

Review

Effect of the Timing of Restoration on Implant Marginal Bone Loss: A Systematic Review

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Background: The advancement in implant dentistry has allowed shortened treatment time by restoring the implants earlier. Whether the timing of restoration has an impact on implant marginal bone level has not been systematically analyzed. The aim of this study is to compare marginal bone loss (MBL) between implants that were restored with the following protocols: 1) immediate restoration/loading (IR/L); 2) early loading (EL); and 3) conventional loading (CL).

Methods: An electronic literature search from three databases (until November 2011) and a hand search in implant-related journals were conducted. Clinical human studies in English language that had reported a comparison of MBL between implants with IR/L, EL, or CL with ≥ 12 -month follow-up were included. In addition, the minimal number of implants had to be 10 for each group. Implants with both immediate placement (IP) and delayed placement (DP) were included and analyzed separately. An assessment of the publication bias for the included randomized clinical trials (RCTs) was performed.

Results: The initial search resulted in 1,640 articles, of which 27 articles in full text were further evaluated for eligibility. Finally, 11 studies (eight RCTs, two controlled clinical trials, and one retrospective study) were qualified and classified into four groups: 1) IR/L + DP versus CL + DP ($n = 6$ articles); 2) IR + DP versus EL + DP ($n = 2$ articles); 3) EL + DP versus CL + DP ($n = 1$ article); and (4) IL + IP versus CL + IP ($n = 2$ articles). A meta-analysis performed for group 1 showed 0.09 mm (95% confidence interval = -0.27 to 0.09 mm) difference in the mean MBL, favoring the IR/L protocol but without significant difference ($P = 0.33$). No significant difference in MBL was found for groups 2 through 4 after adjusting for the implant placement level. The eight RCTs were determined to be at moderate-to-high risk of publication bias.

Conclusions: This meta-analysis does not show an effect of the timing of restorations on implant MBL. The selection of restoration protocols should be based on factors other than MBL. *J Periodontol* 2013;84:159-169.

KEY WORDS

Alveolar bone loss; dental implantation; dental implants; dental prosthesis design; dental prosthesis, implant-supported.

Implant dentistry has evolved to a stage that a high implant survival rate alone, achieved by the conventional loading (CL) approach, could no longer satisfy the patients and health care providers. Long waiting time for the implant to be osseointegrated before the restoration can be placed discourages patient acceptance of implant therapy. The restoration of chewing and phonetic function and esthetics that implants can provide is delayed. Different loading protocols have thus been developed and subsequently classified.^{1,2} According to the 2004 consensus statements,¹ immediate restoration (IR) refers to the insertion of a restoration within 48 hours of implant placement but not in occlusion with the opposing dentition, whereas immediate loading (IL) is to place the restoration in occlusion with the opposing dentition within 48 hours of implant placement. Early loading (EL) is defined when a prosthesis is placed ≥ 48 hours after the implant placement but not later than 3 months afterward.

The rationale for the CL protocol was to keep the implant in an undisturbed environment during the healing period.³ It was believed that applying forces to the implant during that critical period might cause micromovement at the implant-bone surface, which in turn results in fibrous encapsulation and eventually implant failure. Understanding the process of how osseointegration is achieved and

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the advances in implant designs have allowed a faster loading protocol.⁴ The primary stability that is achieved by mechanical locking of the implant to the bone serves to prevent the occurrence of micromovement, even when the implant is subject to occlusal loads. When the primary stability starts to decrease, the secondary stability catches up and takes over to resist occlusal forces. Certainly, methods to decrease the loading, such as splinting, increasing the number of implants, and eliminating lateral contacts, have been applied to optimize the loading condition. As long as the forces do not violate the orchestrated implant healing process, it is possible to restore or load the implant immediately.

