean (SD)	95% CI	*N*	Mean (SD)	95% CI
Definitive abutment group	30	0.09 (0.16)	0.03 to 0.15	29	0.07 (0.13)	0.02 to 0.12	27	0.09 (0.19)	0.01 to 0.17	26	0.14 (0.33)	0.00 to 0.27	19	0.25 (0.49)	0.02 to 0.49
Abutment disconnection group	30	0.10 (0.21)	0.02 to 0.18	30	0.27 (0.55)	0.06 to 0.48	29	0.56 (1.01)	0.17 to 0.94	21	0.56 (0.81)	0.19 to 0.93	16	0.70 (1.04)	0.14 to 1.25
Difference		0.01 (SE = 0.05)	−0.09 to 0.11		0.20 (SE = 0.10)	−0.01 to 0.41		0.47 (SE = 0.19)	0.07 to 0.86		0.42 (SE = 0.19)	0.03 to 0.82		0.45 (SE = 0.28)	−0.16 to 1.05
p		0.786			0.067			0.023*			0.037*			0.135	

*Statistically significant difference.

was 2.89 ± 1.34 mm at the definitive abutment group and 3.13 ± 1.86 mm at the abutment disconnection group. Twelve years after loading, it was 2.56 ± 1.75 mm at the definitive abutment group and 2.77 ± 2.07 mm at the abutment disconnection group. There were no statistically significant differences in mean buccal keratinised mucosa heights at 12-year post-loading (difference = 0.21 mm; 95% CI: −1.06 to 1.49; $p = 0.746$).

Mixed model analysis could not find any association at implant level between less than 2 mm of keratinised mucosa height at delivery of definitive prostheses (4 months after loading) with peri-implant marginal bone loss (difference (< 2–≥ 2 mm) = 0.20; 95% CI: −0.06 to 0.33; $p = 0.268$, Table 6a) and buccal recession (difference (< 2–≥ 2 mm) = 0.10; 95% CI: −0.05 to 0.24; $p = 0.203$, Table 6b) at 12 years after loading. In the definitive abutment group, the height of Keratinised mucosa at loading was < 2 mm for 7 out of 30 patients (23.3%, 95% CI: 10.6 to 42.7). In the repeated abutment changes group, the height of Keratinised mucosa at loading was < 2 mm for 13 out of 30 patients (43.3%, 95% CI: 26.0 to 62.3). The difference was not significant (difference = −20%; 95% CI: −43.3 to 3.3; $p = 0.171$).

The *comparison between the three centres* at 12 years after loading is presented in Table 7. There were statistically significant differences between centres in the number of patients with remade/failed prostheses ($p = 0.021$), patients experiencing complications ($p = 0.014$), peri-implant marginal bone loss ($p = 0.001$) and buccal recessions ($p = 0.002$) between centres. There were no statistically significant differences between centres for patients with failed implants ($p = 0.059$), keratinised mucosa height ($p = 0.110$), and PES ($p = 0.115$).

Post hoc mixed model analyses could not detect any statistically significant differences between groups at the implant level for peri-implant marginal bone loss (difference = 0.46; 95% CI: −0.03 to 0.95; $p = 0.064$, Table 8a), buccal recession (difference = −0.08; 95% CI: −0.66 to 0.49; $p = 0.766$, Table 8b) and total PES score (difference = −0.89; 95% CI: −2.40 to 0.61; $p = 0.234$, Table 8c) at 12 years after loading.

4 | Discussion

The study was designed to evaluate whether a non-abutment removal approach including immediate non-occluding loading could play a clinically significant role in maintaining bone levels compared to repeated abutment disconnection and conventional loading. At 12 years post-loading, significantly more prostheses failed in the repeated abutment changed group. This observation is even more impressive considering that the number of patients evaluated in the present report was reduced both by the naturally occurring drop-outs plus by the unfortunate withdrawal of one of the centres that provided data up to 5 years after loading. In addition, there were also tendencies to have more implant failures and peri-implant bone loss in the repeated disconnection group. This seems to indicate a worse performance of those implants subjected to repeated disconnection that should definitively be explored

TABLE 6A | Mixed model for marginal bone loss (MBL) at 12 years after loading.

Fixed effects parameter estimates								
				95% confidence interval				
Names	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**df**	***t***	***p***
(Intercept)	(Intercept)	0.94	0.25	0.45	1.43	32	3.75	0.001
MBL Bas	MBL Bas	2.18	0.80	0.61	3.76	32	2.72	0.011
KT loading ≥ 2 mm (1 = yes)1	1–0	0.20	0.07	−0.06	0.33	30	2.92	0.269

TABLE 6B | Mixed model for recession changes at 12 years after loading.

