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SYSTEMATIC REVIEW

Immediate versus early or conventional loading dental implants with fixed prostheses: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Statement of problem. Immediate loading of dental implants has gained widespread popularity because of its advantages in shortening treatment duration and improving esthetics and patient acceptance. However, whether immediate loading can achieve clinical outcomes comparable with those of early or conventional delayed loading is still unclear.

Purpose. The purpose of this systematic review and meta-analysis was to compare the efficacy of immediate loading versus early or conventional loading implants in patients rehabilitated with fixed prostheses.

Material and methods. Electronic searches of CENTRAL, EMBASE, and MEDLINE were supplemented by manual searches up to October 2018. Only human randomized controlled trials (RCTs) comparing immediate with early or conventional loading dental implants were included. Quality assessment was performed by using the Cochrane Collaboration tool. For the meta-analysis, the dichotomous and continuous variables were pooled and analyzed by using risk ratios (RRs) and weighted mean differences (WMDs), with 95% confidence intervals (95% CIs). The outcomes assessed included survival rate, marginal bone level changes, peri-implant gingival level, probing depth, and implant stability. The subgroup analyses included healing methods, implant time, occlusal contact, number of missing teeth, and tooth position.

Results. Thirty-nine trials (49 articles) were included from the initial 763 references evaluated. When compared with conventional loading, with implants regarded as a statistical unit, a statistically significant lower survival rate was observed in the immediate loading dental implant (RR=0.974; 95% CI, 0.954, 0.994; *P*=.012). Regarding other outcomes, including marginal bone level changes, peri-implant gingival level, probing depth, and implant stability, no statistically significant differences were observed when comparing immediate versus early or conventional loading (*P*>.05).

Conclusions. Compared with early loading, immediate loading could achieve comparable implant survival rates and marginal bone level changes. Compared with conventional loading, immediate loading was associated with a higher incidence of implant failure. (J Prosthet Dent 2019;122:516-36)

The conventional approach dictates that to achieve proper osseointegration, implants need to be submerged without any load for 3 to 4 months in the mandible and 6 to 8 months in the maxilla.[1] However, shortening the treatment period is beneficial for patients and dentists.

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Clinical Implications

Loading implants conventionally rather than immediately is advised. Based on the currently available randomized clinical trials, immediate loading achieved the same clinical efficacy as early loading.

Recently, immediate and early implant loading protocols have become popular.[2-5] The first clinical trial on immediately or early loaded Brånemark System (Nobelpharma) implants was conducted in 1990.[6] The 10-year results of this study showed that the failure rate for immediately loaded implants was significantly higher than that of the conventional submerged technique implants.[7]

With the development of clinical techniques and implant surface modifications, a number of good-quality randomized controlled trials (RCTs) have reported high survival rates for immediate loading implants, some of which even showed no implant failure.[8-29] Systematic reviews have concluded that clinically significant differences in implant failure associated with different loading times are lacking.[30-32] However, meta-analyses have concluded that immediate loading has resulted in reduced implant survival rates.[33-35] Moreover, controversy also exists among these systematic reviews in regard to marginal bone level changes, implant stability, and probing depth.[33-36] The authors are unaware of a meta-analysis of these issues, presumably because of the high heterogeneity in the description of soft-tissue status, the subjective feeling of patients, and other variables.[33] Therefore, the differences between immediate, early, and delayed loading are unclear.

In addition, the systematic reviews performed by Esposito et al[30] and Sanz-Sanchez et al[33] noted a high or moderate risk of bias in most included RCTs, the influence of statistical units going unnoticed (patient or implant), high heterogeneity shown in meta-analyses, and a significant number of RCTs published or data updated in recent years. Additionally, factors that were not investigated included the healing method, implant time, tooth position, use of surgery guide, and the flap or flapless approach.

The effects of the following elements were evaluated in subgroup analyses: number of missing teeth, immediately functional or nonfunctional loading during the osseointegration period, healing methods in the control group (submerged or transmucosal), implant time (immediate, early, or delayed), tooth position, surgery guide (used or not), definitive or interim prostheses as the initial restoration, and surgery protocols (flap or flapless).

