Int. J. Oral Maxillofac. Surg. 2015; xxx: xxx–xxx
http://dx.doi.org/10.1016/j.ijom.2015.04.002, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Prospective Randomized Study

Early peri-implant bone loss: a prospective cohort study

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M. Cassetta, N. Pranno, S. Calasso, A. Di Mambro, M. Giansanti: Early peri-implant bone loss: a prospective cohort study. Int. J. Oral Maxillofac. Surg. 2015; xxx: xxx–xxx.

Abstract. The aim of this study was to measure the early peri-implant bone level changes before the completion of an implant–abutment connection and to evaluate the influence of demographic, biologically relevant, anatomical, and implant-specific variables on these changes. A prospective cohort study design was used. STROBE guidelines were followed. The sample comprised 493 implants placed using a two-stage surgical procedure. Random allocation was used to determine the implant placement depth. Peri-apical radiographs taken at implant insertion and at the second surgery 2 months later were matched. Kappa statistics were used to compute intra- and inter-examiner reliability. The statistical analysis was performed at the implant level. Two-way analysis of variance (ANOVA) with the Bonferroni adjusted post hoc test was used to evaluate the influence of variables. One-way ANOVA with Tukey's range test and unpaired Student *t*-tests were used to analyze significant variables. Early marginal bone remodelling was −0.86 mm. The timing of implant placement ($P = 0.00$) and the depth of implant placement ($P \leq 0.05$) significantly influenced early bone remodelling. Relevant radiographic early bone loss was found, but implants initially positioned below the alveolar crest and inserted ≥3 months after tooth extraction showed statistically significant higher marginal bone loss during the healing phase.

Key words: early peri-implant bone loss; dental implants; prospective cohort study; early implant placement; delayed implant placement; implant placement depth; radiographic study.

Accepted for publication 7 April 2015

Marginal bone loss around implants appears difficult to avoid, particularly after abutment connection, and minimal or no marginal bone loss following the implant–abutment connection is considered to be an indicator of the long-term success of implant restorations.[1] Understanding the biological rationale for this bone remodelling and the specifics of these changes is of paramount importance in order to predict the stability and the location of the gingival margin.[1] Marginal bone loss originates from a combination of mechanical and biological factors.[2] Factors hypothesized to be associated with marginal bone loss include surgical trauma to the periosteum and bone,[3] the size of the micro-gap between the implant and the abutment,[4] bacterial colonization of the implant sulcus,[5] biological width,[6] and biomechanical factors related to loading.[7] However, with a two-stage implant surgical procedure, marginal bone loss has also been detected during the period between stage I and stage II.[8] Factors involved in this bone loss include surgical complications, a less-than-ideal initial fit between the implant and the surrounding bone, insufficient osseous tissue volume to adequately surround the implant, premature loading with resulting micro-movement of the implant prior to integration, harmful patient habits including tobacco product abuse, and healing impairment resulting from poor overall patient health.[8]

The purpose of this study was to measure any changes in peri-implant marginal bone levels in the interval of time between implant placement and the completion of the implant–abutment connection 2 months later, and to identify variables associated

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with increased rates of early bone remodelling.

It was hypothesized that peri-implant bone loss would already be present before the implant–abutment connection. Furthermore, it was hypothesized that there would be at least one variable associated with increased rates of early implant bone loss that the clinician could modify to improve the outcome.

Materials and methods

Study setting and patient selection

This prospective cohort study was conducted at the Department of Oral and Maxillofacial Sciences of the study institution between February 2008 and February 2013. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for prospective cohort studies were followed. This clinical investigation was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and was undertaken after informing the patient of the content, risks, and benefits of the study; written consent was obtained from each participant. The investigation was reviewed independently and approved by the local ethics committee.

The main inclusion criteria were that the subjects were systemically healthy, aged between 18 and 75 years, and in need of an implant-supported partial fixed dental prosthesis or a single crown. Furthermore, sufficient bone volume was required in the prospective implant region to receive implants with a diameter of at least 3.5 mm and a minimum length of 10 mm. The subjects had a stable occlusal relationship and no severe parafunctional habits, and the implant sites were free of infection and/or tooth remnants.

