Immediate Versus Delayed Loading of Dental Implants in the Maxillae of Minipigs. Part II: Histomorphometric Analysis

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Purpose: *To assess histomorphometric parameters of dental implants placed in partially edentulous maxillae of minipigs.* ***Materials and Methods:*** *In 9 minipigs, 6 XiVE implants were placed on each side of the maxilla, either after implant site preparation by an osteotome technique or by spiral drills. The implants were restored with fixed provisional restorations and loaded either immediately or after healing periods of up to 5 months. After a loading period of 6 months, the animals were sacrificed and the implants were retrieved together with the adjacent bone. Histologic specimens were prepared and bone-to-implant contact (BIC) ratio, interthread bone area, and peri-implant bone area were determined.* ***Results:*** *An analysis of variance revealed that the BIC ratio on the palatal side was significantly influenced by the preparation technique of the implant site ($P = .001$) and by the healing period ($P = .02$). After implant site preparation by an osteotome technique, higher BIC values were achieved for implants that were loaded either immediately or after healing periods of 1 to 3 months. After healing periods of 4 to 5 months, implant site preparation with spiral drills showed slightly better results in regard to BIC. Interthread bone area and peri-implant bone area did not differ significantly statistically for the 2 implant placement techniques and the 3 healing periods.* ***Discussion and Conclusion:*** *After 6 months of functional loading in the maxilla, successful immediately loaded implants performed the same as implants subjected to an unloaded healing period prior to loading as far as histomorphometric data were concerned. Prospective randomized clinical studies should be carried out in humans to compare immediate loading to loading after an unloaded healing phase.* INT J ORAL MAXILLOFAC IMPLANTS 2005;20:540–546

Key words: *delayed loading, histomorphometric analysis, immediate loading, maxilla, osteotome technique*

The basis for having an unloaded, stress-free healing period of 5 to 6 months for dental implants placed in the maxilla was research undertaken in the 1970s and 1980s.[1] Until now, the need for such a long healing period has not been experimentally ascertained.[2] On the contrary, it has been shown that implant movements of up to 28 µm during the healing period have no adverse effect on osseointegration. Some authors have proposed that soft connective tissue apposition to the implant will occur until 150 µm are exceeded.[2–4]

A confined amount of microstrain may even be a favorable stimulus during the healing period. From osteoporosis research, it is known that microstrain leads to an increased bone density.[5] In experimental animal trials, increased bone density has been found for immediately loaded, rigidly splinted implants compared to unloaded ones in the maxilla.[6–8] Unfortunately, these studies were conducted in primates showing a metabolic rate of bone at least 3.3 times

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faster than that of humans.[7,9] As a consequence, caution must be used in the extrapolation of the results of these studies to the human situation.[8] For the present study, it was decided to use Göttingen minipigs, because these animals have a metabolic rate of bone that is quite similar to that of humans.[10]

In the first part of the this study, the authors reported on an experimental trial in which immediate loading of implants placed in the maxilla was compared to loading delayed for up to 5 months in terms of implant stability and implant failure rate.[11] It was the aim of the second part of this study in minipigs to analyze the differences in histomorphometric performance of immediately loaded implants and implants loaded after a delay that survived a period of 6 months of functional loading.

MATERIALS AND METHODS

The study protocol was approved by the Animal Care Committee of the Regional Government of Mittelfranken (Ansbach, Germany). The details of implant placement, loading, assessment of implant stability, and failure rate have been described previously.[11]

In 9 female Göttingen minipigs (Ellegaard Göttingen Minipigs, Dalmose, Denmark), 6 rough-surfaced, self-tapping, cylindric implants 3.8 mm in diameter and 13 mm in length (XiVE; Friadent, Mannheim, Germany) were placed on each side of the maxilla 3 months after removal of the 3 premolars and the first molar. The implant sites were prepared by either spiral drills or an osteotome technique. The implants were placed so that the implant shoulders were located 1 mm above the crestal bone. The implants were supplied with fixed provisional prostheses either immediately after placement or after a healing period of 1, 2, 3, 4, or 5 months. After 6 months of functional loading, the minipigs were sacrificed by inducing cardiac arrest with an intravenous injection of a 20% solution of pentobarbital (Narcoren; Merial, Hallbergmoos, Germany).