EL protocol has been validated for full-arch rehabilitations with various levels of evidence in a review article.⁵ Briefly, EL of overdentures or fixed dentures in either jaw is clinically documented or clinically well documented. IL is clinically well documented for fixed dentures in either jaw and for overdentures in the mandible. However, insufficient scientific or clinical documentation was found for IL of maxillary overdentures. Included in the documentation within the same review article,⁵ implants with IL or EL protocol had a survival rate (87.2% to 100%) comparable to those with CL protocol. High survival rate (average of 96.4% to 98.2%) was also found for early and IR/L implants for single-tooth and partial-arch applications, although most articles were case reports.⁶ It is important to note that some important factors, such as bone quality and quantity, implant design, splinting of implants, and prosthetic design, have to be considered for achieving predictable outcomes.⁷

To further shorten treatment time and maintain soft-tissue architecture, immediate implant placement in fresh sockets and provisionalization has been advocated, especially for the restoration of the esthetic zone.^{8,9} With this technique, less tissue damage might be expected than the standard protocol because only one surgery is required. A systematic review¹⁰ showed that this procedure is predictable for single-tooth replacement in the anterior maxilla, with certain precautions being considered.

Other than the presence of implants *in situ*, MBL with time is another criterion to assess implant success. It can be classified into early and late MBL. Late MBL is most likely related to peri-implantitis.¹¹ The causes of early bone loss are less understood and have been hypothesized, including the following: 1) surgical trauma; 2) the presence of the microgap between the fixture and the abutment; 3) the remodeling process to restore biologic width; and 4) occlusal overloading.¹² It has been shown that the occlusal stresses primarily concentrated at the crestal bone. Bone remodeling is a function of stresses and a net result from bone apposition and resorption.¹³ Excessive

loading may cause progressive marginal bone loss,¹⁴⁻¹⁷ which might be more likely to occur when the bond between the implant and bone has not been established during the initial healing phase. In light of the fact that occlusal loading has a role on bone remodeling, it is the aim of this meta-analysis to evaluate the effect of the timing of restoration on implant MBL.

MATERIALS AND METHODS

A search of three electronic databases, including PubMed, Ovid (MEDLINE), and Cochrane Central, for relevant studies published in English was performed in November 2011 by two examiners (FS and H-LC). There was no limit to the time of publication; however, only articles in English language were considered. The search terms used, in which mh represented the MeSH term and tiab represented the title or abstract, were as follows: “Jaw, edentulous”[mh] OR “Alveolar process”[mh] OR “Alveolar bone loss”[mh] OR “Dental implantation”[mh] OR “Dental implants”[mh] OR “Dental prosthesis design”[mh] OR “Denture”[mh] OR “Dental prosthesis, implant-supported”[mh] OR “Healed socket”[tiab] OR “Fresh socket”[tiab] AND (“Immediate”[tiab] OR “Early”[tiab] OR “Delayed”[tiab] OR “Immediate non-occlusal”[tiab] OR “Functional”[tiab] OR “Non-functional”[tiab]) AND (“Provisionalization”[tiab] OR “Restoration”[tiab] OR “Loading”[tiab]).

In addition, a search for references in the included papers was performed. Finally, a hand search (January 2000 through November 2011) was performed in dental journals, including *Journal of Oral and Maxillofacial Implants*; *Clinical Implant Dentistry*, and *Related Research*; *Clinical Oral Implants Research*; *Implant Dentistry*; *European Journal of Oral Implantology*; *Journal of Oral Implantology*; *International Journal of Oral and Maxillofacial Surgery*; *Journal of Oral and Maxillofacial Surgery*; *Journal of Dental Research*; *International Journal of Prosthodontics*; *Journal of Prosthetic Dentistry*; *Journal of Clinical Periodontology*; *Journal of Periodontology*; and *The International Journal of Periodontics and Restorative Dentistry*.

Articles were included if the following criteria were fulfilled: 1) human clinical trials that compared marginal bone loss between implants with immediate, early, or delayed loading/restoration and ≥ 10 implants in each group with ≥ 12 -month follow-up. The implants could be placed in either healed or fresh sockets but had to be restored with fixed prostheses. Articles were excluded if they fell into one of the following categories: case reports/series, review articles, or clinical trials with < 10 implants with insufficient follow-up time or with implants that were placed along with bone grafts or restored with