Exclusion criteria were the abuse of alcohol or drugs and a general health condition contraindicating a surgical procedure, e.g. infectious disease, heart disease or disease of the circulatory system, metabolic disease, bone metabolism disorders, disturbance of the hematopoietic system, haematological disorders, wound healing disturbances, disorders of the endocrine system, and pregnancy. Local contraindications were, for example, tumours and ulcers. In addition, reason to believe that the treatment might have a negative effect on the subject's psychological situation was also considered an exclusion criterion.

Procedures

The areas for implantation were evaluated on orthopanoramic and intraoral peri-apical radiographs. A computed tomography scan was required only in the case of diagnostic doubt. A two-piece pure titanium (grade 4) dental implant with a cylindrical outer contour was used. The chemically modified, sand-blasted/acid-etched titanium surface (SLA), which extended onto the implant shoulder, covered the entire length of the implant (Osseotheread; Impladent, Formia, LT, Italy). This implant was characterized by a cone-Morse connection; the abutments had a smaller diameter than their respective implant platforms (platform switching).

Antibiotic therapy of 1 g of amoxicillin was prescribed 1 h before the intervention and twice a day for the following 5 days. Patients were treated with a local anaesthetic by infiltration with mepivacaine (20 mg/ml) associated with adrenaline 1:100,000. Pain control was managed using ibuprofen. The patients used the analgesic after surgery according to their individual needs. The flap design for the placement of the implants was an envelope full-thickness flap. A distance of at least 2 mm from neighbouring teeth was taken. Each implant had a minimum thickness of 2 mm of bone around it. In no case was a temporary removable prosthesis used, so as to avoid hampering the healing process. All patients were treated with a two-stage implant surgical procedure. Implants were exposed 2 months after insertion, and a healing abutment was screwed on. At the time of suture removal, a temporary acrylic resin restoration was put in place. The final restoration was delivered at the 6-month follow-up.

Assessment of marginal bone

The level of the marginal bone was recorded at the time of the second surgery (T1) by taking a standardized radiograph and matching this to the peri-apical radiograph taken at the time of implant insertion (T0) (Figs. 1 and 2). These peri-apical radiographs were obtained using the long-cone parallel technique and the Rinn XCP film holding system (Rinn XCP; Dentsply Rinn, Elgin, IL, USA). Care was taken to ensure that the alignment of the X-ray film in the film holder was parallel to the long axis of the implants. Digital radiographs were stored using a digital intraoral imaging system (DenOptix QST Digital X-ray Phosphor Plate System; Gendex Dental Systems, Hatfield, PA, USA). The stored images were displayed on a monitor, and direct measurements were performed using the software VixWin PRO (Gendex). Linear measurements from the implant shoulder to the marginal bone level were obtained mesially and distally using the software programme. These measurements were assigned a positive value if the marginal bone level was coronal to the implant shoulder, a value of zero when the

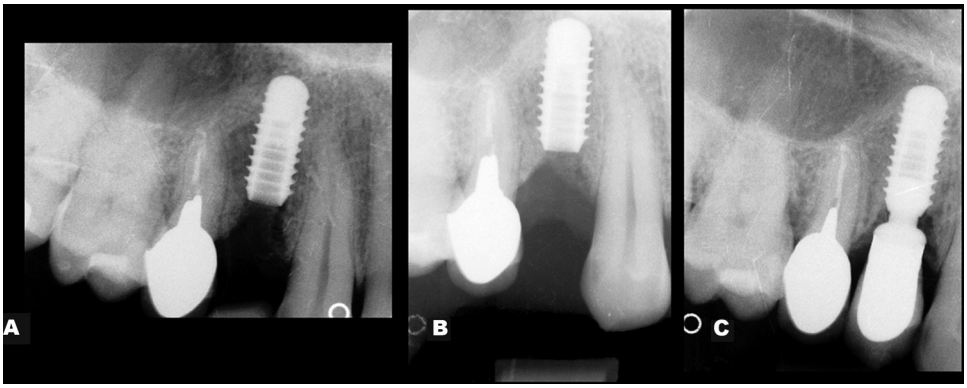

Fig. 1. A single implant, diameter 4.8 mm and length 14 mm, inserted 4 weeks after extraction of the fractured 1.4 (early delayed implant placement). The marginal bone level at the time of implant placement (T0) below the ridge (A), at the 2-month follow-up (T1) (B), and at the time of final prosthesis delivery (6-month follow-up) (C).

