The Effects of Different Loading Times on the Bone Response Around Dental Implants: A Histomorphometric Study in Dogs

Sérgio Jorge Jayme, DDS, MScD[1]/Rafael Ramos de Oliveira, DDS, MScD[2]/
Valdir Antonio Muglia, DDS, MScD, DSc[3]/Arthur Belém Novaes Jr, DDS, MScD, DSc[4]/
Ricardo Faria Ribeiro, DDS, MScD, DSc[5]

Purpose: *The aim of this study was to evaluate, through histomorphometric analysis, the effect that different loading times would have on the bone response around implants.* ***Materials and Methods:*** *Three Replace Select implants were placed on each side of the mandible in eight dogs (n = 48 implants). One pair of implants was selected for an immediate loading protocol (IL). After 7 days, the second pair of implants received prostheses for an early loading protocol (EL). Fourteen days after implant placement, the third pair of implants received prostheses for advanced early loading (AEL). Following 12 weeks of prosthetics, counted following the positioning of the metallic crowns for the AEL group, the animals were sacrificed and the specimens were prepared for histomorphometric analysis. The differences between loading time in the following parameters were evaluated through analysis of variance: bone-to-implant contact, bone density, and crestal bone loss.* ***Results:*** *The mean percentage of bone-to-implant contact for IL was 77.9% ± 1.71%, for EL it was 79.25% ± 2.11%, and for AEL it was 79.42% ± 1.49%. The mean percentage of bone density for IL was 69.97% ± 3.81%, for EL it was 69.23% ± 5.68%, and for AEL it was 69.19% ± 2.90%. Mean crestal bone loss was 1.57 ± 0.22 mm for IL, 1.23 ± 0.19 mm for EL, and 1.17 ± 0.32 mm for AEL. There was no statistical difference for any of the parameters evaluated (P > .05).* ***Conclusion:*** *Different early loading times did not seem to significantly affect the bone response around dental implants.* INT J ORAL MAXILLOFAC IMPLANTS 2010;25:473–481

Key words: *animal study, bone density, bone-to-implant contact, dental implants, early loading, immediate loading, osseointegration*

The healing of dental implants in the jawbone is based on the principle of osseointegration[1,2]; this principle originally called for a healing period of several months and was aimed at the establishment of a direct bone-to-implant contact (BIC) that, according to definition, must be proved by means of histologic analysis.

The current success rates for oral rehabilitation with dental implants in the mandible have reached more than 95%.[3] The original Brånemark implant protocol called for a stress-free submerged healing time of 3 to 6 months to ensure osseointegration.[4,5] The prolonged undisturbed healing time was thought to be necessary to avoid fibrous tissue encapsulation around the implants instead of osseointegration[5]; however, later clinical and experimental evidence revealed that implants could osseointegrate even when left exposed to the oral cavity during healing.[6] Traditionally, during this healing period patients were rehabilitated by means of removable prostheses; however, because provisional prostheses are often uncomfortable because of a lack of stability and retention, it would be beneficial if the healing period could be shortened without jeopardizing implant success. With the high clinical success rates obtained with the original implant protocol, clinicians and

[1]Graduate Student of Prosthodontics, Department of Dental Materials and Prosthetics, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.
[2]Graduate Student of Periodontology, Department of Bucco-Maxillo-Facial Surgery and Traumatology and Periodontology, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.
[3]Assistant Professor of Prosthodontics, Department of Dental Materials and Prosthetics, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.
[4]Professor of Periodontology, Department of Bucco-Maxillo-Facial Surgery and Traumatology and Periodontology, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.
[5]Professor of Prosthodontics, Department of Dental Materials and Prosthetics, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

Correspondence to: Dr Ricardo Faria Ribeiro, Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Av. do Café s/n, 14040-904, Ribeirão Preto, SP, Brasil. Email: rribeiro@forp.usp.br

Fig 1 Implants in position.

researchers have now focused on further development and refinement of implant therapy with new implant designs and treatment concepts.[3,6,7]