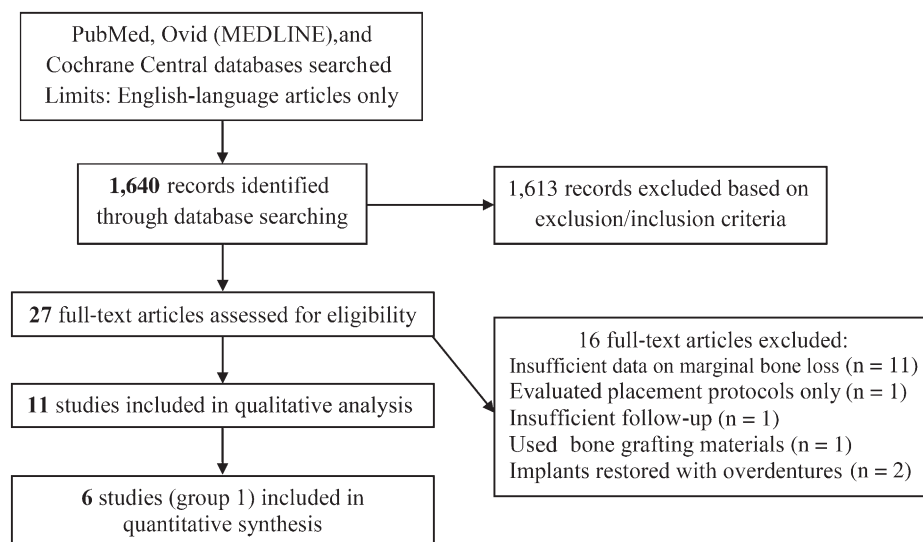


Figure 1.
Flowchart of the screening process.

removable overdentures. Articles with different implant systems or with different implant placement protocols (e.g., healed versus extraction sockets) between experimental groups were also excluded. Potential articles were independently reviewed in full text by two examiners (FS and H-LC). The final decision on the included articles was made by mutual agreement of the two examiners.

Data Analyses

The outcome was implant MBL as assessed radiographically. Data including implant numbers and mean value and standard deviation of marginal bone loss at 1-year follow-up were extracted from each included article and transported to a commercially available software package[†] for the meta-analysis. The contributions of each article to the primary outcome were weighed based on the sample size, and the random-effect model was chosen. Publication bias was examined by the funnel plot in which the standard error of the difference in mean marginal bone loss was plotted against the difference in mean from the included articles. The reporting of this meta-analysis adhered to the Preferred Reporting Items for Systematic Review and MetaAnalyses statement.¹⁸

Risk of Bias Assessment

The criteria used for assessment of the risk of bias for the selected randomized controlled trials were derived from the checklist of the Cochrane Center¹⁹ and the CONSORT (Consolidated Standards of Reporting Trials) statement,²⁰ including the following: 1) representative of general population; 2) defined inclusions/exclusions; 3) randomization methods; 4) allocation

concealment method; 5) mask of the examiner; 6) intervention different only; and 7) patient drop-out and analysis accounts for patient losses. One of three categories were given after the assessment: 1) low risk of bias if no or one criterion was missing; 2) moderate risk of bias when two criteria were missing; and 3) high potential risk of bias if ≥ 3 criteria were missing. Two reviewers (FS and H-LC) assessed the risk of publication bias for the included randomized clinical trials.

RESULTS

The screening process was represented in Figure 1. The initial screening yielded a total of 1,640 articles. After initial screening of their titles and abstracts, 27 articles were further evaluated in full text,

of which 11 articles²¹⁻³¹ were selected for this systematic review. Interexaminer agreement in selecting articles was 0.9. The reasons for exclusion after full-text evaluation included the following: 1) no report on MBL³²⁻³⁹ 2) investigating the effect of the timing of implant placement;⁴⁰ 3) MBL reported as a range only;⁴¹⁻⁴³ 4) insufficient follow-up;⁴⁴ 5) the use of grafting materials;⁴⁵ and 6) the use of overdentures as final restorations.^{46,47}

Characteristics of the Included Articles

Study design and length of the follow-up. The 11 articles were subcategorized into four groups based on their loading and placement protocols: Group 1: IR/L versus CL implants, in which the implants were placed in healed ridges (six articles); Group 2: IR versus EL implants, in which the implants were placed in healed ridges (two articles); Group 3: ER versus CL implants, in which the implants were placed in healed ridges (one article); and Group 4: IL versus CL implants, in which the implants were placed in fresh sockets (two articles).

Table 1 summarizes the characteristics of the included studies. A meta-analysis was performed for group 1, whereas a summary of the main outcome was provided for groups 2 through 4.

Eight articles^{22-24,26-28,30,31} were classified as a randomized controlled trial, two^{25,29} were controlled clinical trials, and the other one²¹ was a retrospective study.

