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Meta-Analysis
Dental Implants

Effect of implant loading protocols on failure and marginal bone loss with unsplinted two-implant-supported mandibular overdentures: systematic review and meta-analysis

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Abstract. The aim of this study was to compare implant failure and radiographic bone level changes with different loading protocols for unsplinted two-implant-supported mandibular overdentures. An electronic search of two databases (PubMed, Cochrane Library) was performed, without language restriction, to identify randomized controlled trials (RCTs) comparing immediate or early versus conventional dental implant loading protocols for unsplinted two-implant-supported mandibular overdentures. Data were extracted independently by two reviewers. The Cochrane tool was used to assess the quality of included studies. A meta-analysis was performed. Eight RCTs were identified, seven of which were included; one trial was excluded because related outcomes were not measured. Four of the seven studies were considered to have a high risk of bias and three an unclear risk. Meta-analysis revealed no difference between immediate versus conventional or early versus conventional implant loading protocols regarding implant failure (risk difference (RD) −0.02, 95% confidence interval (CI) −0.13 to 0.10; RD 0.09, 95% CI −0.03 to 0.20) or marginal bone loss (mean difference (MD) 0.09, 95% CI −0.10 to 0.28; MD −0.05, 95% CI −0.12 to 0.02) for implants supporting mandibular overdentures. These findings should be interpreted with great caution given the serious numerical limitations of the studies included.

Key words: dental implants; implant failure; meta-analysis; implant placement loading protocols; systematic review.

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The prosthetic management of the edentulous patient has long been a major challenge for the prosthodontist. The classical treatment plan for edentulous patients is the conventional complete denture. However, this treatment is associated with several complications, in particular related to stability and retention, leading to constant fear of denture loosening during different jaw movements. These problems occur more frequently with the mandibular denture[1].

With the advent of dental implants for the retention and/or support of removable prostheses, these functional deficiencies associated with conventional dentures have improved greatly[2,3].

In the McGill Consensus Statement published in 2002, many investigators agreed that the basic restoration for the edentulous mandible should be an implant-supported overdenture with two-implants placed in the anterior mandible[4]. Mandibular overdentures with two implants, retained by unsplinted attachments, are considered a simple and cost-effective treatment option[5–7].

In the early days of implantology, Brånemark and collaborators empirically advocated an unloaded healing period of 3 months for the mandible and 6 months for the maxilla following implant placement, to facilitate an uneventful osseointegration, avoid soft tissue encapsulation, and improve implant survival rates[8].

The osseointegration process induced is characterized by an intimate interfacial contact between bone and the implant surface, which determines clinical success. Implant surface macro- and micro-geometry, together with the surgical and prosthodontic protocols employed, appear to determine successful treatment outcomes[9–11].

Unfortunately, most patients perceive the period between tooth loss and definitive rehabilitation as traumatic and uncomfortable, because provisional prostheses mostly provide compromised function and aesthetics[12]. Substantial benefits may be derived by shortening the provisional prosthesis period, as well as reducing the treatment duration[13].

In previous systematic reviews, several authors have tried to determine the implant loading time that is most efficient for fixed and removable prostheses[14], and for removable overdentures with different implant numbers and different prosthetic designs[15–17]. Nevertheless, more robust evidence is needed to determine whether immediate or early implant loading provides the same satisfactory results over time for the unsplinted two-implant-supported mandibular overdenture, as this treatment approach is considered standard care for the edentulous mandible. This would then encourage routine prescription of an equally efficacious clinical protocol.

The aim of this systematic review was to answer the following question: ''In patients requiring unsplinted two-implant-supported overdentures, do the immediate or early implant loading protocols show similar outcomes in terms of implant failure and peri-implant marginal bone levels, when compared to the conventional loading protocol?''

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[18].