The implants were removed together with the surrounding bone and fixated in Schaffer's solution (2 parts 96% ethanol, 1 part 37% formaldehyde) for 24 hours. The specimens were dehydrated in a graded series of ethanols. Thereafter, they were embedded in methylmetacrylate resin (Technovit 7200; Heraeus Kulzer, Dormagen, Germany). The samples were cut parallel to the longitudinal axis of the implants in an orovestibular direction. Using the Sage and Schliff "sawing and grinding" technique, they were ground to a thickness of 20 μm (Exakt Apparatebau, Norderstedt, Germany).[12] Staining with toluidine blue was performed. At magnifications of up to 60×, the images were assessed digitally (Axiocam; Zeiss, Göttingen, Germany). Osiris medical imaging software version 3.1 was used for image analysis (University Hospitals of Geneva, Division of Medical Information, Digital Imagery Unit, Geneva, Switzerland).

The bone-to-implant contact (BIC) ratio was defined as the length of the bone surface border in direct contact with the implant divided by the complete implant periphery (× 100%), from the most coronal thread down to the most apical thread. The interthread bone area was defined as the area of bone inside the threads divided by the complete area inside the threads (× 100%). Bone area was measured beginning with the fourth thread down to the most apical thread. In the area surrounding the implant, up to a lateral distance of 2 mm from the implant, the peri-implant bone area was determined as the bone area divided by the tissue area (× 100%), again, from the fourth thread to the most apical thread (Fig 1).[13,14] The vertical distance of the crestal bone resorption on both the buccal and palatal sides was assessed from 1 mm below the implant shoulder to the point of the first BIC (Fig 2).

Statistics

Because of the small case numbers, implants loaded after healing periods of 1, 2, or 3 months and implants loaded after 4 or 5 months were pooled into 2 groups. This grouping reflects the occurrence of implant failures. For description of continuous variables, mean values with standard deviations (SDs) have been given. Because of the intra-animal association between histomorphometric measurements, the mean values and SDs given are rough approximations of the SDs in the underlying population. To analyze the influence of preparation technique and healing period adjusted for implant coating, implant position, and individual animal on histomorphometric measurements, analyses of variance (ANOVAs) were performed. *P* values $\leq .05$ were considered significant. All calculations were done using SAS version 8.1 (SAS Institute, Cary, NC).

RESULTS

Direct BIC was achieved for both of the implant site preparation techniques and for all of the different healing periods (Fig 2). The BIC ratio and interthread and peri-implant bone areas are given in Table 1. For the osteotome technique, a higher BIC percentage was observed for all healing periods except for 4 to 5 months compared to the implant site preparation with spiral drills. An ANOVA revealed that the BIC ratio on the palatal side was significantly influenced

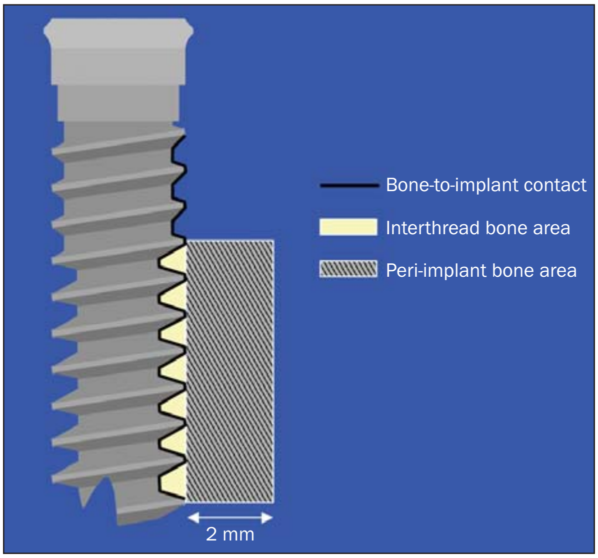

Fig 1 For histomorphometric analysis, BIC ratio was defined as the length of the bone surface border in direct contact with the implant over the complete implant periphery (× 100%), from the most coronal thread to the most apical thread. The interthread bone area was defined as the area of bone inside the threads divided by the complete area inside the threads (× 100%) from the fourth thread to the most apical thread. The peri-implant tissue was the tissue surrounding the implant up to a lateral distance of 2 mm. The peri-implant bone area was determined as the bone area found in this region divided by the tissue area (× 100%), from the fourth thread to the most apical thread.