Implant sample size. The total number of test and control implants that were available for data analysis

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Table 1.
Characteristics of the Selected Articles

Reference	Study Design	Follow-Up (months)	Site	Group	Restoration Time	Loading Protocol	No. Implants at Baseline	No. Implants Available for Analysis	Flap Reflection	Insertion Torque (Ncm)	Restoration Type	MBL (mm)†	P Value
Group 1: immediate loading/restoration versus conventional loading in healed ridges													
Degidi and Piatelli, ²¹	RET	12	Max/mand	T C	<48 h 4 to 6 m	IL or IR C	338 314	221 79	Y	>25	F or P F, P, or S	0.70 ± 0.20 0.60 ± 0.20	>0.05
Degidi et al. ²²	RCT	12*	Max lateral incisor	T C	<24 h 6 m	IR C	30 30	30 30	Y	>25	S	0.69 ± 0.38 0.58 ± 0.28	>0.05
Güncü et al. ²³	RCT	12	Mand first molars	T C	<24 h >3m	IL C	12 12	11 12	Y	NA	S	0.45 ± 0.39 0.68 ± 0.30	>0.05
Hall et al. ²⁴	RCT	12	NA	T C	<4 h ≈6.5 m	IR C	14 14	13 14	NA	NA	NA	0.64 ± 1.17 0.78 ± 1.58	>0.05
Ryser et al. ²⁵	CCT	12	Max/mand	T C	NA NA	IR C	32 44	32 42	Y	NA	S	0.30 ± 0.50 0.50 ± 0.46	>0.05
Schincaglia et al. ²⁶	RCT	12	Mand molars	T C	<24 h 3 to 4 m	IL C	15 15	14 15	Y	≥20	S	0.77 ± 0.38 1.20 ± 0.55	0.022 (favors test group)
Group 2: immediate restoration versus early loading in healed ridges													
Galli et al. ²⁷	RCT	14	Max/mand	T C	<48 h 2 m	IR EL	25 27	24 27	Y	>30 for S >20 for P	P or S	1.14 ± 0.58 1.18 ± 0.54	>0.05

Table 1. (continued)
Characteristics of the Selected Articles

Reference	Study Design	Follow-Up (months)	Site	Group	Restoration Time	Loading Protocol	No. Implants at Baseline	No. Implants Available for Analysis	Flap Reflection	Insertion Torque (Ncm)	Restoration Type	MBL (mm)†	P Value
Ganeles et al. ²⁸	RCT	12	Max/mand post. teeth	T C	<24 h 28-34 d	IR EL	197 186	168 155	Y	NA	P or S	0.90 ± 0.90 0.63 ± 0.95	< 0.001 (favors test group) >0.05 after adjustment for placement level
Group 3: early loading versus conventional loading in healed ridges	CCT	48	Max	T C	6 weeks 6 m	ER C	36 23	34 22	NA	40.5 ± 6 39.7 ± 7	S	1.06 ± 0.15 1.16 ± 0.1	>0.05
Turkyilmaz et al. ²⁹													
Group 4: immediate loading versus conventional loading in extraction sockets													
Crespi et al. ³⁰	RCT	24	Max teeth except molars	T C	Immediately >3m	IL C	20 20	20 20	N	>25	S	1.02 ± 0.53 1.16 ± 0.51	>0.05
Prosper et al. ³¹	RCT	60	First and second mand molars	T C	Immediately 3m	IL C	60 60	58 58	Y	NA	S	1.31 ± 0.44 1.01 ± 0.59	>0.05

Max = maxilla; mand = mandible; post = posterior; T = test; C = control; h = hours; m = months; d = days; IL = immediate restoration; IR = immediate loading; EL = early loading; C = conventional loading; F = full-arch prostheses; P = partial-arch prostheses; S = single crown; MBL = marginal bone loss; NA = not available; RCT = randomized controlled trial; CCT = controlled clinical trial; RET = retrospective study.
 * Degidi et al.²² reported marginal bone loss up to 36 months; however, only 1-year data were used for the meta-analysis and were included in this table.
 † The data were obtained at the follow-up time reported in this table.

was 310 and 182 in group 1, 192 and 182 in group 2, 34 and 22 in group 3, and 80 and 80 in group 4. Of the 11 articles, a multicenter study²⁸ provided the largest sample size, with 168 immediately loaded and 155 early restored implants, whereas the study with the smallest sample size²³ had 11 and 12 immediately and delayed restored implants, respectively.