Eligibility criteria and definitions

Inclusion criteria encompassed the following: (1) Study design: all randomized controlled trials (RCTs), including parallel group and split-mouth designs. (2) Participants: any subject receiving dental implants. (3) Interventions and controls: immediate or early (intervention) versus delayed (control) loading protocols for unsplinted two-implant overdentures. The same type of implant had to be used in both groups. Only those studies with a minimum follow-up of 1 year after loading were considered.

The definitions of the loading protocols used in this review were those reported by Alsabeeha et al.[17], as follows: (1) for conventional loading, the overdenture is attached in a second procedure after a healing period of 3–6 months, with a two-stage (submerged) implant placement protocol; (2) for early loading, the overdenture with attachment system is in contact with the opposing dentition and placed at least 48 h after implant placement, but not later than 3 months afterwards, with a one-stage (non-submerged) implant placement protocol; (3) for immediate loading, the overdenture with attachment system is placed in occlusion with the opposing dentition within 48 h of implant placement, with a one-stage (non-submerged) implant placement protocol.

The outcome measures were (1) implant failure, defined as implant mobility or the removal of stable implants dictated by progressive marginal bone loss or infection, and (2) radiographic marginal bone level changes on intraoral radiographs taken with a parallel technique, from surgical placement to 1 year in function.

The following were exclusion criteria: non-randomized trials, retrospective studies, case series, and case reports; studies with follow-up of less than 1 year; studies not reporting implant failure and/or marginal bone loss.

Information sources

The PubMed and Cochrane Library electronic databases were searched to identify RCTs without time or language restrictions, comparing submerged versus non-submerged dental implants. In addition, a manual search of the following implant-related journals was done: *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *European Journal of Oral Implantology*, *Implant Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral and Maxillofacial Implants*, *Journal of Periodontology*, and the *International Journal of Periodontics and Restorative Dentistry*. Moreover, online databases providing information about clinical trials in progress were checked (clinicaltrials.gov; www.centerwatch.com/clinicaltrials; www.clinicalconnection.com). The last search was performed on 6 March 2017.

Search strategy

Two reviewers (MHH, AYA) independently performed the search. Combinations of controlled terms (medical subject headings, MeSH) and key words were used whenever possible. The search terms used for the MEDLINE (PubMed) and Cochrane Library databases are shown in Table 1.

Selection of studies

The full search results from all databases were pooled after the removal of duplicates. Two reviewers (MHH, AYA) then independently performed a thorough screening of the titles and abstracts to produce a shortlist of publications. Articles for full-text analysis were included only with the mutual agreement of the two reviewers. Any disagreements were resolved by discussion and consensus with a third reviewer (AFS).

Data extraction and management

Data extraction was performed after mutual agreement on the final list of publications for inclusion. Data were extracted independently by the two reviewers (MHH, AYA), who were reciprocally

Table 1. Systematic search strategy.

MEDLINE (PubMed) database
#1 ''Dental Implants''[Mesh]
#2 ''Dental Prosthesis, Implant-Supported''[Mesh]
#3 oral implant
#4 mandibular implant supported overdenture
#5 osseointegrated implant
#6 implant-support mandibular overdentures
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 immediate loading[Title/Abstract]
#9 early loading[Title/Abstract]
#10 delayed loading[Title/Abstract]
#11 conventional loading[Title/Abstract]
#12 implant loading[Title/Abstract]
#13 immediate implant loading[Title/Abstract]
#14 early implant loading[Title/Abstract]
#15 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 randomized controlled trial[Publication Type]
#17 controlled clinical trial[Publication Type])
#18 clinical trial as topic[MeSHTerms:noexp]
#19 randomized[Title/Abstract]
#20 randomly[Title/Abstract]
#21 trial[Title]
#22 (#16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 (animals[MeSH Terms])
#24 not humans[MeSH Terms])
#25 (#23 OR #24)
#26 (#22 NOT #25)
Search combination
#7 AND #15 AND #26
Cochrane database
#1 ''dental implant'':ti,ab,kw*
#2 oral implant:ti,ab,kw
#3 implant supported overdenture:ti,ab,kw
#4 osseointegrated implant:ti,ab,kw
#5 implant supported prosthesis
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 immediate loading:ti,ab,kw
#8 early loading:ti,ab,kw
#9 delayed loading:ti,ab,kw
#10 conventional:ti,ab,kw
#11 loading protocol:ti,ab,kw
#12 implant loading:ti,ab,kw
#13 implant loading protocols:ti,ab,kw.
#14 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
Search combination #6 AND #14