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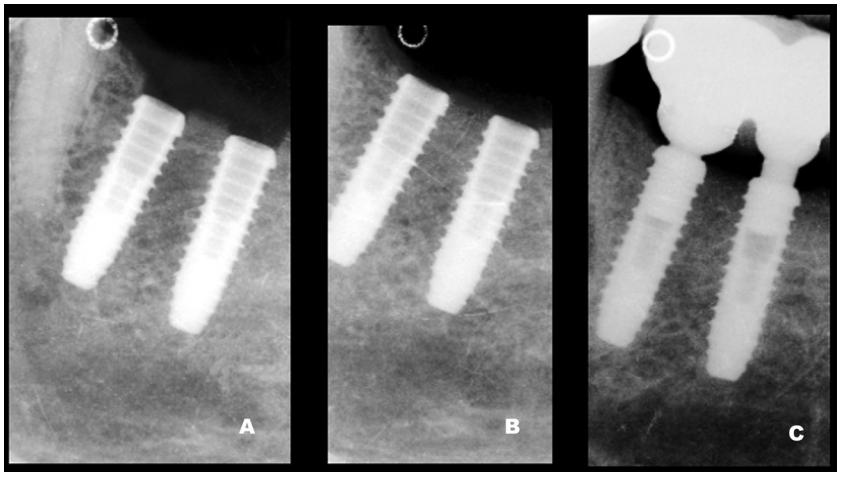

Fig. 2. Two implants, diameter 3.5 mm and length 14 mm, inserted in a healed site (prolonged delayed implant placement). The marginal bone level at the time of implant placement (T0) below the ridge (A), at the 2-month follow-up (T1) (B), and at the time of final prosthesis delivery (C).

marginal bone level was located at the implant shoulder, or a negative value if the marginal bone level was located apical to the implant shoulder (Fig. 3).

The predictor variables, i.e. the clinical exposure factors, correlated with changes in peri-implant bone level, were grouped into the categories outlined below.

Biologically relevant variables

The biologically relevant variables assessed included the following: (1) Gender (male or female). (2) Age: the study population was separated into two groups according to the age at the time of implant placement as $\leq$50 or >50 years. (3) Depth of implant placement: the study population was divided into three groups on the basis of the position of the implant shoulder compared to the alveolar crest level, determined clinically at the time of insertion: supra-crestal implants (with the mesial and/or distal implant shoulder placed above the crest of the alveolar bone), crestal implants (with the mesial and/or distal implant shoulder placed within 0.5 mm or less of the alveolar ridge level), or sub-crestal implants (with the mesial and/or distal implant shoulder placed at least 0.5 mm below the alveolar ridge level). Random allocation to the three groups was performed using Clinstat (Martin Bland, York, UK). (4) Timing of implant placement in relation to tooth extraction: this was classified into two categories: 'early delayed', defined as implant placement within weeks after tooth extraction, and 'prolonged delayed', defined as implant placement $\geq$3 months after tooth extraction. (5) Type of edentulism: absence of a single tooth (mono-edentulism) and absence of more than one tooth (partial edentulism).

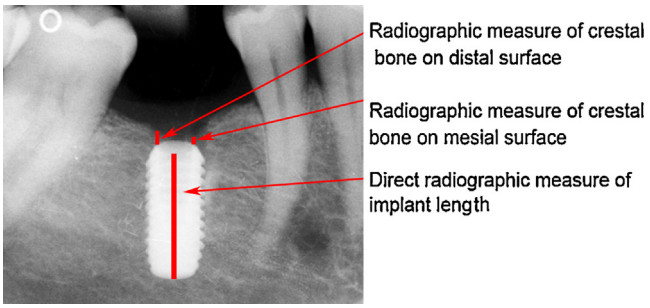

Fig. 3. Direct measurements on a standardized, digital peri-apical radiograph at the time of implant placement (T0). To ensure measurements were calibrated, an object of known size was placed in the image on the same plane as the implant. To adjust the measurements for magnification error, the following equation was used to determine the corrected crestal bone levels: corrected crestal bone level = measured crestal bone level × (actual implant length, e.g. length of implant based on manufacturing standards/measured implant length).