Table 1. Strategy of electronic search

	Search Terms	
Database	**CENTRAL and MEDLINE**	**EMBASE**
Population	((("Dental Implants"[Mesh]) OR "Dental Implantation"[Mesh]) OR dental implant*[Title/Abstract]) OR oral implant*[Title/Abstract]	('tooth implant'/exp) OR ('tooth implantation'/exp) OR (dental AND implant*: ab, kw, ti) OR (oral AND implant*: ab, kw, ti)
Intervention	("Immediate Dental Implant Loading"[Mesh]) OR ((immediate*[Title/Abstract]) AND ((((((load*[Title/Abstract]) OR crown*[Title/Abstract]) OR bridge*[Title/Abstract]) OR prosthes*[Title/Abstract]) OR restoration*[Title/Abstract]) OR rehabilitat*[Title/Abstract]))	((immediate*: ab, kw, ti) AND ((((((load*: ab, kw, ti) OR crown*: ab, kw, ti) OR bridge*: ab, kw, ti) OR prosthes*: ab, kw, ti) OR restoration*: ab, kw, ti) OR rehabilitat*: ab, kw, ti))

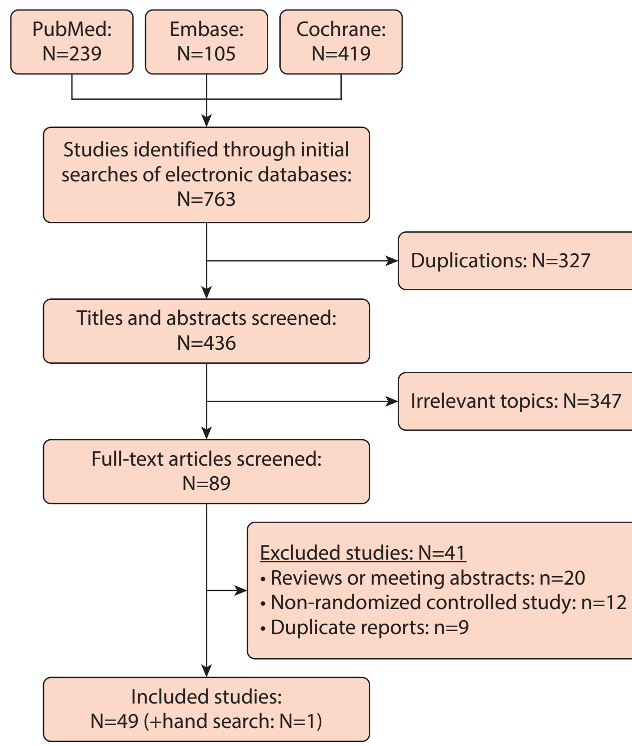

Figure 1. Flow diagram of studies identified, included, and excluded.

The purpose of this systematic review was to determine the impact of immediate loading implants on the clinical outcomes of fixed restorations when compared with early or conventionally loaded implants.

MATERIAL AND METHODS

A prospective protocol was developed a priori according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) and the Meta-analysis of Observational Studies in Epidemiology recommendations.[37,38] The PICOS strategy was used for the search: P (population)=patients requiring at least 1