There has also been a change of focus in implant therapy from being originally a strictly functional rehabilitation toward a treatment modality with a major emphasis on esthetics. Immediate implant restoration with functional loading provides better patient comfort, allows immediate masticatory function, and offers good esthetics.[8] In addition, it also eliminates the inconvenience of a second surgery for the placement of healing abutments. This often leads to early soft tissue healing and results in early stabilization of the peri-implant mucosa, thereby ensuring higher implant survival.[7]

Several experimental studies have shown that immediate loading of implants does not necessarily lead to fibrous tissue healing. Instead, a BIC develops over time that is comparable to that of implants that are loaded conventionally.[7,9–11] Implants and adjacent bone retrieved from humans have confirmed these experimental results in both the mandible and maxilla, with BIC of up to 93%.[8,12,13]

The peri-implant bone adjusts its architecture in relation to functional load bearing. The strains induced by these loads affect the bone remodeling process. It is suggested that the magnitude of the load between implant and bone determines the implant success.[14] Therefore, one key for implant success seems to be whether or not the bone surrounding the implant adequately remodels. One millimeter of the bone adjacent to the implant undergoes necrosis after implant placement. This necrotic bone provides important structural support during the initial healing phase; later, newly formed bone replaces the necrotic bone.[15]

Functional activities generate strains on the bone that either directly or indirectly play a role in the cellular adaptation of bone tissue.[16] The maintenance of osseointegration involves continued remodeling activity at the periphery of the implant.[17] In this context, it is no longer considered that immediate loading leads to connective tissue healing of implants.[18] In fact, a certain amount of microstrain may lead to improved mineralization of the peri-implant bone.[19] Some experimental studies available in the literature provide data on BIC and bone density (BD) with immediately loaded implants.[9,20–24] These parameters can provide important information on the course of bone remodeling around immediately loaded implants. Therefore, the aim of this study was to verify, in the dog mandible, the BIC, BD, and crestal bone loss (CBL) around implants with different loading times

MATERIAL AND METHODS

The University Animal Research Committee approved the experimental protocol (Process 05.1.1318.53.1). Eight young adult male mongrel dogs (each weighing about 25 kg) were used. The dogs had intact maxillae and mandibles, were in good general health, and had no viral or fungal oral lesions. The animals were not fed 12 hours before the surgery to prevent vomiting. They were sedated and then anesthetized intravenously with thiopental (1 mL/kg; 20 mg/kg thiopental diluted in 50 mL of saline). A full-thickness flap was raised in the region of the four mandibular premolars, and the teeth were sectioned in the buccolingual direction and extracted with forceps. The flaps were repositioned and sutured with absorbable 4-0 sutures. During the healing period, the animals were evaluated periodically and received monthly ultrasound prophylaxis. Impressions were obtained of the right and left lower mandible (Xantopren & Optosil, Heraeus Kulzer), and casts were generated and used during the prosthetic phase. The animals received a soft diet throughout the study period.

After a healing period of 3 months, the animals received 20,000 IU penicillin and streptomycin (1.0 g/10 kg) the night before surgery. This dose provided antibiotic coverage for 4 days; thus another dose was given 4 days later to provide coverage for a total of 8 days. This broad-spectrum antibiotic is commonly used to treat infections in small animals.[25] After the sedation and anesthesia described earlier were repeated, a horizontal crestal incision was made from the distal region of the canine to the mesial region of the first molar, and implants were placed according to the manufacturer's instructions. Three 4.3- × 10-mm implants (Replace Select Tapered, Nobel Biocare) with rough surfaces (TiUnite, Nobel Biocare) were placed at the level of the bone crest (Fig 1) on each side of the mandible of each animal, for a total of 48

Fig 2a Provisional acrylic crown was placed on the implant selected for immediate loading and the two remaining implants received healing abutments.

Fig 2b Metallic crown for the IL group, placed 1 week later.

Fig 3 After 7 days, the implant selected for EL received a crown. Note the gap left for retention on the proximal surfaces.