Implant location, restoration type, and protocol and surgical specifications. *Group 1:* Two studies^{21,25} did not restrict the type of teeth to be restored. One²² only studied maxillary lateral incisors; two^{23,26} only studied mandibular molars. One study²⁴ did not mention the type of tooth studied. One study²¹ included fully and partially edentulous ridges; four studies^{22,23,25,26} included single missing teeth. Most immediately restored implants did not contact in centric occlusion during temporization,^{22,24,25} except those replacing fully edentulous ridges²¹ and single mandibular molars.^{23,26} Three studies^{21,22,26} specified the minimal insertion torque values (≥ 20 or >25 Ncm) that allowed for immediate restoration/loading procedures. In five studies,^{21-23,25,26} mucoperiosteal flaps were raised during the implant surgery, whereas the other²⁴ one did not mention the type of surgical method.

Group 2: In both studies,^{27,28} the test implants were immediately restored within 48 hours without occlusal contacts, whereas the control implants were loaded on days 28 through 34²⁸ or at month 2.²⁷ Implants were placed in partially edentulous ridges or single-tooth gaps in both studies. All tooth types were studied in one article,²⁷ whereas only posterior teeth in both jaws were studied in another article.²⁸ One study²⁷ specified that the minimal insertion torque values for immediate restoration procedures were >20 or >30 Ncm in partially edentulous and single-tooth restorations, respectively. Mucoperiosteal flaps were raised in both studies.

Group 3: One study²⁹ was available for data extraction. Implants in the test group were restored at 6 weeks after implant placement, whereas the control group implants were restored 6 months after the surgery. Only single implants were studied. All implants were placed in the maxilla, replacing all types of teeth.

Group 4: Single-tooth implants located in the maxilla except molar sites³⁰ or in the mandibular molar sites³¹ were studied. The test implants were loaded immediately, whereas the controls were loaded 3 months after. Mucoperiosteal flaps were raised in one study³¹ but not the other one.³⁰ Minimal insertion torque (>25 Ncm) was required for immediately loaded implants.³⁰

RESULTS

Group 1

The meta-analysis showed that the weighted mean difference in marginal bone loss among implants

that were loaded or restored immediately and those that were conventionally loaded was -0.09 mm (95% confidence interval = -0.27 to 0.09 mm), favoring the test group but without statistical significance ($P = 0.33$) (Fig. 2). The funnel plot showed asymmetric distributions, indicating the possibility of publication bias (Fig. 3). Because of the fact that most articles showed no significant differences, the results of the funnel plot might be negligible.

Groups 2 through 4

Figure 4 summarizes the comparison of the marginal bone loss for groups 2 and 4. Two articles^{27,28} were available for comparisons between IR and EL implants. In one multicenter, randomized controlled study,²⁷ 14 months after implant surgery, the mean marginal bone loss was not different (1.14 ± 0.58 and 1.18 ± 0.54 mm for the immediate and early restoration group, respectively). In the other multicenter study,²⁸ implants that were immediately restored lost significantly more marginal bone than early loaded ones (0.90 ± 0.90 versus 0.63 ± 0.95 mm). However, after adjusting for the differences in implant position in relation to marginal bone level, such differences did not exist anymore. When comparing MBL between implants that were early and conventionally loaded in healed ridges, no differences (1.06 ± 0.15 versus 1.16 ± 0.1 , respectively) were found 4 years after implant surgery.²⁹ For implants that were placed in fresh sockets, whether they were loaded immediately or conventionally, the bone level was not significantly different.^{30,31}

Results of Risk of Bias Assessment

The eight included randomized controlled trials^{22-24,26-28,30,31} were categorized into either moderate or high risk of bias (Table 2). The potential bias originated from the following: 1) no specification of the inclusion/exclusion criteria²⁴; 2) no mention of randomization methods^{27,30,31}; 3) no mention of allocation concealment method^{22,26,27,30,31}; 4) no masking of the examiners^{24,30}; and 4) no analysis accounting for patient losses.²⁴