blinded to the other's data extraction. The following information was extracted: name of author(s), publication year, study design, intervention type, implant system, observation period, number of patients, number of implants placed, number of implants failed, prosthesis failure, and marginal bone loss.

If the articles included were missing any relevant information, the corresponding authors were contacted by e-mail. In the case of no response, reminder e-mails were sent.

Quality assessment—risk of bias

The assessment of the risk of bias of the included trials was done independently by two reviewers (MHH, AYA) using the Cochrane Collaboration tool[19]. Seven specific sources of bias were assessed, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective reporting, and other bias. The risk of bias for each of these criteria was rated as low, high, or unclear. The validity of each RCT was summarized as 'low risk of bias' if the risk of bias was low for all possible sources of bias, 'unclear risk of bias' if there was an unclear risk of bias in at least one possible source of bias, and 'high risk of bias' if the risk of bias was high for at least one possible source of bias. Disagreements were resolved by discussion; a third reviewer was consulted if necessary.

Statistical analyses

With regard to the measures of the treatment effect, the effect estimate of an intervention was expressed as the risk difference (RD) together with the 95% confidence interval (CI) for dichotomous outcomes, and as the mean difference (MD) together with the 95% CI for continuous outcomes. Continuous data were recorded as the mean ± standard deviation. The statistical unit was the patient and not the implants.

All statistical tests were performed using RevMan software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark)[20]. The significance of any variations in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity, and heterogeneity was considered significant if the P-value was <0.1. Heterogeneity between the studies was assessed using the I^2 statistic, which describes the variation due to heterogeneity rather than to chance[21]. I^2 over 50% was considered as moderate to high heterogeneity.

A meta-analysis was undertaken when studies of similar comparisons reported the same outcome measure. The MD for the marginal bone loss was calculated and compared between the two interventions studied (submerged and non-submerged implant placement). The RD for implant failure was calculated and compared between the two interventions studied. Confidence intervals were set at 95% (95% CI).

Weighted means across the studies were calculated using a fixed-effects model. Where statistically significant heterogeneity was detected ($P < 0.1$), a random-effects model was used to assess the significance of treatment effects.

If a sufficient number of trials (more than 10) were included in any meta-analysis, publication bias was to be assessed by funnel plot, with the possible causes examined in the event of funnel plot asymmetry.

Results

The electronic search yielded a total of 522 articles (276 from PubMed and 246 from the Cochrane Library). The inter-investigator agreement for the data extraction was considered very good ($\kappa = 0.87$). One additional relevant article was identified from reference cross-checking. Of the

eight potentially eligible RCTs[22–29], seven trials[22–24,26–29] fulfilled the inclusion criteria and were subsequently analysed in this systematic review (Fig. 1). One trial was excluded because related outcomes were not measured[25]. Details of all of the included studies are summarized in Table 2.

Characteristics of the studies included

The trials included compared submerged (two-stage) versus non-submerged (one-stage) implant placement. Two trials were conducted in New Zealand[26,29], two in Egypt[22,23], one in India[24], one in Turkey[28], and the most recent one was conducted in the USA[27]. All trials were conducted in university dental clinics.

The follow-up period ranged from 1 year to 3 years. A prior calculation for the sample size was undertaken in three trials[22,23,27].

With regard to the outcomes of studies comparing immediate versus delayed loading, four trials reported implant failure[22–24,27], and four reported peri-implant marginal level changes[22–24,27]. Of those studies comparing early versus delayed loading, three trials reported implant failure[26,28,29], and three reported peri-implant marginal level changes[26,28,29].