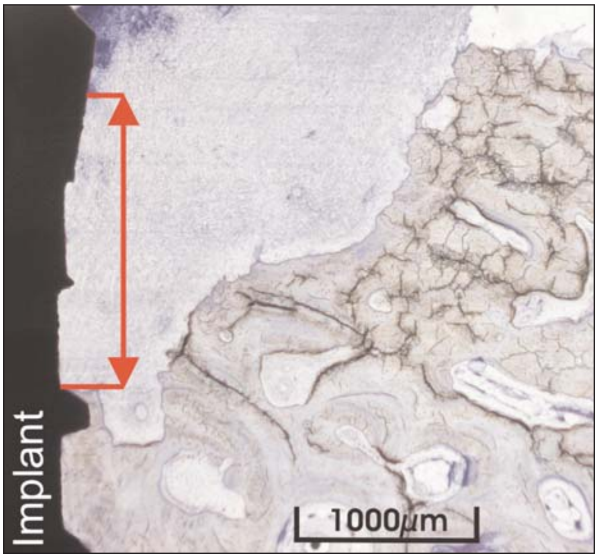

Fig 2 Distance *(arrow)* of crestal bone resorption (toluidine blue; original magnification ×1.25).

by the preparation technique of the implant site (P = .001) and by the healing period (P = .02). For the buccal side, no significant differences were found with regard to preparation technique (P = .16) or healing period (P = .18).

In regard to interthread bone area, no clear tendencies were observed.

For immediately loaded sites, on the buccal side, interthread bone area was higher when the spiral drill technique was used. On the palatal side, it was higher when the osteotome technique was used. After healing periods of 1 to 3 months, the interthread bone area was lower for implant sites prepared by spiral drills. However, after 4 to 5 months, interthread bone area was greater at sites prepared with spiral drills. The ANOVAs showed that there were no significant differences in regard to preparation technique or healing period for either the buccal side (P = .57 and P = .054, respectively) or the palatal side (P = .69, P = .71).

For immediately loaded implants, peri-implant bone area was greater both buccally and palatally when the osteotome technique was used. After 1 to 3 months of healing, peri-implant bone area was greater on the buccal side when the spiral drill technique was used. However, on the palatal side, an opposite result was found. After a healing period of 4 to 5 months, roughly equivalent values were assessed for the peri-implant bone area for both of the preparation techniques on the buccal side, while a higher value was found for the preparation of the implant site on the palatal side. No statistically significant differences were found between different techniques or healing periods on either the buccal side (P = .76 and P = .78, respectively) or the palatal side (P = .78 or P = .61).

In the peri-implant region, an infiltration of the gingiva with inflammatory cells was visible in some of the specimens. There was osteoclastic activity at the coronal part of the crestal bone (Fig 3). The results of the crestal bone resorption are summarized in Table 2. At the time of stage-2 surgery, crestal bone loss was higher for sites prepared with spiral drills compared to those prepared with an osteotome technique, except in the case of sites on the palatal side allowed a healing period of 4 to 5 months.

After 6 months of functional loading, a larger amount of crestal bone resorption could be seen for the implant site preparation with spiral drills after immediate loading and a healing period of 4 to 5 months. For the sites that were immediately loaded and those that were allowed a healing period of 4 to 5 months, crestal bone loss was higher for sites pre-

Table 1 Results of the Histomorphic Analysis (Mean ± SD)

Implant site preparation technique/healing period (mo)	n	BIC (%)		Interthread bone area (%)		Peri-implant bone area (%)	
		Buccal	Palatal	Buccal	Palatal	Buccal	Palatal
Osteotome							
0	6	82 ± 7	79 ± 7	79 ± 9	81 ± 6	81 ± 10	77 ± 7
1–3	5	87 ± 10	82 ± 24	83 ± 18	80 ± 15	68 ± 10	84 ± 13
4–5	17	72 ± 22	75 ± 16	68 ± 19	68 ± 22	74 ± 17	68 ± 21
Spiral drills							
0	5	79 ± 6	59 ± 30	87 ± 5	70 ± 22	76 ± 22	71 ± 20
1–3	12	58 ± 31	53 ± 26	58 ± 32	67 ± 25	72 ± 16	63 ± 20
4–5	16	77 ± 22	76 ± 18	73 21	75 ± 18	74 ± 20	79 ± 19

n = no. of implants.

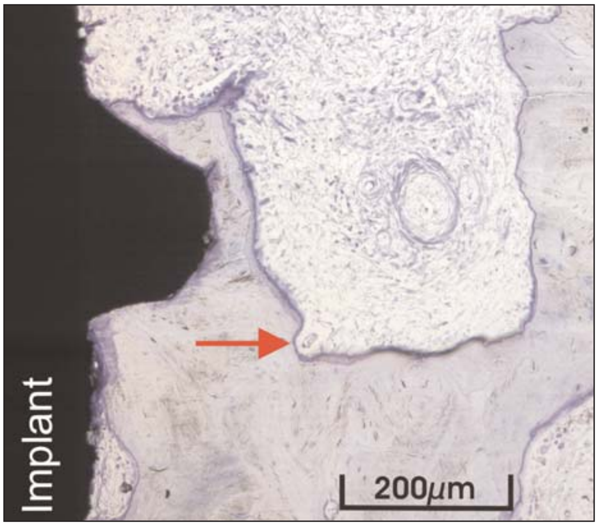

Fig 3 Detail of Fig 2 revealing direct BIC around the thread and osteoclastic activity *(arrow)* at the crestal aspect of the peri-implant bone (toluidine blue; original magnification ×5).

pared using the spiral drill technique. However, for sites allowed a healing period of 1 to 3 months, crestal bone loss was higher for sites prepared using the osteotome technique.