Table 2. Characteristics of included studies

Study	Country	Design (RCT)	Follow-up (mo)	Age: Mean (Minimum, Maximum) Test/ Control *Global	Patients (Implant), No. (Test/Control)		Implant	Loading Time of the Control Group (wk)
					Initial	Final		
Testori et al (2003)[72]	Italy	Parallel	24	56/54.2	14 (52)/18 (49)	14 (50)/18 (48)	Osseotite and Osseotite NT; Implant Innovations Inc	8
Hall et al (2006, 2007)[62,63]	New Zealand	Parallel	12	43.25 (23, 71)*	14 (14)/14 (14)	14 (13)/12 (12)	Southern Implants Ltd	26
Oh et al (2006)[61]	USA	Parallel	6	45.2/47.3	12 (12)/12 (12)	9 (9)/12 (12)	Zimmer Dental	16
Romanos et al (2006, 2016)[14,15]	Germany	Split mouth	180	50.75*	12 (36)/12 (36)	10 (30)/10 (30)	Ankylos implants; Dentsply Sirona Ceramed	12
Testori et al (2007),[42] Galli et al (2008),[4] Capelli et al (2010)[43]	Italy	Parallel	60	51.6 (27, 74)/51.3 (34, 73)	25 (52)/27 (52)	24 (51)/26 (NR)	Full OSSEOTITE Tapered Implants (FOSS); Biomet 3i	8
Cannizzaro et al (2008)[16]	Italy	Parallel	36	40.1 (18, 62)/37.4 (19, 64)	20 (52)/20 (56)	20 (52)/20 (56)	Tapered SwissPlus; Zimmer Dental	12(L); 16(U)
Cannizzaro et al (2008, 2012)[5,46]	Italy	Split mouth	9	35 (18, 57)*	15 (30)/15 (30)	15 (29)/15 (29)	Biomet 3i	6
Cannizzaro et al (2008)[55]	Italy	Parallel	12	62 (45, 65)/56 (42, 69)	15 (90)/15 (87)	15 (89)/15 (84)	Tapered SwissPlus; Zimmer Dental	8
Crespi et al (2008)[11]	Italy	Parallel	24	45.6 (24, 62)/48.8 (27, 68)	20 (20)/20 (20)	20 (20)/20 (20)	Outlink; Sweden & Martina	12
Donati et al (2008, 2015)[44,45]	Italy	Three armed	60	45.4*	NR (104)/NR (57)	NR (89)/NR (51)	OsseoSpeed; Astra Tech Dental	12
Ganeles et al (2008),[47] Zollner et al (2008),[48] Nicolau et al (2013)[49]	Several countries	Parallel	36	46.3*	138 (197)/128 (186)	124 (178)/115 (162)	SLActive; Institut Straumann AG	4
Guncu et al (2008)[64]	Turkey	Split mouth	12	41.1 (30, 55)/41.1 (30, 55)	12 (12)/12 (12)	12 (11)/12 (12)	Branemark System, TiUnite, Mk III; Nobel BiocareGothenburg	12
Merli et al (2008, 2012)[12,13]	Italy	Parallel	36	50.3 (28, 72)/48.7 (19, 68)	30 (35)/30 (34)	29 (34)/27 (31)	ELEMENT; Thommen Medical	6
Schincaglia et al (2008)[93]	Italy	Parallel	12	51.9 (31, 75)/49.2 (35, 68)	15 (15)/15 (15)	15 (14)/15 (15)	Mk III WP TiUnite implant Nobel BiocareGothenburg	12-16
De Rouck et al (2009)[65]	Belgium	Parallel	12	55/52	24 (24)/25 (25)	24 (23)/25 (23)	NobelReplace tapered TiUnite; Nobel BiocareGothenburg	12
Degidi et al (2009)[17]	Italy	Parallel	36	31.5 (18, 55)*	30 (30)/30 (30)	30 (30)/30 (30)	XiVE Plus; Dentsply Sirona	24
Guncu et al (2009)[58]	Turkey	Split mouth	12	40 (27, 56)/40 (27, 56)	12 (12)/12 (12)	11 (11)/11 (11)	Branemark System, TiUnite, Mk III; Nobel Biocare AB Gothenburg	12
Shibly et al (2010, 2012)[50,51]	USA	Parallel	24	(25, 94)*	30 (30)/30 (30)	26 (26)/29 (28)	NR	12-16
Danza et al (2010)[18]	Italy	Parallel	12	NR	NR (20)/NR (20)	NR (20)/NR (20)	SFB screw internal hex implant; Alpha Bio Ltd	12(L); 24(U)
Prosper et al (2010)[103]	Italy	Parallel	60	58.3 (26, 72)*	36 (60)/35 (60)	36 (58)/35 (58)	Bioactive Covering; Winsix	12
Velde et al (2010)[59]	Belgium	Split mouth	18	55.7 (39, 75)*	13 (36)/13 (34)	12 (32)/12 (32)	Straumann SLA TE implants; Straumann AG	6
Zembić et al (2010)[73]	Switzerland	Split mouth	36	54.8 (37.8, 68.6)*	11 (22)/11 (22)	10 (19)/10 (20)	Branemark MK IV, TiUnite; Nobel Biocare AB	6
den Hartog et al (2011)[56]	Netherlands	Parallel	18	38.4 (18, 66)/40.1 (18, 67)	31 (31)/31 (31)	31 (30)/31 (31)	NobelReplace Tapered Groovy; Nobel Biocare AB, Goteborg	12
Barewal et al (2012) (1)[19]	USA	Parallel	36	NR (20, 82)*	8 (8)/15 (15)	7 (7)/14 (14)	Astra Tech	6
Barewal et al (2012) (2)[19]					8 (8)/15 (15)	7 (7)/14 (13)		12
Grandi et al (2012, 2013)[26,27]	Italy	Multi-center Parallel	36	51.8 (39, 65)/55.3 (43, 65)	40 (81)/40 (80)	38 (77)/39 (78)	JDEvolution; JDentalCare	8