Quality assessment

The final risk of bias assessment of the included trials is summarized in Table 3 and illustrated in Figs 2 and 3. Each trial was assessed as having a low, unclear, or high risk of bias. Four trials were judged to have a high risk of bias[24,27–29], and three were judged to have an unclear risk of bias[22,23,26].

Meta-analysis

Meta-analyses were performed for studies with similar comparisons and similar outcome measures. The comparisons, as well as the numbers of studies and participants, are summarized in Table 4.

The first comparison was between immediate and delayed implant loading. The meta-analysis of four trials that compared immediate and delayed implant loading protocols in relation to implant failure showed no statistically significant difference between the two interventions ($I^2 = 49\%$; RD −0.02, 95% CI −0.13 to 0.10, $P = 0.76$) (Fig. 4)[22–24,27].

The meta-analysis of four trials that compared immediate and delayed implant loading protocols regarding marginal bone loss showed no statistically significant

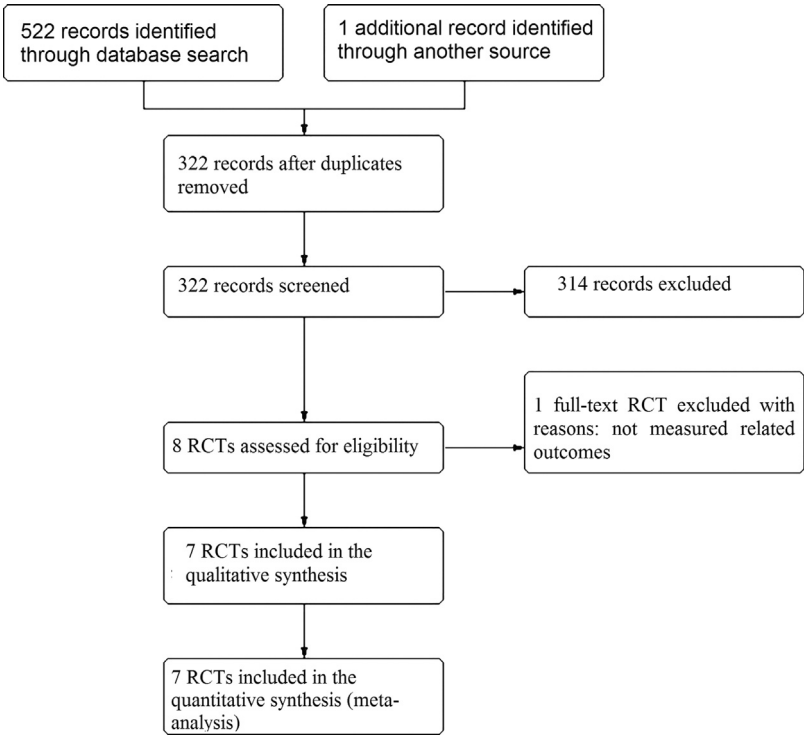

Fig. 1. Flow diagram showing the details of the data search, identification, and selection process.