Anatomical variables

The anatomical variables assessed were the arch (maxilla or mandible) and the implant location, either anterior (incisor and canine area) or posterior (premolar and molar area).

Implant-related variables

Implant-related variables included (1) implant length: short implants (10 mm) and long implants (12 mm, 14 mm); (2) implant diameter: narrow implants with diameters of 3.5 mm and 4.2 mm; wide implants with diameters of 4.8 mm, 5.5 mm, and 6.5 mm.

Minimization of potential sources of bias

In order to reduce potential sources of bias, the same operator performed all the surgeries and radiographic follow-ups (MC). Furthermore, two researchers, who were not involved in the clinical part of the investigation, evaluated the peri-apical radiographs independently (SC, AD). With regard to the placement depth variable, the allocation of implants to the three subgroups was determined using software. The computer-generated randomization maximized the statistical power, which permitted the creation of groups of the same size. Likewise the selection and allocation bias was minimized.

Statistical analysis

Descriptive statistics, including mean values and standard deviations, were used. A database was created using Excel (Microsoft, Redmond, WA, USA), with appropriate checks to identify errors. Kappa statistics were used to compute inter-examiner and intra-examiner reliability for the marginal bone measurements. To determine intra-examiner reliability, two examiners (SC, AD) measured and then re-measured (2 months later) a set of 25 random implants. To determine inter-examiner reliability, each examiner measured the set of 25 random implants that had been measured previously by the other examiner. The intra-examiner kappa coefficients were 0.85 and 0.89. The inter-examiner kappa coefficient was 0.77.

The statistical analysis was performed at the implant level. Early marginal bone loss data were illustrated using box plots. Two-way analysis of variance (ANOVA) with the Bonferroni adjusted post hoc test was used to evaluate the influence of different variables on the marginal bone levels (gender, age, depth of placement, timing of placement, type of edentulism,

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arch, location, and implant diameter and length). If any of the interaction terms was significant by two-way ANOVA, one-way ANOVA with Tukey's range test was used to analyze these significant variables with more than two clusters. Unpaired Student *t*-tests were used to analyze the significant variables with only two clusters. All analyses were performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). For each test, the significance level was set at $P < 0.05$.

Results

The potentially eligible population consisted of patients referred to the Department of Oral and Maxillofacial Sciences of the study institution. Two hundred and thirty-eight patients were examined for eligibility; 124 were confirmed to be eligible, all of whom participated for the entire duration of the study. The subject pool comprised 75 females (60.5%) and 49 males (39.5%). The age of subjects at the time of implant placement ranged from 22 to 72 years, with a median of 55 years. A total of 493 implants were inserted. In no case was regenerative surgery required. No healing disturbance was recorded during the healing phase. Detailed information related to the implants inserted is given in Table 1.

At the 2-month follow-up, a mean bone loss of 0.86 mm was observed from implant insertion. One hundred and seventy-five (35.5%) implant sites gained bone and 318 (64.5%) lost bone. Three (0.6%) implant sites lost more than 2 mm of bone. A bone loss of more than 3 mm occurred with two implants (0.4%). Regarding the biologically relevant variables, a higher early mean marginal bone loss was observed in female subjects, in subjects aged ≤50 years, in subjects with partial edentulism, and in implants placed sub-crestally and at ≥3 months after tooth extraction (Fig. 4 and Table 2). Evaluating the anatomical and implant-related variables, a higher early marginal bone loss was recorded in the upper arch, in the posterior area, and in wide and long implants (Fig. 4 and Table 2).

However, only the implant placement depth (Tables 3 and 4) and the timing of implant placement (Table 5) had a statistically significant influence on early peri-implant marginal bone loss.