(*continued on next page*)

Table 2. (*Continued*) Characteristics of included studies

Study	Country	Design (RCT)	Follow-up (mo)	Age: Mean (Minimum, Maximum) Test/Control *Global	Patients (Implant), No. (Test/Control)		Implant	Loading Time of the Control Group (wk)
					Initial	Final		
Margossian et al (2012) (1)[53]	France	Three armed	24	NR	40 (105)/37 (98)	40 (105)/37 (98)	First-generation full Osseotite NT certain; Biomet 3i	20
Margossian et al (2012) (2)[53]					40 (104)/37 (98)	40 (97)/37 (98)		
Meloni et al (2012)[20]	Italy	Split mouth	12	46 (28, 70)/46 (28, 70)	20 (20)/20 (20)	20 (20)/20 (20)	NobelReplace Tapered Groovy; Nobel Biocare, Goteborg	16-20
Alfadda et al (2014)[54]	Canada	Parallel	12	61.5*	20 (80)/22 (88)	16 (64)/24 (96)	TiUnite dental implants; Nobel Biocare, Goteborg	12
Gothberg et al (2014)[57]	Sweden	Parallel	12	68.0/66.1	26 (78)/24 (72)	23 (74)/22 (70)	Branemark TiUnite implants; Nobel Biocare, Goteborg	12
Jokstad et al (2014)[21]	Canada	Parallel	60	62 (42, 82)/62 (47, 78)	21 (84)/21 (84)	17 (68)/18 (71)	Branemark System Mk III or Mk IV TiUnite; Nobel Biocare AB, Goteborg	12-16
Kokovic et al (2014)[28]	UAE	Split mouth	60	49 (20, 62)*	12 (36)/12 (36)	12 (36)/12 (36)	SLA Straumann TE; Straumann AG	6
Grandi et al (2015) (1)[52]	Italy	Three armed	12	51.4 (22, 73)/45.5 (21, 66)	35 (35)/35 (35)	33 (32)/35 (34)	JDEvolution; JDentalCare tapered thread titanium implants and double acid-etched treated surface	3
Grandi et al (2015) (2)[52]				51.4 (22, 73)/46.1 (24, 75)		33 (32)/35 (35)		16
Cesaretti et al (2016)[104]	Cuba	Parallel	36	64.5 (51, 76)/58.9 (41, 79)	15 (36)/15 (35)	14 (34)/14 (33)	SLA surface; Institute Straumann AG and a polished neck of 2.8 mm	12
Esposito et al (2016) (1)[22]	Sweden	Three armed	4	51.3 (35, 67.6)/55.1 (42.5, 67.7)	27 (84)/27 (82)	27 (84)/27 (82)	AnyRidge Xpeed; Megagen Implant	12
Esposito et al (2016) (2)[22]				51.3 (35, 67.6)/54.3 (40.1, 68.5)	27 (84)/27 (83)	27 (84)/27 (83)		6
Rieder et al (2016) (1)[29]	Germany	Four armed	8	44.8 (17, 76)*	12 (12)/12 (12)	11 (11)/12 (12)	SLActivea surface; Straumann AG	4-6
Rieder et al (2016) (2)[29]						12 (12)/10 (10)		
Vercruyssen et al (2016)	Belgium	Parallel	0.3	(45, 71)/(49, 70)	7 (42)/8 (48)	7 (42)/8 (47)	Ankylos implants; Dentsply Sirona	12
Zuffetti et al (2016)[74]	Italy	Split mouth	120	51.6 (27, 74)/51.3 (34, 73)	25 (52)/27 (52)	21 (43)/25 (49)	FOSS; Zimmer Biomet 3iFL	8
Chidagam et al (2017)[24]	India	Parallel	72	23.1 (19, 31)*	10 (10)/10 (10)	10 (10)/10 (10)	NR	12
Giacomel et al (2017)[25]	Brazil	Three armed	9	47.7 (30, 61)/47.7 (30, 61)	15 (15)/15 (30)	15 (15)/15 (28)	NR	12