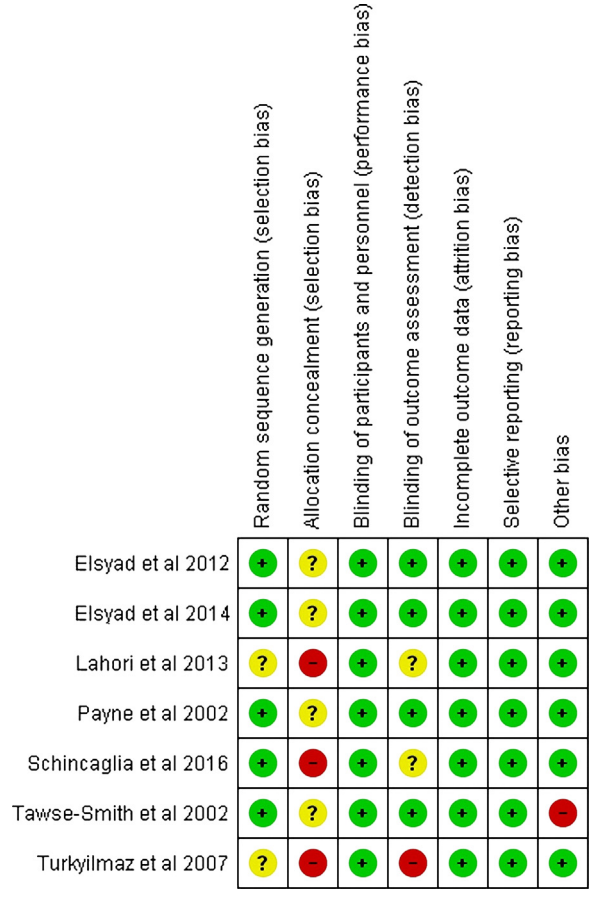

Fig. 2. Risk of bias summary: review authors' judgements regarding each risk of bias item for each study included.

Table 2. Characteristics of included studies. All implants were placed in the canine area of the mandible and all prostheses were two-implant-supported mandibular overdentures.

Study	Follow-up, months	Age, mean years	Implant system placed in both groups	Prosthesis attachment type	Total implants placed, *n*	Total subjects, *n*	Intervention (loading)	Loading time, days	Subjects per group, *n*	Implants per group, *n*	Subjects analysed	Implant failure	MBL (mm) Mean ± SD
Payne et al.[26] 2002	24	51.6	ITI; SLA, non-submerged solid titanium screws[a]	Ball	48	24	Early	42	12	24	12	0	0.09 ± 0.06
							Conventional	90	12	24	10	0	0.17 ± 0.12
Tawse-Smith et al.[29] 2002	24	65	Southern Implants and Sterioss; self-tapping screws, shaped, externally hexed, surface-enhanced	Ball	96	48	Early	42	24	48	24	5	0.12 ± 0.19
							Conventional	90	24	48	24	1	0.13 ± 0.29
Turkyilmaz and Turner[28] 2007	24	62.4	Brånemark TiUnite RP MKIII[b]	Ball	40	20	Early	7	10	20	10	0	1 ± 0.3
							Conventional	90	10	20	10	0	0.9 ± 0.3
Elsyad et al.[23] 2012	36	59.7	Spectra System ScrewPlant[c]	Ball	72	36	Immediate	0	18	36	15	0	0.52 ± 0.53
							Conventional	90	18	36	15	2	0.44 ± 0.22
Elsyad et al.[22] 2014	24	59.4	tioLogic[d], ScrewPlants[c]	Locator	72	36	Immediate	0	18	36	16	0	1.05 ± 0.18
							Conventional	90	18	36	17	2	0.87 ± 0.13
Lahori et al.[24] 2013	12	69.1	Straumann Bone Level, SLActive, intraosseous diameter 4.1 mm[e]	Ball	20	10	Immediate	0	5	10	5	1	0.76 ± 0.10
							Conventional	90	5	10	5	0	0.85 ± 0.05
Schincaglia et al.[27] 2016	12	66.2	OsseoSpeed[f]	Locator	60	30	Immediate	0	15	30	15	2	0.54 ± 0.5
							Conventional	90	15	30	15	0	0.25 ± 0.5

MBL, marginal bone loss; SD, standard deviation; SLA, sandblasted and acid-etched.
[a] Institut Straumann AG, Waldenburg, Switzerland.
[b] Nobel Biocare AB, Göteborg, Sweden.
[c] Implant Direct LLC, Calabasas, CA, USA.
[d] Dentaurum Implants GmbH, Ispringen, Germany.
[e] Institut Straumann AG, Basel, Switzerland.
[f] Astra Tech/Dentsply, Mölndal, Sweden.