Fig 4 After 14 days, the implant selected for AEL received a prosthesis. Note the splinting of the crowns with acrylic resin.

implants in the study. One implant was selected for an immediate loading (IL) protocol (Fig 2), and the two remaining implants in the hemimandible received healing abutments until the delivery of prostheses according to the loading time. After 7 days, the second implant received a prosthesis for an early loading (EL) protocol (Fig 3). Fourteen days after implant placement, the third implant received a prosthesis for an advanced early loading (AEL) protocol (Fig 4). Determination of which implants received the different loading protocols[26,27] was randomly assigned through a coin toss.

After the implants were placed, an impression was made and the implants selected for the IL protocol received a provisional acrylic resin restoration (Duralay, Reliance Dental) made directly over the implant. Metallic crowns were fabricated over the casts with standard abutments in a nickel-chromium alloy (VeraBond II, Aalba Dent), with a gap for retention in the proximal faces to facilitate splinting between the crowns, according to the sequence of loading, with chemically activated resin (Duralay, Reliance Dental). The crown margins were placed at the gingival level. When the implants selected for EL received the definitive metallic crowns 1 week later, the provisional acrylic resin restorations on the IL implants were removed and replaced by the definitive metallic crowns. During the time that the prostheses remained in place, ultrasound prophylaxis was done weekly until sacrifice (during prophylaxis, the dogs were sedated with an intramuscular injection of preanesthetic, ie, 2% xylazine hydrocloride, 20 mg/kg). Intraoral adjustments were performed to eliminate any direct occlusal contact, which was verified with double-sided occlusal marking film (Accu Film II, Parkell).

Following a period totaling 12 weeks of prosthetics, counted following the positioning of the metallic crowns for the AEL group, the animals were sedated and then sacrificed with an overdose of thiopental. The crowns and abutments were removed to facilitate the preparation of histologic samples. The hemimandibles were also removed, dissected, fixed in 4% formalin (pH 7.0) for 10 days, and then transferred to a solution of 70% ethanol until processing. The specimens were dehydrated in increasing concentrations

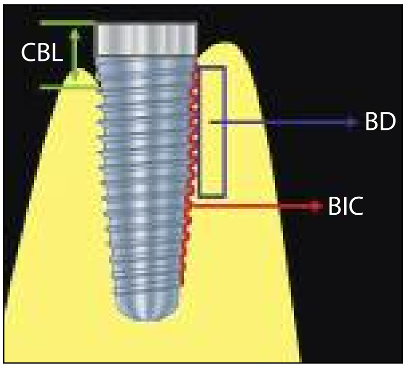

Fig 5 Schematic representation showing the parameters used for histomorphometric analysis.

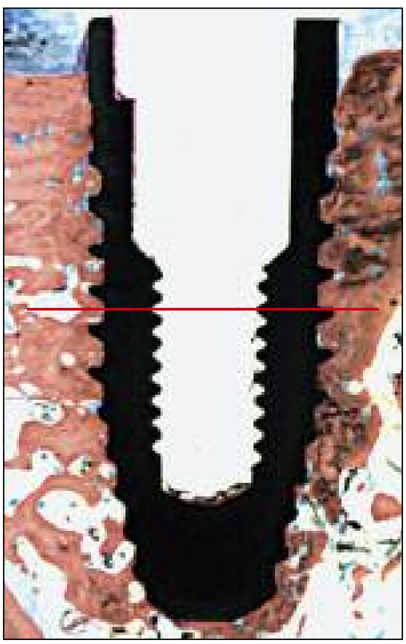

Fig 6 Representative histologic section from the IL group (Stevenel's blue and Alizarin red S; original magnification ×1.5).

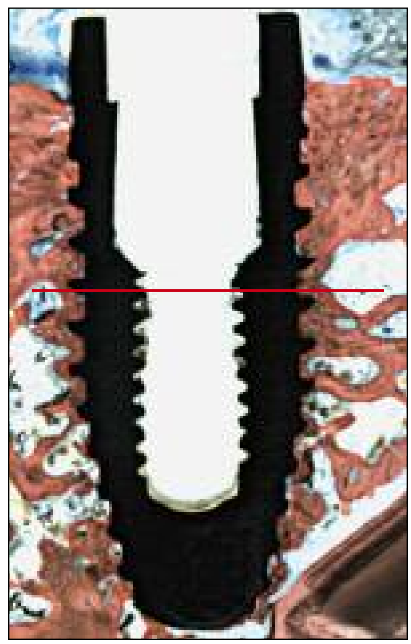

Fig 7 Representative histologic section from the EL group (Stevenel's blue and Alizarin red S; original magnification ×1.5).