DISCUSSION

This study suggests that the timing of restoration does not influence MBL around implants at short-term follow-up. Evidence on the long-term effect is limited, although it is less likely a difference will be seen. For a successful implant, most MBL occurred during the first year of function, after which the loss is negligible. Additionally, once the osseointegration is achieved and permanent restorations are placed, the differences between various loading protocols do not exist anymore. One study²² was available for 3-year follow-up and did not show difference in MBL between immediately and conventionally loaded implants (0.85

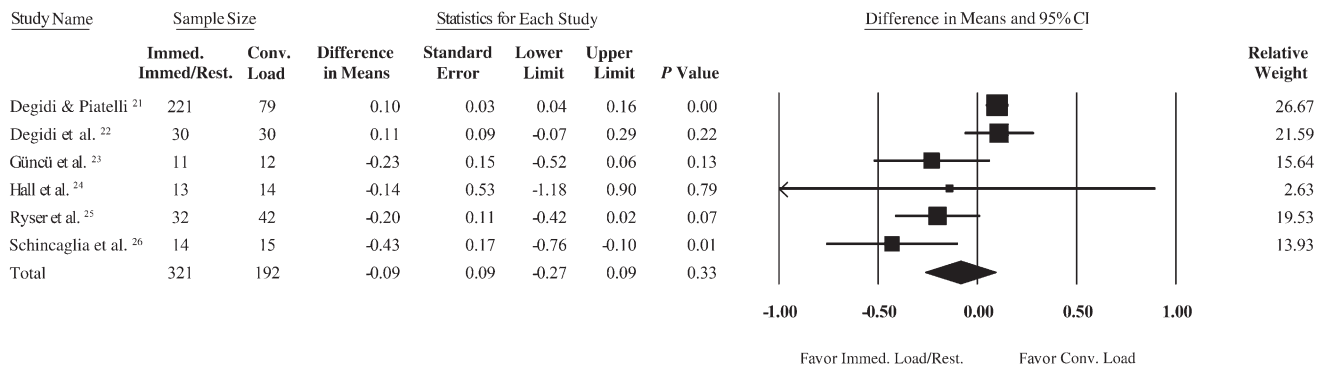


Figure 2.

A meta-analysis for the comparison of marginal bone loss for group 1. The weighted mean difference in marginal bone loss between implants with immediate and delayed restorations was -0.09 mm (95% confidence interval = -0.27 to 0.09 mm), favoring immediate restoration but without statistical significance ($P = 0.33$).

± 0.71 versus 0.75 ± 0.63 mm). Another³¹ provided 6-year data, which concluded that MBL of immediately placed and restored implants was comparable to that of immediately placed and conventionally loaded implants.

Implant insertion torque has to be considered for the application of IR/L and EL protocol because it is related to primary stability and implant survival. An animal study⁴⁸ showed that high insertion torque increased implant primary stability. Implant failure rate was reduced by 20% when every 9.8 Ncm was added to the insertion torque.⁴⁹ An adequate torque value for immediate and early loaded implants has not been established yet. One study⁴⁹ suggested that, to achieve osseointegration, ≥ 32 Ncm is necessary, whereas a recent clinical trial⁵⁰ showed that 25 Ncm seemed more than sufficient to yield a favorable clinical outcome. Most studies included in the present review suggested that the insertion torque of ≥ 20 Ncm had to be achieved before the implants could be immediately restored or loaded. Modifications of surgical procedures, e.g., undersized site preparation, have shown to enhance primary stability and should be considered for immediately loaded implants.⁵¹

In one study,²⁶ single implants replacing the mandibular molars were immediately loaded and showed significantly less MBL. It is possible that occlusal loading might help maintain marginal bone level. Bone remodels in reaction to the stresses that are applied to it.¹³ Additionally, whether the remodeling is anabolic or catabolic depends on the magnitude of forces. Excessive forces cause microfracture and eventual bone resorption; conversely, optimal forces can stimulate bone apposition. At molecular levels, bone cells are capable of sensing mechanical stimuli, resulting in bone mass and morphology changes as an adaptive response.⁵² Almost all intracellular trans-

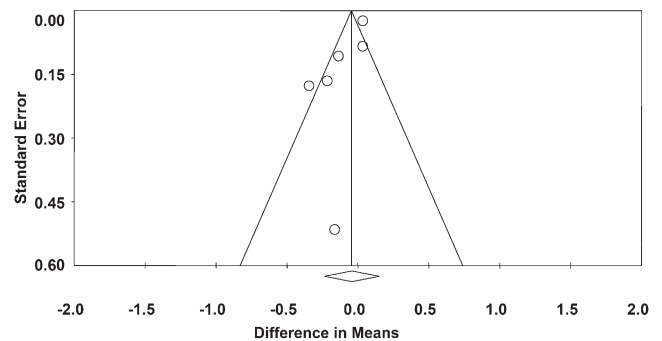


Figure 3.