Table 3. Risk of bias assessment for the RCTs included.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk
Payne et al.[26] 2002	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Tawse-Smith et al.[29] 2002	Low	Unclear	Low	Low	Low	Low	High	High
Turkyilmaz and Tumer[28] 2007	Unclear	High	Low	High	Low	Low	Low	High
Elsyad et al.[23] 2012	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Elsyad et al.[22] 2014	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Lahori et al.[24] 2013	Unclear	High	Low	Unclear	Low	Low	Low	High
Schincaglia et al.[27] 2016	Low	High	Low	Unclear	Low	Low	Low	High

RCT, randomized controlled trials.

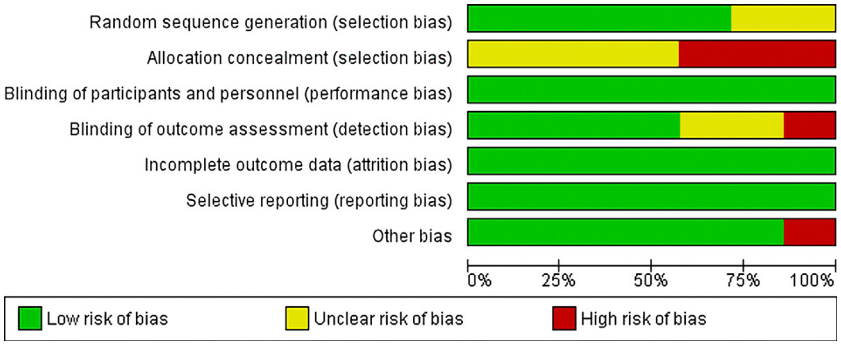

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages for all included studies.

difference between the two interventions ($I^2 = 80\%$; MD 0.09, 95% CI −0.10 to 0.28, $P = 0.35$) (Fig. 5)[22–24,27].

The second comparison was between early and delayed implant loading. The meta-analysis of three trials that compared early and delayed implant loading protocols regarding implant failure showed no statistically significant difference between the two interventions ($I^2 = 31\%$; RD 0.09, 95% CI −0.03 to 0.20, $P = 0.13$) (Fig. 6)[26,28,29].

The meta-analysis of three trials that compared early and delayed implant loading protocols in relation to marginal bone loss showed no statistically significant difference between the two interventions ($I^2 = 4\%$; MD −0.05, 95% CI −0.12 to 0.02, $P = 0.14$) (Fig. 7)[26,28,29].

Discussion

This review provides a meta-analysis of the RCTs reporting data associated with the research question posed. Although the format employed in this review is regarded as providing the highest level of contemporary scientific evidence today[30], the pooled results are limited in number. The pooled data of the seven RCTs selected revealed no significant risk difference

Table 4. Comparisons: immediate or early versus conventional implant loading.

Comparison I: Immediate versus conventional implant loading

Outcome	Studies	Participants	Implants	Statistical method	Effect estimate
Implant failure	4	51 (Immediate) 52 (Conventional)	102 (Immediate) 104 (Conventional)	RD (M–H, fixed, 95% CI)	−0.02 (−0.13, 0.10)
Marginal bone loss	4	51 (Immediate) 52 (Conventional)	102 (Immediate) 104 (Conventional)	MD (IV, random, 95% CI)	0.09 (−0.10, 0.28)

Comparison II: Early versus conventional implant loading

Outcome	Studies	Participants	Implants	Statistical method	Effect estimate
Implant failure	3	46 (Early) 44 (Conventional)	92 (Early) 88 (Conventional)	RD (M–H, fixed, 95% CI)	0.09 (−0.03, 0.20)
Marginal bone loss	3	46 (Early) 44 (Conventional)	92 (Early) 88 (Conventional)	MD (IV, fixed, 95% CI)	−0.05 (−0.12, 0.02)

CI, confidence interval; IV, inverse variance; MD, mean difference; M–H, Mantel–Haenszel; RD, risk difference.