Statistically significant differences were found between different healing periods on both the buccal (P = .02) and palatal (P = .02) sides. However, no difference between healing periods was observed at the time of stage-2 surgery on either side (P = .16 for the buccal side; P = .15 for the palatal side).

The histomorphometric data assessed for the different techniques of preparation of the implant sites did not differ statistically significantly on either the buccal or palatal sides either at the time of stage-2 surgery (P = .57 and P = .74, respectively; ANOVA) or after 6 months of loading (P = .90 and P = .65, respectively; ANOVA).

DISCUSSION

It has been stated that immediate loading of dental implants is beneficial to the patient, because function and esthetics are restored in a minimal amount of time in partially dentate and edentulous situations.[15] Several clinical and experimental animal studies have shown that osseointegration can be achieved for immediately loaded implants in the mandible as well as in the maxilla. A review of the related literature has been provided by Szmukler-Moncler and colleagues[2] and Gapski and associates.[16]

Histologic data on immediately loaded implants have demonstrated not only direct BIC but also favorable bone density around the implants.[6–8,15,17] However, only 1 experimental study has investigated immediate loading in the maxilla.[8] Unfortunately, the animal model that was adopted exhibited a bone formation rate more than 3 times faster than that of humans. For deeper insight into the consequences of immediate loading in the maxilla, histologic data should be collected from experimental animals that exhibit a bone formation rate similar to that of humans. Therefore, it was the aim of the present study to assess histomorphometric data from the bone surrounding immediately loaded implants in the maxillae of minipigs and to compare the results to implants loaded after a delay.

It is known from experimental trials that peri-implant bone heals according to a certain cascade of events: *(1)* angiogenesis, *(2)* osteoprogenitor cell migration, *(3)* woven bone scaffold formation, *(4)* deposition of lamellar bone, and *(5)* secondary bone remodeling.[18] To date, there are very limited quantitative histologic data for the early healing process in humans. While immediate loading of implants in the mandible is well accepted, immediate loading in the maxilla is still controversial. It has been assumed that loading implants immediately after their placement in low-density maxillary bone increases the risk of

Table 2 Course of the Crestal Bone Resorption (Mean ± SD)

Implant site preparation technique/ healing period (mo)	Crestal bone loss at stage-2 surgery (mm)			Crestal bone loss after 6 mo of loading (mm)		
	n	Buccal	Palatal	n	Buccal	Palatal
Osteotome						
0	N/A	N/A	N/A	6	2.33 ± 0.82	2.17 ± 0.41
1–3	18	0.06 ± 0.24	0.06 ± 0.24	5	2.20 ± 0.84	2.60 ± 1.52
4–5	17	0.35 ± 1.06	0.35 ± 1.06	17	3.00 ± 0.71	2.65 ± .070
Spiral drills						
0	N/A	N/A	N/A	5	2.60 ± 1.14	2.80 ± 0.84
1–3	22	0.18 ± 0.50	0.18 ± 0.50	12	2.08 ± 0.79	1.58 ± 1.08
4–5	17	0.53 ± 1.94	0.35 ± 1.22	16	3.31 ± 2.02	3.50 ± 2.07

n = no. of implants.

implant failure, because the process of osseointegration is in its initial phase.[16] However, histologic data obtained from experimental animal studies in the maxilla have shown no adverse effects on either the osseointegration process or the bone morphology around the implants.[8] These data have even demonstrated that early loading increased the BIC and allowed faster remodeling when compared to unloaded controls.

The hypothesis of mechanical stimulation of bone remodeling around implants has been confirmed in experimental animals in previous studies.[19] In these studies, brief exposure to extremely low-amplitude mechanical strains enhanced the biologic fixation of cementless implants. In specific experimental settings, experimentation was undertaken to determine the maximum amount of micromotion that can increase new bone formation.[20] For oral implantation, an upper limit of micromotion of 150 μm has been proposed. Micromotion up to this limit provides optimal BIC and peri-implant bone area.[21] Based on this knowledge, the higher BIC rate of immediately loaded implants compared to unloaded implants has been explained by the beneficial role of relative micromovement in stimulating bone formation in a peri-implant location.[8] However, this hypothesis could not be confirmed in the mandible of animals with a bone formation rate similar to that of humans.[10] The histologic data of this trial revealed that BIC and peri-implant bone area did not differ statistically significantly for immediately loaded and unloaded implants.