The funnel plot for the meta-analysis showed asymmetric distributions, indicating the possibility of publication bias. Nevertheless, because of the fact that most papers showed no statistical differences, the results of the funnel plot might be negligible.

duction signal cascades are activated in this response, from intracellular cyclic adenosine monophosphate, inositol trisphosphate, calcium guanine regulatory proteins, to mitogen-activated protein kinase. The end results are the recruitment of either osteoblasts or osteoclasts. Animal studies have shown higher percentage of bone-implant contacts,^{53,54} higher peri-implant bone density,^{53,55} and the presence of transversely oriented collagen fibers in the peri-implant bone⁵⁶ for immediately loaded implants. More clinical studies are needed to test the beneficial role of IL on maintaining marginal bone.

Immediate implant placement and provisionalization is technically more challenging but can be predictable as long as certain criteria are met. A systematic review¹⁰ reported 100% short-term implant survival rate in almost all included articles. This approach might also help preserve peri-implant hard and soft tissue. Case series investigating

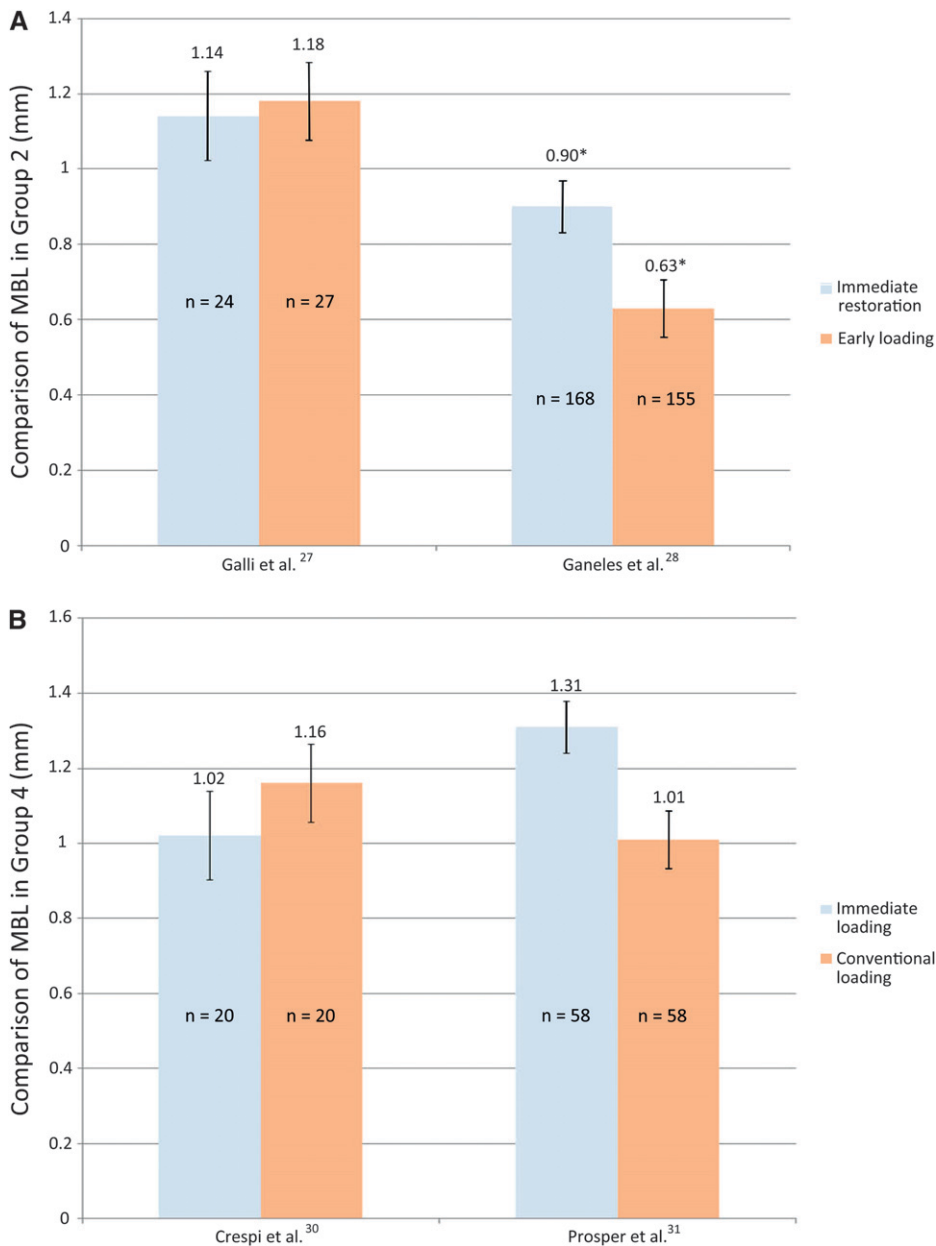


Figure 4.

Bar charts summarizing the comparison of MBL in group 2 (A) and group 4 (B). A significant difference was found by Ganeles and Wismeijer⁶ (as marked with *). According to the original article, after adjusting for implant placement level, the difference did not exist anymore.

implants that were placed and restored immediately in the esthetic zone showed minimal marginal bone changes (ranging from 0.3⁵⁷ to 0.67⁵⁸ to \approx 1 mm⁵⁹). Additionally, limited loss of papilla height (<0.5 mm) was reported.⁶⁰ There was even some papilla rebound after several years of function.^{58,59} The preservation of papilla height might have been the combined results of the reduced number of surgical procedures, maintenance of the bone spike of the adjacent teeth, and the contours of the temporary restorations. One

concern about this approach is the recession of facial mucosa, which was progressive with time.⁵⁸ Up to 1 year, the mean recession was 0.55 mm. At the mean follow-up time of year 4, the recession was 1.13 mm. Gingival biotype is correlated with the amount of recession, with thick tissue biotype yielding less loss.⁵⁸