L, in mandible; U, in maxilla. (1) and (2) mean different comparisons from same trial. *Data of both test and control group.

dental implant; I (intervention)=restoration within 1 week of implant placement[39]; C (comparison)=delayed (also termed "conventional") loading defined as restorations 8 weeks after insertion, early loading between 1 and 8 weeks[40]; O (outcome)=implant survival rate, marginal bone level changes, peri-implant gingival level, plaque index, probing depth, implant stability, the rate of peri-implantitis or peri-implant mucositis, and subjective feeling of patients; S (study design)=randomized controlled trials (RCTs). The focus question was "Is there a difference in postoperative outcomes when an immediate implant loading protocol is compared with early or conventional loading in fixed restoration(s)?"

From inception until October 2018, a comprehensive electronic search was conducted in CENTRAL (The Cochrane Central Register of Controlled Trials), EMBASE, and MEDLINE via PubMed (The National Library of Medicine). The search strategy is shown in Table 1, and the results filter was set to humans and randomized controlled trials.

There were no restrictions on regions or languages. The computer search was supplemented with a manual search of the reference lists in all retrieved literature. In addition, a search of the online databases in the following journals was performed: *British Journal of Oral and Maxillofacial Surgery, Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, European Journal of Oral Implantology, Implant Dentistry, The International Journal of Oral & Maxillofacial Implants, International Journal of Oral and Maxillofacial Surgery, International Journal of Periodontics and Restorative Dentistry, International Journal of*

Prosthodontics, Journal of Clinical Periodontology, Journal of Dental Implantology, Journal of Dental Research, Journal of Oral Implantology, Journal of Oral and Maxillofacial Surgery, Journal of Periodontology, Journal of Periodontal Research, Journal of Prosthetic Dentistry.

Two reviewers (J.C., M.C.) selected studies by independently screening the titles and abstracts of search results based on the following inclusion criteria: at least 1 dental implant with a fixed prosthesis; at least 15 participants; studies on immediate loading versus early or conventional loading; at least 1 of those aforementioned outcomes reported; and randomized controlled trials (RCTs). There was no restriction on the follow-up period. Animal studies or studies involving zygomatic implants or implants used for orthodontic anchorage were excluded. Additionally, review studies, case reports, case series, and meeting abstracts were also excluded. The full text of potential articles was reconfirmed and evaluated for data extraction. Any disagreement was resolved by further discussion or an additional author's (Y.W.) evaluation. When multiple articles reported the same trial, the most recent one with completed data was included. Authors of studies were contacted by e-mail when data were found to be incomplete or not reported.