Fixed effects parameter estimates								
				95% confidence interval				
Names	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**df**	***t***	***p***
(Intercept)	(Intercept)	0.47	0.65	−0.81	1.75	32	0.71	0.480
KT loading ≥ 2 mm (1 = yes)1	1–0	0.10	0.07	−0.05	0.24	32	1.30	0.203
Rec baseline	Rec baseline	1.05	0.07	0.91	1.20	32	14.08	< 0.001

TABLE 7 | Comparison between different centres at 12-year post-loading.

	Luongo (*n* = 17)	**Bressan (*n* = 17)**	**Grusovin (*n* = 13)**	***p***
Patients with remade/failed prostheses	0 (0%)	4 (23.5%)	0 (0%)	0.021*
Patients with implant failures	0 (0%)	3 (17.7%)	0 (0%)	0.059
Patients with complications	0 (0%)	7 (41.1%)	4 (30.8%)	0.014*
Pink esthetic score (PES)	10.11 (2.15)	9.92 (1.89)	11.61 (2.40)	0.115
Buccal recession in mm[a]	0.11 (0.42)	0.80 (0.91)	−0.21 (0.58)	0.002*
Patient functional satisfaction (very satisfied/satisfied)	100%	100%	100%	Not available
Patient aesthetic satisfaction (very satisfied/satisfied)	100%	100%	100%	Not available
Patients willing to redo the therapy	100%	100%	100%	Not available
Bone loss in mm	1.26 (1.07)	0.15 (0.43)	0.21 (0.50)	0.001*
Keratinised mucosa height in mm	1.61 (0.49)	3.31 (2.33)	2.71 (1.77)	0.110

[a]Positive values correspond to a decrease of recession.
*Statistically significant differences.

TABLE 8A | Mixed model for marginal bone loss (MBL) at 12 years after loading for between-group differences.

Fixed effects parameter estimates								
				95% confidence interval				
Names	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**df**	***t***	***p***
(Intercept)	(Intercept)	0.11	0.16	−0.22	0.44	21	0.69	0.500
MBL Bas	MBL Bas	2.89	0.39	2.10	3.69	37	7.39	< 0.001
Group 1 (abutment disconnection)	1–0	0.46	0.24	−0.03	0.95	27	1.93	0.064

TABLE 8B | Mixed model for recession changes at 12 years after loading for between-group differences.

Fixed effects parameter estimates								
				95% Confidence Interval				
Names	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**df**	***t***	***p***
(Intercept)	(Intercept)	1.01	0.07	0.87	1.16	25	14.34	< 0.001
Rec baseline	Rec baseline	0.18	0.60	−1.05	1.41	30	0.29	0.770
Group 1 (abutment disconnection)	1–0	−0.08	0.28	−0.66	0.49	32	−0.30	0.766

TABLE 8C | Mixed model for total PES score at 12 years after loading for between-group differences.

Fixed effects parameter estimates								
				95% confidence interval				
Names	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**df**	***t***	***p***
(Intercept)	(Intercept)	11.96	0.50	10.00	12.12	17	22.05	< 0.001
Group 1 (abutment disconnection)	1–0	−0.89	0.73	−2.40	0.61	26	−1.22	0.234

by additional trials with larger sample sizes or by a well-conducted systematic review.

Another important finding of this trial was that immediate loading procedures did not affect the implant success negatively, which is in agreement with the findings of a Cochrane systematic review [8].

Finally, no increased peri-implant marginal bone loss and buccal recessions were observed at implants with less than 2 mm of keratinised mucosa height. This observation is in agreement with the findings of another study [16], in which no statistically significant association was found between the presence of peri-implant keratinised mucosa at the time of delivery of the definitive prosthesis and changes in bone levels and bleeding on probing after 5 years. More specifically, in the other study [16], when keratinised mucosa height was analysed as a dichotomous variable (present or absent), implants with the presence of keratinised mucosa at the delivery of the definitive prosthesis at both vestibular and lingual aspects showed a trend to less bleeding on probing (estimate = −0.8%; 95% CI [−1.69; 0.08]; $p = 0.0741$) but a statistically significant greater MBL loss compared to implants where keratinised mucosa was only present at one site (estimate = 0.18 mm; 95% CI [−0.1; 0.3]; $p = 0.0041$). It was concluded that while the height of the keratinised mucosa did not seem to alter the clinical outcomes, its presence both at vestibular and lingual sites was associated with an increased marginal bone loss when compared to implants having at least one side without keratinised mucosa. Both observations from the present and the other similar study [16] appear in contradiction with what is generally believed and reinforce once more the need and urgency to properly study the actual role of the keratinised mucosa on long-term soft-tissue health. Therefore, trials should be conducted to evaluate the actual effectiveness of soft tissue augmentation procedures to prophylactically increase the keratinised mucosa in order to decrease possible future bone loss and soft tissue recessions.