In the present study, after a period of functional loading of 6 months, a significant difference in terms of BIC and peri-implant bone area could not be found between immediately loaded implants and implants loaded after submerged healing periods of up to 5 months in the maxilla. The BIC at the end of the submerged healing period was not assessed. Therefore, comparison with studies that have determined the BIC of nonloaded and immediately loaded implants is not possible.[22]

It is not known whether the BIC at the time of stage-2 surgery was lower in the submerged implants than in the immediately loaded implants, which had already been exposed to occlusal forces for a certain period of time. However, even if BIC and peri-implant bone area had been shown to be reduced at the time of stage-2 surgery for the implants loaded on delay, the interval of functional loading generally leads to a remodeling of the peri-implant bone, which makes it impossible to distinguish them from immediately loaded implants. The effect of immediate loading on the BIC that may be observed when immediately loaded implants are compared to an unloaded control becomes irrelevant when a comparison is made between immediately loaded implants and implants loaded on delay after the same interval of functional loading. Similar results can be found for the crestal bone resorption. At the end of the observation period, comparable values could again be found for this parameter for immediately loaded implants and implants loaded on delay. Independent of the healing period, the degree of crestal bone resorption could have been decreased by intense oral hygiene.[23] However, this would have to have been performed under general anesthesia in short, frequent intervals. Since general anesthesia is a stressful and demanding procedure that may harm the lives of the animals when applied repeatedly, intensified oral hygiene was not carried out in the present study.

Although histomorphometric data revealed no differences between immediately loaded implants and implants loaded after submergence for several months after the same period of functional loading, experimental data collected previously have shown that the implant failure rate is significantly higher for immediately loaded implants when compared to implants loaded after a healing period of 4 or 5 months.[11] One of the main causes for these failures appears to be the unrestricted occlusal loads that are exerted on the implants in the experimental setting, which exceed the limits that have been defined for micromotion. As a consequence, complete loss of the affected implants or fibrous tissue healing can occur, similar to the pseudoarthrosis observed in an unstabilized fracture site.[24–26] It seems that contrary to the mandible, rigid splinting of implants in the maxillae of minipigs does not guarantee that micromotion will be kept below the critical level for immediately loaded implants.[10] The chosen animal model has certain limitations because the maxillary shape does not allow the establishment of cross-arch fixation of the suprastructure to avoid cantilevers. Therefore, more favorable results could be expected in humans. Moreover, in a clinical situation, compliance of the patients allows the avoidance of occlusal overload during the developmental phase of osseointegration. However, randomized clinical trials are needed to support or refute this assumption.

In the present study, an osteotome technique was chosen as an option to improve initial implant stability by compression of the peri-implant bone. It has been hypothesized that a necrotic zone of bone adjacent to the implant surface, as has been found after the preparation of the implant site by spiral drills, will not occur with the osteotome technique.[10,27] The necrotic zone was 1 of the negative factors mentioned for immediate loading. It has been claimed that this dead layer should be replaced with new bone before a load is applied to an implant.[28] The histomorphometric data of the present study revealed that after a 6-month period of functional loading, a significantly greater BIC ratio was observed on the palatal side of implants loaded either immediately or after a healing period of 1 to 3 months in sites where the osteotome technique was used. However, in the first part of this study,[11] it was shown that the use of an osteotome technique does not necessarily reduce the implant failure rate when immediate loading is applied.[11] Moreover, increased crestal bone resorption has been previously described for an osteotome technique, although this could not be confirmed in the present study.[29] Therefore, it seems that the 2 implant site preparation techniques can be considered equivalent in the maxilla.

CONCLUSION

From the data of the present study in minipigs, it can be concluded that after 6 months of functional loading in the maxilla, successful immediately loaded implants performed as well as implants subjected to an unloaded healing period prior to the provision of a suprastructure as far as histomorphometric data are concerned. However, a previous study showed that the failure rate of implants in the maxilla was significantly increased compared to the failure rate of implants loaded after a healing period of 5 months.[11] Apparently, these failures are most likely related to occlusal overload in the experimental setting.

Despite the limited number of histologic specimens, the favorable histomorphometric results of the successful immediately loaded implants encourage researchers to undertake prospective randomized clinical studies in humans to compare immediate loading to loading after an unloaded healing phase.

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