Fig 8 Representative histologic section from the AEL group (Stevenel's blue and Alizarin red S; original magnification ×1.5).

of alcohol up to 100%, infiltrated, embedded in resin (LR White, London Resin), and sectioned using the "sawing and grinding" technique.[28]

Histomorphometric Analysis

One longitudinal histologic section from each implant (mesiodistal), 20 to 30 μm wide, was stained with Stevenel's blue and Alizarin red S and was captured with a video camera (Leica Microsystems) joined to a stereomicroscope (Leica Microsystems) with a magnification of 1.5μ. The images were analyzed with an imaging program (Image J, National Institutes of Health). The following measurements were made (Fig 5):

- BIC: BIC was defined as the length of the bone surface border in direct contact with the implant/complete implant periphery (×100 [%]) starting from the most coronal thread and extending to the most apical thread.
- BD: The BD around implants was determined as bone area/tissue area (×100 [%]) present within a rectangle that measured 1 × 5 mm, corresponding to 512 × 2,560 pixels. The rectangle was positioned on the most coronal thread.
- CBL: Through linear measurements (expressed in millimeters) from the top of the implant to the first BIC, the amount of CBL was determined. When the crestal bone was coronal to the top of the implant, 0 mm was used as measurement.

A blinded single examiner made the measurements. Figures 6 to 8 show representative histologic sections from each group.

Statistical Analysis

Prior to statistical analysis, multiple measurements per animal and treatment were aggregated using their arithmetic mean. Mean values and standard deviations were calculated. The data were grouped using the dogs as units for analysis. The mean differences were verified through nonparametric analysis of variance with a significance level of 5%. All calculations were performed using a specific statistical program (SPSS version 15, SPSS).

RESULTS

Clinical Findings

Postextraction healing was uneventful in all animals. At implant placement surgery 12 weeks later, the extraction sites appeared to be clinically healed. After implant placement, healing was also uneventful, with no complications observed throughout the experimental period. During the healing period, all the implants remained stable until the end of the investigation.

Histologic Observations

In all three groups, implants were surrounded by bone tissue that was composed of lamellar, woven bone, and newly formed bone. The bone tissue was characterized by parallel or concentric formations. Central canals were of different diameters, were covered by an active endosteum, and at some points were in close contact with the implant surface. Additionally, some denser areas of bone were observed closer to the implant surface.

Histomorphometric Results

The average percentage of direct BIC in the IL group was 77.9% ± 1.71% (range, 58.96% to 84.21%); in the EL group, average BIC was 79.25% ± 2.11% (range, 68.81% to 86.33%); and in the AEL group it was 79.42% ± 1.49% (range, 68.39% to 84.33%) (Table 1). The differences between groups were not statistically significant ($P > .05$). Figures 9 to 11 show implant frequency distribution in relation to the BIC percentages for the IL, EL, and AEL implants, respectively. The IL and EL groups showed a higher frequency of implants (n = 9) with values between 70% and 80% BIC versus the AEL group (n = 7 implants with 70% to 80% BIC). In the IL group, only 1 implant showed a BIC between 50% and 60%. Another 3 implants in the IL group, 5 in the EL group, and 6 in the AEL group showed values varying between 80% and 90% BIC. Percentages of less than 50% were not found in any group.

BD analysis (Table 2) revealed that the percentage of bone inside the rectangle for the IL group was 69.97% ± 3.81% (range, 42.63% to 81.05%), for the EL group it was 69.23% ± 5.68% (range, 49.47% to 85.88%), and for the AEL group it was 69.19% ± 2.90% (range, 44.15% to 85.31%). The differences between groups were not statistically significant ($P > .05$).