Two authors (T.A.A., J.Y.) independently assessed the risk of bias in the included studies. The quality assessment of the included RCTs was performed by using the Cochrane Collaboration's tool.[41] Seven criteria were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Studies were classified as low risk if all criteria were met, moderate risk if 1 criterion is missed, and high risk if 2 or more were missed.

For this meta-analysis, the dichotomous variables (such as, implant survival rate) were pooled and analyzed by using risk ratios (RRs) and 95% confidence intervals (95% CIs). As for continuous outcomes (such as, marginal bone level changes), weighted mean differences (WMDs) with 95% CI were used. The Q-test estimated heterogeneity, with significance set at α=.1 and quantified with the I^2 index (high heterogeneity: I^2>75%; low heterogeneity: I^2<25%). The random-effect model was used when significant heterogeneity was found between the test and control study. Otherwise, the fixed-effect model was applied. Subgroup analyses were carried out based on items listed in the introduction. All analyses were performed by using a statistical software program (STATA-12; StataCorp LP) (α=.05). Forest plots were used to illustrate the effects of the intervention, and funnel plots were created to screen for publication bias.

RESULTS

The screening process is depicted in Figure 1. Eighty-nine articles were selected for full-text analysis after the evaluation of titles and abstracts (agreement=87.4%; kappa=0.63). Forty-nine articles met inclusion criteria and were assessed for reliability (Table 2). After evaluation, 49 full-text articles that belonged to 39 trials were identified. Of the 39 studies, 18 belonged to 8 trials, which were divided into the following 8 series: In the first series, 2 articles reported the data at 2 years and 15 years, respectively.[14,15] In the second series, 3 articles showed results at varying time periods.[4,42,43] In the third series, 2 articles reported the outcomes at 1 year and 5 years.[44,45] In the fourth series, 2 articles reported the data at 9 months and 4 years.[5,46] In the fifth series, 3 articles showed the results at 5 months, 1 year, and 3 years.[47-49] In the sixth series, 2 articles reported the data at 1 and 3 years.[12,13] In the seventh series, 2 articles showed the results at 1 and 2 years.[50,51] In the eighth series, 2 articles reported the data at 1 and 3 years.[26,27]

Table 2 shows the methodological characteristics of the selected studies. Nine of 39 articles were split-mouth trials, and 30 studies were parallel studies. Seven of 30 parallel trials had 2 test groups that met the inclusion criteria; therefore, each comparison was regarded independently.[19,22,25,29,44,45,52,53]

This systematic review pooled data from 1868 participants (914 in a test group and 954 in control), and a total of 3746 implants were inserted (1880 in an experimental group and 1866 in control) at baseline. A total of 1785 participants were followed up (864 in the experimental group and 921 in the control group), and 3486 implants (1749 in the experimental group and 1737 in control group) were reported at the end of the trial. The maximum follow-up period was 180 months,[14] and the minimum was 10 days[23]

Figure 2 depicts the risk of bias for RCTs. Six studies showed a low risk of bias,[5,16,18,46,52,54,55] 8 trials showed medium risk of bias,[17,20,22,28,56-59] and the remaining showed high risk of bias. Funnel plots and the Begg test were used to detect publication bias.

According to previous systematic reviews, the patient[60] and implant[33] are regarded as statistical units in the current meta-analysis. The results of the 2 methods are as follows: for implant as a statistical unit, the mean survival rates were 96.8% in the test and 98.6% in the control group. In 9 of 29 included trials, the survival rate of implants was 100%.[11,14-18,20,22,24,53] The results from the meta-analyses of the remaining 20 studies are