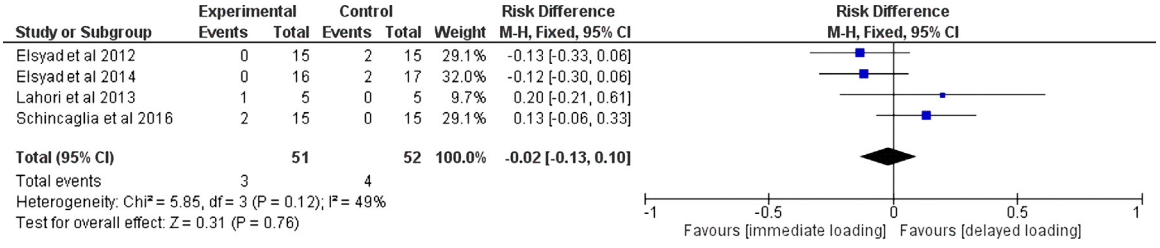

Fig. 4. Forest plot for the comparison of immediate versus delayed implant loading protocols with regard to implant failure.

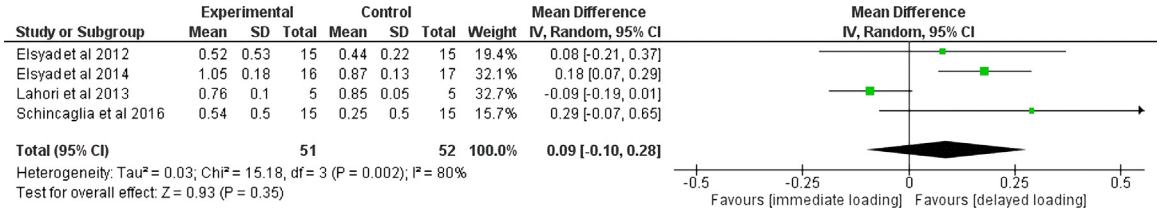

Fig. 5. Forest plot for the comparison of immediate versus delayed implant loading protocols with regard to marginal bone loss.

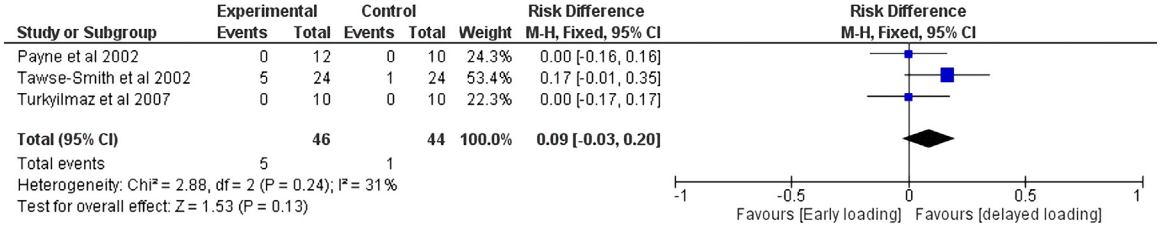

Fig. 6. Forest plot for the comparison of early versus delayed implant loading protocols with regard to implant failure.

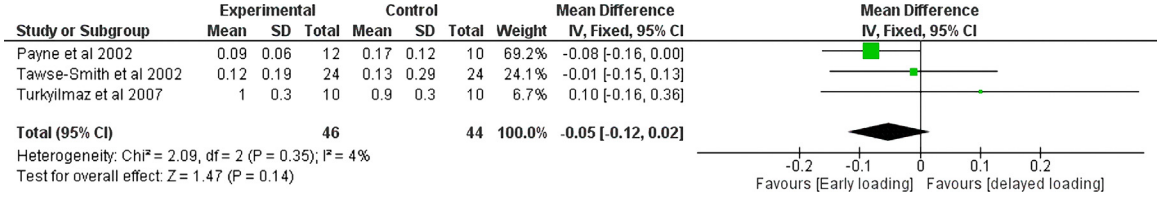

Fig. 7. Forest plot for the comparison of early versus delayed implant loading protocols with regard to marginal bone loss.

between immediate versus delayed and early versus delayed loading protocols regarding implant failure. Similarly, no statistically significant difference was found between the loading protocols regarding marginal bone loss.