CBL for the IL group was 1.57 ± 0.22 mm (range, 0.00 to 2.21 mm), for the EL group it was 1.23 ± 0.19 mm (range, 0.00 to 1.97 mm), and for the AEL group it was 1.17 ± 0.32 mm (range, 0.00 to 1.76 mm) (Table 3). The differences between groups were not statistically significant ($P > .05$). Figure 12 presents the implant frequency distribution in relation to the CBL for the IL, EL, and AEL groups. The IL and EL groups had 3 implants with no bone loss, and the AEL group had 5 implants without bone loss (0 mm). The IL, EL, and AEL groups showed CBL varying between 1 and 2 mm for 9, 12, and 10 implants, respectively. Only 1 implant in the IL group showed CBL of 3 mm or more. CBL between 2 and 3 mm was observed around 3 IL implants and 1 implant each in the EL and AEL groups.

Table 1 Direct Bone-Implant Contact (BIC) Percentages Around Implants with Different Loading Times

	BIC (%)		
Animal	IL	EL	AEL
1	78.88	79.88	79.69
2	77.11	76.57	78.23
3	78.37	80.35	78.96
4	78.12	75.75	79.12
5	74.27	79.15	81.79
6	79.04	81.60	77.43
7	78.14	79.31	78.79
8	79.95	81.40	81.39
Mean	77.99	79.25	79.42
SD	1.71	2.11	1.49
P	NS	NS	NS

Significance of differences determined within nonparametric analysis of variance (NS = not significant; $P = .817$).

DISCUSSION

The high predictability with delayed loading of dental implants in the mandible has led to a reevaluation of traditional surgical and prosthetic protocols.[29] Nowadays, comparable success rates can be expected from IL implants, and it has been shown that immediate loading of dental implants does not cause untoward effects on the bone/implant interface and, in fact, produces a higher percentage of BIC than in submerged implants.[7,9–11] Factors such as the primary stability and splinting of dental implants,[30] adequate BD, and absence of overloading have been reported to influence the osseointegration process and prognosis of IL implants.[22,31]

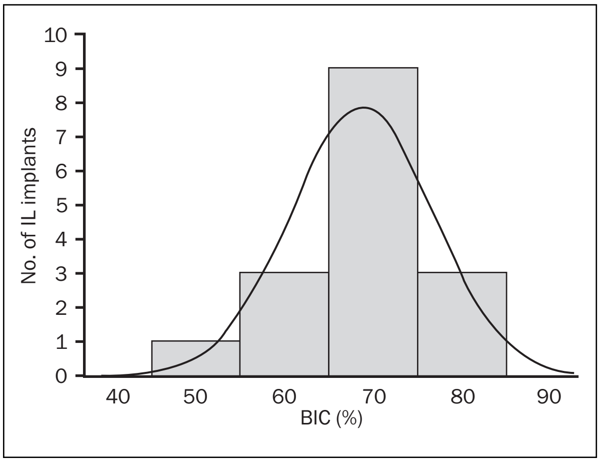

Fig 9 Histogram showing a normal distribution for BIC in the IL group, with the majority of the values around the mean.

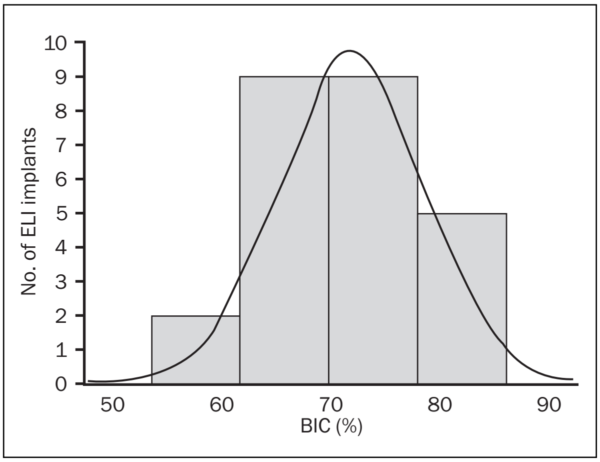

Fig 10 Histogram showing a normal distribution for BIC in the EL group, with the majority of the values around the mean.