Our results are in partial agreement with another controlled but non-randomised study in which the same implant, but not indexed, was used [4]. No statistically significant difference in marginal bone loss was found 3 years after implant placement at implants placed in posterior mandibles. Another small RCT including only 16 patients [7] was unable to disclose any statistically significant difference, but this could be due to the small sample size. Other RCTs using different implant systems reported statistically significant differences of 0.2 [3], 0.3 [5, 6] and 0.5 [5, 6] mm in favour of those implants whose abutments were not disconnected. From a clinical point of view, differences in bone loss ranging from 0.2 to 0.5 mm may not have a clinically noticeable impact, but when a difference in failures of prosthesis is observed, even if after 12 years, maybe that clinicians should be more careful in handling repeated abutment disconnections. Therefore, the empiric rule that the less you manipulate the abutments, the better could be for the maintenance of the implant supporting tissues appears valid.

Post hoc mixed model analyses could not detect any statistically significant differences between groups confirming results from patient-level analysis for peri-implant marginal bone loss, buccal recession and total PES score at 12 years after loading. Post hoc in Latin means 'after this'. A post hoc analysis refers to a statistical analysis specified after a study has been concluded and the data collected. These analyses are not part of the original study protocol. A major concern with post hoc analyses is the increased risk of false positive results, as multiple tests are conducted without the appropriate safeguards. While post

hoc analyses can reveal new insights and generate hypotheses for future research, they should not be presented as definitive findings.

The comparison amongst centres revealed multiple statistically significant differences, and some of them may have clinical consequences. For instance, one centre had more prosthesis failures than the other two centres. Also, differences between centres in peri-implant bone loss may have a clinical impact. While it could be difficult to explain such differences, they may be indicative that these procedures could be sensibly operator-dependent.

The main limitations of the present trial are the small sample size and the use of non-indexed abutments on indexed implants. The problem of using non-indexed abutments on indexed implants was present only if abutments were removed, since it was difficult to reposition them exactly in the same position. In ordinary clinical practice, this problem is easily avoidable by using the correct and dedicated indexed abutments. Another limitation was the invalidation of the allocation concealment procedure by one of the centres, as described in detail in previous publications of this trial [11–13]. Despite verbal and written instructions and explanations on why not to open the envelopes to know the randomisation codes before implant installation, some clinicians still do it. This problem is definitively underestimated since it is difficult to control when sealed envelopes, used to conceal allocation, are actually opened. Therefore, centrally computerised random allocation concealment after patients' data is entered on digital case report forms should be preferred. Finally, in the present study, implants of the two groups were loaded at different time points (immediately and after 3 months), which could be a confounding factor. In a Cochrane systematic review comparing immediate versus conventional loading, it was found that patients with conventionally loaded implants lost 0.1 mm more peri-implant marginal bone than patients subjected to immediate loading procedures [8]. While this difference was found to be statistically significant, from a clinical point of view, such a difference is unnoticeable. However, such a difference could be tentatively explained by the observation that immediately loaded implants usually are subjected to fewer abutment changes. What is unique about this trial is the duration of the follow-up. Many more trials with such long follow-up would be needed in order to have a more precise idea of the actual prognosis of implant-supported rehabilitations.

The present results can be generalised with confidence to those patients in other settings having similar characteristics to those included in the present study.

5 | Conclusion

More prosthesis failures were observed at 12 years after loading at implants that underwent at least three repeated abutment disconnections compared to implants subjected to no abutment disconnection. Immediate non-occlusal loading is a viable alternative to conventional loading. No increased bone loss or buccal recessions were noticed at implants with less than 2 mm of keratinised mucosa compared to those having more than 2 mm of keratinised mucosa.

Ethics Statement

The study was approved on 17 December 2009 by the ethical committee of the University of Naples, Federico II (protocol number 187/09) up to 3 years and then again up to 10 years by the same ethical committee (protocol number 719/19 on 23 May 2019). The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to.

Consent

All patients received thorough explanations and signed a written informed consent form prior to being enrolled in the trial, in order to document that they understood the scope of the study (including procedures, follow-up evaluations, and any potential risks involved), were allowed an opportunity to ask questions pertaining to this study, and were apprised of treatment alternatives. The study was open to qualifying patients with no consideration given to sex or race.

Conflicts of Interest

This trial was partially funded by Dentsply Sirona Implants, the manufacturer of the implants and other products evaluated in this investigation; however, 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, with the exception of rejecting the proposal of changing the protocol after the trial was started, allowing the use of indexed abutments.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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