A head-to-head comparison of MBL between implants after immediately placed and restored protocol and immediately placed and conventionally restored protocols is limited. The present review identified two articles^{30,31} that had addressed this issue, both of which did not show a difference in MBL between the two experimental groups.

Limitations of this systematic review include small sample size, only English articles as a selection criterion, and heterogeneities in the study designs of the included papers. Nonetheless, this review provides updated information on potential effects of the timing of restorations on implant marginal bone level. Future research should focus on the effect of immediate/early loading on grafted bone.

CONCLUSIONS

Eleven studies²¹⁻³¹ (eight randomized controlled trials, two controlled clinical trials, and one retrospective study) were qualified for the evaluation of implant MBL between different loading protocols. Nine articles²¹⁻²⁹ evaluated implants that were placed in healed sockets, of which six²¹⁻²⁶ and two^{27,28} studies compared MBL between IL/R and CL and between IR and EL, respectively. The other study²⁹ made the comparison EL loading and CL. Two articles^{30,31} investigated marginal bone level changes of implants that were placed in fresh sockets and received either immediate or delayed loading. Available evidence did not show an effect of the timing of restoration on marginal bone level.

Table 2.
Assessment of Publication Bias for Included Randomized Controlled Trials

Criteria	Degidi et al. ²²	Güncü et al. ²³	Hall et al. ²⁴	Schincaglia et al. ²⁶	Galli et al. ²⁷	Ganeles et al. ²⁸	Crespi et al. ³⁰	Prosper et al. ³¹
Representative of general population	N	Y	N	N	N	N	N	Y
Defined inclusions/exclusions	Y	Y	N	Y	Y	Y	Y	Y
Randomization methods	Y	Y	Y	Y	N	Y	N	N
Allocation concealment method	N	N	Y	N	N	Y	N	N
Examiner masked	Y	NA	NA	Y	Y	Y	N	Y
Intervention different only	Y	Y	Y	Y	Y	Y	Y	Y
All patients accounted for at end of study	Y	N	N	Y	Y	N	Y	Y
Analysis accounts for patient losses	N/A	Y	N	N/A	N/A	Y	N/A	N/A
Estimated potential risk of bias	Moderate	High	High	Moderate	High	Moderate	High	Moderate

N = no; Y = yes; NA = not available; N/A = not applicable.

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