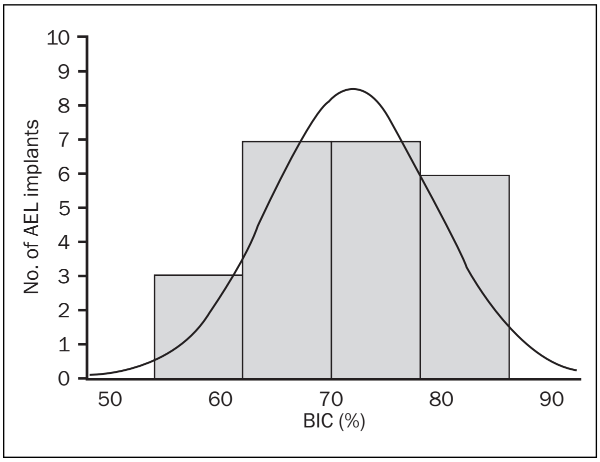

Fig 11 Histogram showing a normal distribution for BIC in the AEL group, with the majority of the values around the mean.

Table 2 Bone Density (BD) Percentages Around Implants with Different Loading Times

	BD (%)		
Animal	IL	EL	AEL
1	65.79	68.34	65.21
2	72.45	62.35	72.17
3	68.70	75.56	68.69
4	69.31	68.33	72.23
5	65.47	61.99	68.48
6	75.76	75.17	65.10
7	68.02	66.39	69.84
8	74.27	75.67	71.83
Mean	69.97	69.23	69.19
SD	3.81	5.68	2.90
P	NS	NS	NS

Significance of differences determined with nonparametric analysis of variance (NS = not significant; $P = .921$).

The classic two-stage protocol is associated with longer treatment time, and the elimination of a long healing period offers advantages in terms of cost of treatment and convenience to patients. It has also been reported that the new restoration is uniformly judged superior to the pretreatment situation within 1 week, especially in contrast to conventional removable complete dentures.[32,33]

Different experimental trials have highlighted several histologic aspects of IL implants; unfortunately, the animals used in these studies showed metabolic rates that were at least twice of that of humans.[7–10,20,34] In addition, in animal studies more parameters can be kept constant than would be possible in a clinical trial, so a very cautious approach to interpretation of the histologic results with respect to the clinical situation has to be made.[21] However, these data can provide important information about the early bone response around implants.

The long-term maintenance and success of osseointegrated implants involve continued remodeling activity at the periphery of the implant to avoid bone fatigue fracture[9] and to replace bone that may have sustained microfractures as a result of cyclic loading.[35,36] Mechanical loading plays an important role in the development, maintenance, and adaptation of the skeleton.[37] Wolff's law demonstrates the connection between mechanical events, such as bone remodeling, bone formation, and bone resorption.[38–40] Bone adaptation is dependent upon strain magnitude, duration, frequency, history, type, and distribution.[41]

In an animal study performed by Berglundh et al[42] it was reported that implants exposed to a functional load exhibit a higher degree of BIC and that functional loading may enhance osseointegration. The data of the present investigation regarding BIC were comparable with values found in the current literature, which range from 72% to 85%.[20,21,43] The high predictability of IL

Table 3 Crestal Bone Loss (CBL) Around Implants with Different Loading Times

	CBL (mm)		
Animal	IL	EL	AEL
1	1.55	1.36	1.28
2	1.68	1.37	0.66
3	1.20	0.82	0.74
4	1.33	1.12	1.13
5	1.68	1.20	1.42
6	1.55	1.40	1.60
7	1.64	1.36	1.30
8	1.89	1.21	1.26
Mean	1.57	1.23	1.17
SD	0.22	0.19	0.32
P	NS	NS	NS

Significance of differences determined with nonparametric analysis of variance (NS = not significant; *P* = .753).