The early loaded implants showed less marginal bone loss when compared to conventional ones, although this was not statistically significant. A possible hypothetical explanation for this observation could be that stimuli at the bone–implant interface lead to functional adaptation of the bone to the loading situation and to an improved differentiation of the bone structures, resulting in a higher marginal bone level[31]. The trauma of the second stage surgery is avoided, and the more superficial placement of the non-submerged implants may result in less bone loss. Another factor that may play a role in decreasing the amount of bone loss around implants placed immediately with a non-submerged protocol is less extensive countersinking[32].

The MD for marginal bone loss was 0.09 mm for the comparison between immediate and conventional implant loading and −0.05 mm for the comparison between early and conventional implant loading. According to Ahlqvist et al., these are not clinically significant values. They performed a 2-year study and found that only with a difference greater than 0.47 mm were the differences in bone levels noted and identified[33].

Indeed, the assessment of peri-implant radiographic bone loss is a secondary or surrogate outcome measure. A surrogate outcome can be defined as a measure of the disease process, but cannot be recommended as a primary parameter to evaluate, for example, the effectiveness of oral implants. Such surrogate outcomes may, however, be useful diagnostic tools for the early detection of potential problems, thereby allowing early treatment to preserve healthy conditions.

All implants in the studies included were placed in the canine regions of the mandible. It is well known that the bone density of the anterior mandible is higher than that in other areas of the mouth. This higher bone density results in higher implant torque values, better primary stability, and increased success of implants[34].

One trial investigating the early loading of unsplinted two-implant-supported mandibular overdentures compared with conventional loading, demonstrated a higher implant failure rate for the early loading protocol[29]. This particular study demonstrated seven failed implants (in five patients) in the early loading group. Nonetheless, the two other RCTs performing the same comparison showed no implant failure in either the early or conventional loading group[26,28].

In a previous systematic review conducted by Esposito et al., current trials were reviewed to determine the influence of various loading times, and no significant impact on implant failure or marginal bone loss was reported[14]. Both fixed and removable prostheses were included in that review. From a clinical standpoint, the loading of fixed and removable prostheses are considered different and the rationale for the direct comparison of these two systems is questionable. Kawai and Taylor conducted a systematic review on the effect of loading protocols and reported no significant impact on implant failure or marginal bone loss[15]. They reviewed only removable prostheses; nonetheless, they included different numbers of implants and included splinted and unsplinted attachment systems, which would have had different effects on the outcome. Therefore, in the present review it was sought to use a more robust approach: implant loading protocols were assessed only for unsplinted two-im-

plant-supported overdentures, and only RCTs were included given their acknowledged position at the top of the scientific hierarchy of reported evidence.

Nonetheless, numerous confounding factors may have affected the long-term outcomes reported. For example, the investigators placed implants of different brands and with different surface treatments, which may also have directly impacted the outcomes considered. The follow-up periods varied from 12 months to 3 years. A longer follow-up period might have led to an increase in failure rate, especially if it extended beyond functional loading, because other prosthetic factors can influence implant failure from that point onwards. This might have led to an underestimation of actual failures in some studies and limits the ability to draw any conclusions beyond this period. The results of long-term follow-up studies are awaited. These confounding factors, and possibly others as well, should be taken into consideration in future clinical trials. Finally, it must be acknowledged that four of the seven RCTs selected were considered as presenting a high risk of bias. Consequently the limited number of studies included demands caution in interpreting the results and drawing conclusions from the limited number of reports on the topic.

In conclusion, the meta-analysis revealed no statistically significant difference regarding implant failure or marginal bone loss for implants supporting mandibular overdentures with different loading protocols. This finding should be interpreted with great caution given the serious numerical limitations of the studies included. Moreover, four of the seven RCTs analysed were considered as presenting a high risk of bias.

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Competing interests

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Ethical approval

Not applicable.

Patient consent

Not applicable.

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