Discussion

The two hypotheses of the present study were confirmed by the results. Peri-implant bone loss was observed before prosthetic loading, i.e. before the implant–abutment connection. The amount of early peri-implant bone loss was relevant and was influenced by variables such as the implant placement depth and the timing of implant placement. More specifically, implants placed sub-crestally and implants placed at ≥3 months after tooth extraction showed higher early marginal bone loss – both are variables that the clinician can control.

In terms of the limitations of this study, standardized digital peri-apical radiographs

Table 1. Implants and treatment characteristics ($N = 493$).

Variables	Number of implants	%
Sex		
Male	236	47.9%
Female	257	52.1%
Age, years		
≤50	133	27.0%
>50	360	73.0%
Implant placement depth		
Crestal	162	32.9%
Supra-crestal	154	31.2%
Sub-crestal	177	35.9%
Implant placement timing		
Prolonged delayed	212	43.0%
Early delayed	281	57.0%
Type of edentulism		
Mono-edentulism	150	30.4%
Partial edentulism	343	69.6%
Arch		
Maxilla	203	41.2%
Mandible	290	58.8%
Implant location		
Anterior	59	12.0%
Posterior	434	88.0%
Implant length		
Short	172	34.9%
Long	321	65.1%
Implant diameter		
Narrow	318	64.5%
Wide	175	35.5%

Table 2. The early (2-month follow-up) average change in mesiodistal peri-implant bone levels (AvBL; mm) ($N = 493$).

Variables	Average change in mesiodistal peri-implant bone levels (AvBL)			
	Mean	Max.	Min.	SD
Sex				
Male	−0.20	−2.85	2.50	0.70
Female	−0.41	−3.40	2.50	0.68
Age, years				
≤50	−0.52	−3.25	1.55	0.58
>50	−0.40	−3.40	2.50	0.88
Implant placement depth				
Crestal	−0.31	−2.85	1.55	0.64
Supra-crestal	−0.03	−0.45	0.55	0.30
Sub-crestal	−0.55	−3.40	2.50	0.88
Implant placement timing				
Prolonged delayed	−0.50	−3.40	1.65	0.72
Early delayed	−0.17	−2.65	2.50	0.64
Type of edentulism				
Mono-edentulism	−0.21	−2.65	1.55	0.61
Partial edentulism	−0.35	−3.40	2.50	0.73
Arch				
Maxilla	−0.40	−3.40	2.50	0.87
Mandible	−0.25	−2.65	0.85	0.53
Implant location				
Anterior	−0.17	−2.30	1.65	0.64
Posterior	−0.33	−3.40	2.50	0.70
Implant length				
Short	−0.27	−3.25	2.50	0.67
Long	−0.37	−3.40	2.50	0.71
Implant diameter				
Narrow	−0.38	−3.25	1.65	0.67
Wide	−0.41	−3.40	2.50	0.71

SD, standard deviation.