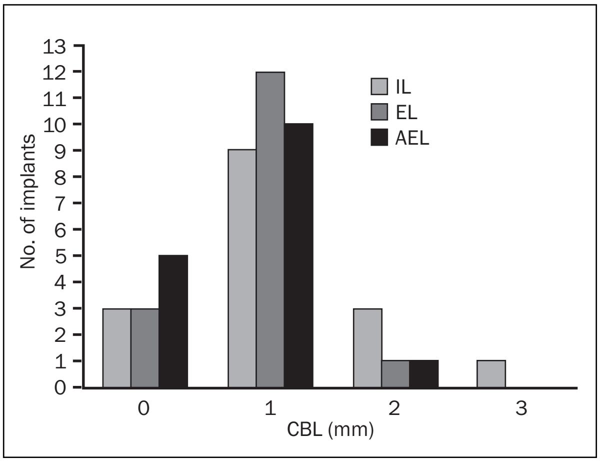

Fig 12 Frequency distribution of the number of implants in relation to CBL.

implants supplied with fixed provisional restorations has also been shown in previous reports.[44,45] This fact seems to indicate that fixed prostheses may help to keep the occlusal forces that are applied to the bone-to-implant interface within a physiologic range.[18,32,46,47] It is well known that initial implant mobility does not inevitably prevent osseointegration.[48] However, it has been suggested that micromovement of about 28 μm or less has no adverse effect on osseointegration, whereas micromovement of 150 μm or more may lead to fibrous tissue healing.[18,49,50] Microstrain may therefore act as a favorable stimulus during the healing period of implants. Results obtained through research within an osteoporotic model revealed that strains resulted in increased BD.[19] Similar results were found in dental implants.[51] However, in the present study, BD was not increased by IL, EL, or AEL ($P > .05$). This could be explained by the excellent bone quality that was obtained after tooth extraction through the 12-week healing period.

Furthermore, in the present study, bone resorption was evaluated through analysis of CBL, a measurement made from the top of the implant to the first BIC. To standardize implant placement and to provide a reference for the measurement of CBL, all implants were placed at the level of the bone crest. As observed in this study, no significant difference in CBL was observed between all groups ($P > .05$), although numerically higher CBL was noted in the IL group. Additionally, initial breakdown of the implant-tissue interface generally begins at the crestal region in successfully osseointegrated dental implants. Possible etiologic factors of early implant bone loss (from implant placement to 1-year postloading) include surgical trauma, formation of biologic width, implant crest remodeling, and other factors. These factors may have contributed to the CBL achieved in all groups evaluated. However, surgical trauma has been regarded as one of the most commonly suspected etiologies for early CBL.[52] Failures in bone adhesion were reported when implants were placed in monkeys and overloaded.[53] The possibility of triangular or crater-type defects in a rabbit model was observed following application of excessive occlusal force.[54] However, this observation was contradicted by other investigators; no peri-implant bone resorption was observed in monkeys after excessive occlusal force of 300 N was applied.[55] Additionally, in other animal studies, continuously loaded implants were reported to be surrounded by compact and mineralized tissues with a density that was 100% to 150% higher than that of the original spongy bone.[56] It is important to emphasize that it is well established that the polished collar around these type of implants never retains crestal bone and, as such, the height of the collar will always equal the minimum bone loss expected.[57]

One of the major rationales for avoiding immediate loading has been the presence of a necrotic layer of bone adjacent to the implant surface, which is mainly related to surgical trauma.[5] It has been postulated that this necrotic layer should be replaced by new bone before loading.[58] However, bone remodeling does not occur at the same time around the entire implant; otherwise, mobility would be expected during the bone remodeling process. It appears that remodeling is variable, with osteoclastic and osteoblastic activity balanced, so that implant stability is maintained during osseointegration.[9,59] Because of inadequate implant site preparation, an increased amount of necrotic bone in the periphery of an implant can be produced, which may lead to the loss of the implant.[60] However, it seems that, in the majority of cases, the reduction of the vital BIC can be compensated effectively by rigid splinting fixation, as was used in the present study.

Clinical studies have supported the fact that the clinical outcomes following immediate loading are comparable and even superior to those observed following conventional loading.[61–63] The results of this study confirm these results; loading time did not compromise the histomorphometric bone response, as represented by BIC, BD, and CBL. There were no significant differences among the three groups, suggesting that outcomes using these different loading protocols may be similar.

CONCLUSIONS

Within the limits of this study it can be concluded that, in dog mandibles, different early loading times do not seem to significantly affect the bone response around implants.

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