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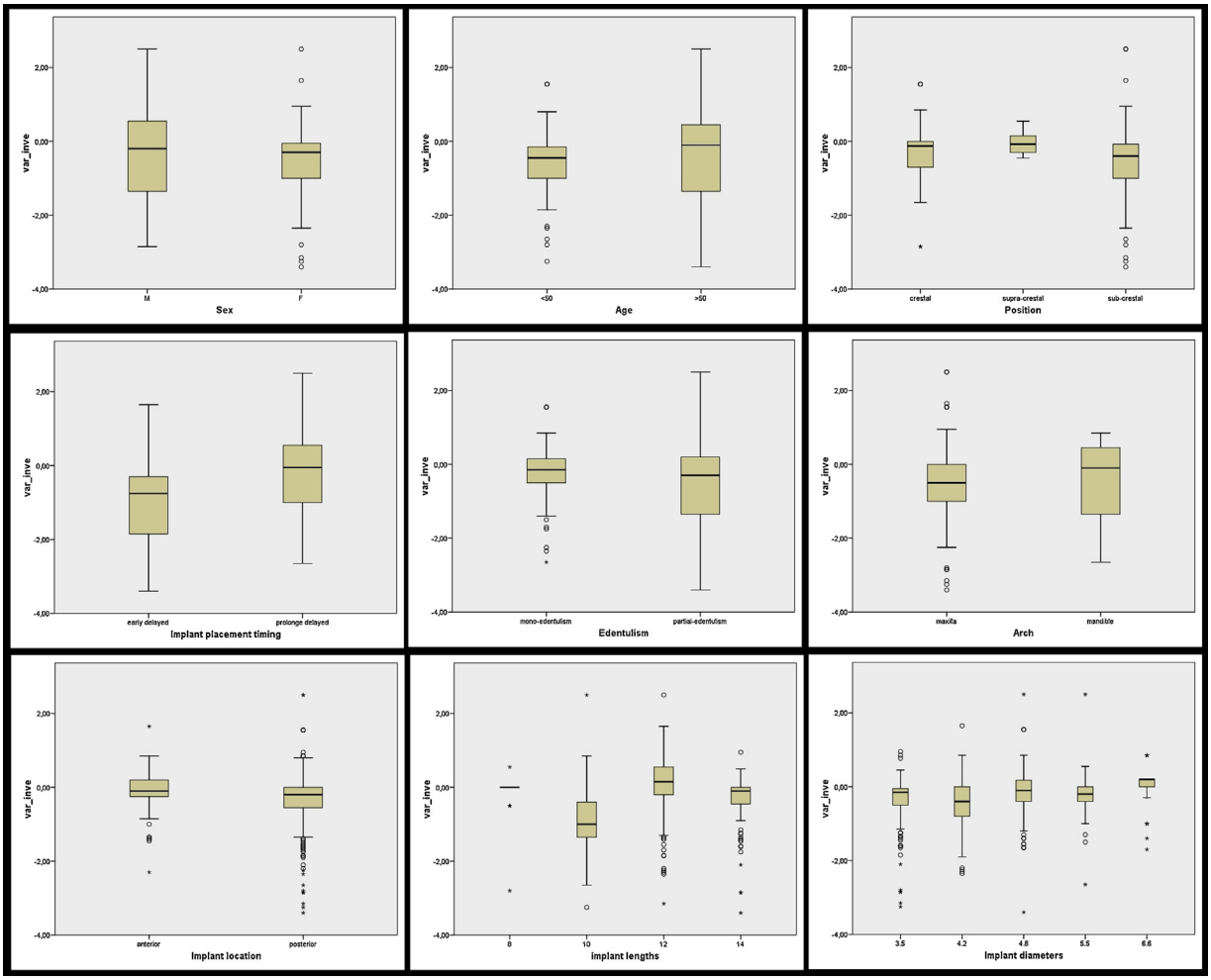

Fig. 4. Box plots showing the median, quartile, and minimum and maximum values of peri-implant early marginal bone loss (mm) in relation to the individual predictor variables, i.e. the clinical exposure factors. Boxes contain 50% of all values; the horizontal lines inside the boxes indicate the medians and the vertical lines extend to 1.5 of the interquartile range. Circles depict outliers.

were used to evaluate marginal bone level changes. As stated by De Smet et al.,[9] absolute and corrected radiographic measurements of mean bone level differences around implants taken from digital and conventional intraoral films are within a range of 0.2 mm, indicating that standardized peri-apical radiographs are precise. Using the intraoral radiographs, however, only mesial and distal bone levels were assessed; no assessment was made of the facial or lingual sites. This is an intrinsic limitation in interpreting peri-apical films, but also a common method used for bone level assessment around teeth and implants. A further limitation of the study was that no customized radiographic jig was used to take reproducible radiographs. Finally, the present study also failed to assess implant exposure through the soft tissue into the oral cavity during the initial healing phase, which often causes bone loss from bacterial invasion of the healing screw to the implant connection area, or the establishment of a connective tissue zone above the bone.[10]

Reports in the literature related to marginal bone loss often assess the conditions at attachment of the prosthesis or at second stage surgery as the baseline from which future bone loss is measured.[10] Manz, in a study on marginal bone loss with radiographs taken at implant placement, at the time of second stage surgery, and after the first 6 months of loading, reported an overall average of 0.94 mm of bone loss between implant placement and second-stage uncover, using the top of the implant as a baseline.[11] Heat generated during the drilling procedure, the elevation of the periosteal flap, and excessive pressure applied to the hard tissue during implant placement may contribute to implant bone loss during the healing period.[12]

Regarding the positioning of the implant, some authors recommend a subcrestal placement of two-piece implants, 2–3 mm below the cement–enamel junction of the neighbouring teeth in the aesthetic areas, in order to achieve an 'acceptable emergence profile'.[13–15] Moreover, apical positioning of the implant shoulder is often recommended as the discrepancy increases between the diameter of the implant and the natural tooth to be replaced.[16] However, this apical positioning of the implant will result in an excessive length of the soft tissue dimension due to the marginal bone loss that occurs from healing, with concomitant persistent inflammation and possibly further loss of supporting bone.[15] The manufacturers of implants with a Morse taper connection also recommend inserting the implant 2 to 3 mm sub-crestally in clinical practice,[17] but the results of this study show greater early peri-implant bone loss when the implant is placed below the alveolar crest.

With regard to the ideal timing of implant placement after dental extraction,

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Table 3. Two-way analysis of variance (ANOVA) used to evaluate the influence of different variables on early marginal bone loss ($N = 493$).

Source	Dependent variable	Type III sum of squares	df	Mean square	*F*	Sig.
Corrected model	Sex	0.018[a]	1	0.018	0.074	0.785
	Age	0.639[b]	1	0.639	2.793	0.096
	Implant placement depth	131.312[c]	67	1.960	4.054	0.000
	Implant placement timing	2.814[d]	1	2.814	11.716	0.001
	Type of edentulism	0.801[e]	1	0.801	3.736	0.054
	Arch	0.025[f]	1	0.025	0.100	0.752
	Implant location	0.627[g]	1	0.627	4.533	0.034
	Implant length	1.759[h]	1	1.759	7.833	0.010
	Implant diameter	2.967[i]	1	2.967	13.255	0.011
Intercept	Sex	467.428	1	467.428	1911.596	0.000
	Age	522.409	1	522.409	2284.442	0.000
	Implant placement depth	833.948	1	833.948	1724.902	0.000
	Implant placement timing	464.142	1	464.142	1932.570	0.000
	Type of edentulism	510.637	1	510.637	2381.021	0.000
	Arch	400.992	1	400.992	1602.245	0.000
	Implant location	608.332	1	608.332	4396.688	0.000
	Implant length	674.229	1	674.229	780.624	0.000
	Implant diameter	999.211	1	999.211	850.513	0.000
Bone remodelling	Sex	0.018	1	0.018	0.074	0.785
	Age	0.639	1	0.639	2.793	0.096
	Implant placement depth	131.312	67	1.960	4.054	0.000*
	Implant placement timing	2.814	1	2.814	11.716	0.001*
	Type of edentulism	0.801	1	0.801	3.736	0.054
	Arch	0.025	1	0.025	0.100	0.752
	Implant location	0.627	1	0.627	4.533	0.056
	Implant length	1.759	1	1.759	7.833	0.059
	Implant diameter	2.967	1	2.967	13.255	0.054
Error	Sex	59.174	242	0.245		
	Age	55.341	242	0.229		
	Implant placement depth	204.027	422	0.483		
	Implant placement timing	58.121	242	0.240		
	Type of edentulism	51.900	242	0.214		
	Arch	60.565	242	0.250		
	Implant location	33.483	242	0.138		
	Implant length	209.017	491	0.864		
	Implant diameter	284.310	491	1.175		
Total	Sex	673.000	244			
	Age	715.000	244			
	Implant placement depth	2368.000	490			
	Implant placement timing	622.000	244			
	Type of edentulism	745.000	244			
	Arch	580.000	244			
	Implant location	853.000	244			
	Implant length	1022.000	493			
	Implant diameter	1491.000	493			
Corrected total	Sex	59.193	243			
	Age	55.980	243			
	Implant placement depth	335.339	489			
	Implant placement timing	60.934	243			
	Type of edentulism	52.701	243			
	Arch	60.590	243			
	Implant location	34.111	243			
	Implant length	214.066	492			
	Implant diameter	291.488	492			

[a] $R^2 = 0.000$ (adjusted $R^2 = -0.004$).
[b] $R^2 = 0.011$ (adjusted $R^2 = 0.007$).
[c] $R^2 = 0.392$ (adjusted $R^2 = 0.295$).
[d] $R^2 = 0.046$ (adjusted $R^2 = 0.042$).
[e] $R^2 = 0.011$ (adjusted $R^2 = 0.007$).
[f] $R^2 = 0.018$ (adjusted $R^2 = 0.014$).
[g] $R^2 = 0.015$ (adjusted $R^2 = 0.011$).
[h] $R^2 = 0.024$ (adjusted $R^2 = 0.020$).
[i] $R^2 = 0.025$ (adjusted $R^2 = 0.021$).
* Statistically significant, $P \leq 0.05$.

Table 4. One-way analysis of variance (ANOVA) and Tukey's range test used to evaluate the influence of the depth of implant placement on early marginal bone loss ($N = 493$).

(I) Implant placement depth	(J) Implant placement depth	Mean difference (I–J)	SE	Sig.	95% CI	
					Lower bound	Upper bound
Crestal	Supra-crestal	0.28175*	0.07482	0.001	0.1020	0.4615
	Sub-crestal	−0.23628*	0.07228	0.003	−0.4099	−0.0626
Supra-crestal	Crestal	−0.28175*	0.07482	0.001	−0.4615	−0.1020
	Sub-crestal	−0.51803*	0.07326	0.000	−0.6940	−0.3420
Sub-crestal	Crestal	0.23628*	0.07228	0.003	0.0626	0.4099
	Supra-crestal	0.51803*	0.07326	0.000	0.3420	0.6940

SE, standard error; CI, confidence interval.
* Statistically significant, $P \leq 0.05$.

Table 5. Unpaired Student *t*-test used to evaluate the influence of the timing of implant placement on early marginal bone loss ($N = 493$).

Bone loss	Sig.	Mean difference	SE difference	95% CI of the difference	
				Lower	Upper
Prolonged delayed versus early delayed	0.000*	0.67101	0.00220	0.66669	0.67533

SE, standard error; CI, confidence interval.
* Statistically significant, $P \leq 0.05$.

advantages and disadvantages have been attributed to different protocols.[18] There is increased interest in shortening the overall treatment time and minimizing the number of surgical interventions.[19,20] Various approaches have been proposed, such as immediate implant placement at the time of extraction, or early implant placement following a few weeks of soft tissue healing prior to implant insertion.[19,20] In the present study, the early implant placement protocol was adopted. This protocol combines some of the advantages of immediate placement, mainly through utilizing the socket walls before alveolar bone resorption, but at the same time allows for primary healing after tooth extraction, ensuring enough soft tissues for flap closure if required and reducing the risk of infection during implant placement.[21] In light of the results of a recent systematic review, it was suggested that the early implant placement protocol may offer advantages with regard to the preservation of the hard and soft tissues around implants, particularly when implants are placed to restore missing teeth in aesthetically relevant areas.[18] The results of the present study confirm the advantages of early implant placement following extraction, showing a significantly lower early marginal bone loss when the implant is inserted 4 weeks after tooth extraction.

In conclusion, awareness of factors that influence early peri-implant bone loss, such as the accurate and precise timing and positioning of the implant shoulder, can improve the aesthetic predictability and the success of the final restoration. The results of this study show that when using two-piece submerged titanium implants, the amount of early peri-implant marginal bone loss is considerable and is significantly affected by the implant placement depth and the timing of implant placement.

Funding

None.

Competing interests

None.

Ethical approval

This investigation was reviewed independently and approved by the local ethics committee (Policlinico Umberto I, Rome, Italy; Prot.304/07).

Patient consent

Patient consent was required; written consent was obtained from each participant.

Acknowledgements. The authors gratefully acknowledge the editing help offered by Ms Alison Driver.

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Please cite this article in press as: Cassetta M, et al. Early peri-implant bone loss: a prospective cohort study, *Int J Oral Maxillofac Surg* (2015), http://dx.doi.org/10.1016/j.ijom.2015.04.002