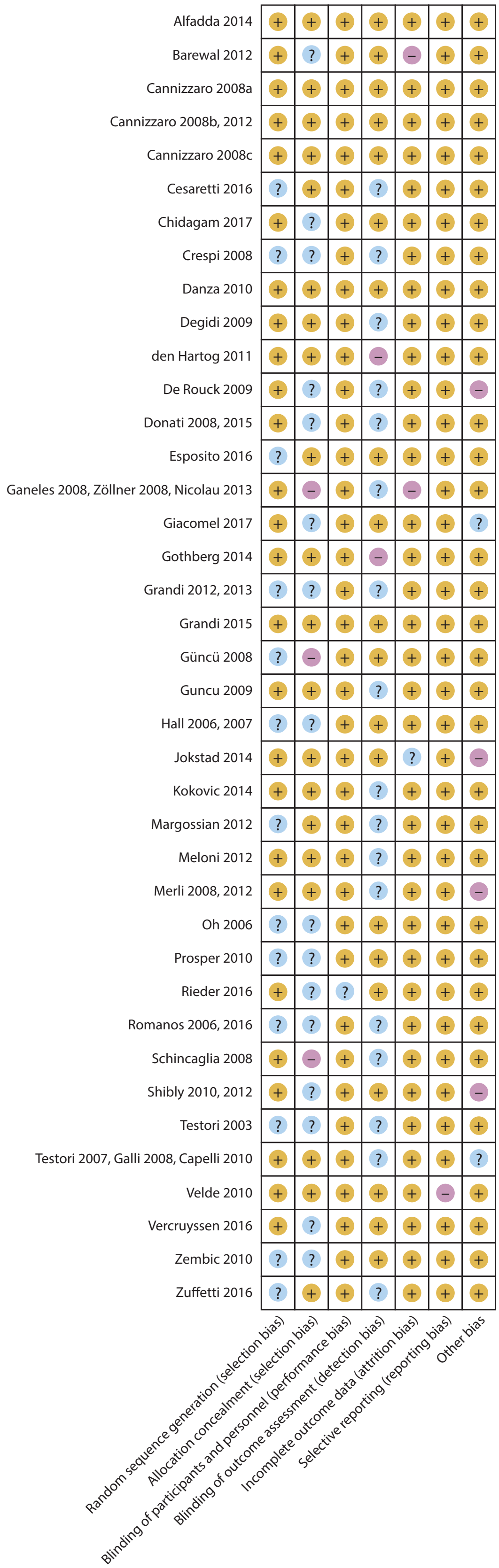

Figure 2. Risk of bias summary for selected randomized controlled trials.

reported in Figure 3. The meta-analysis resulted in a statistically significant lower survival rate for the test (immediate loading) group compared with that for the conventional group (RR=0.974; 95% CI, 0.954, 0.994; *P*=.012). No publication bias was detected by the Begg test (*P*=.261; Fig. 4). In the subgroup analyses, a lower survival rate was shown in the immediately loaded implants than in conventional loading in regard to the following: nonsubmerged technique (RR=0.969; 95% CI, 0.946, 0.994; *P*=.013), delayed implant (RR=0.974; 95% CI, 0.953, 0.996; *P*=.020), occlusal contact (RR=0.969; 95% CI, 0.947, 0.992; *P*=.009), single missing tooth (RR=0.958; 95% CI, 0.921, 0.998; *P*=.038), several missing teeth (RR=0.955; 95% CI, 0.920, 0.991; *P*=.015), surgical guide stent (RR=0.953; 95% CI, 0.920, 0.988; *P*=.009), operative area not only restricted in the maxillary nonmolar or mandibular posterior region (RR=0.972; 95% CI, 0.951, 0.995; *P*=.015), flap operations in both groups (RR=0.972; 95% CI, 0.950, 0.994; *P*=.015), and interim prostheses used for immediate loading while definitive restorations placed in the control group (RR=0.966; 95% CI, 0.943, 0.991; *P*=.007) (Table 3).

For patient as a statistical unit, the mean survival rate was 95.0% in the test group and 97.3% in the control group. Of the 27 included studies, there was no implant failure in 8 studies.[11,14-18,20,22,24,53] The overall effect of the meta-analyses showed a higher rate of implant failure in the test group but without a statistically significant difference (RR=0.963; 95% CI, 0.927, 1.001; *P*=.059) (Fig. 5). No publication bias was detected by the Begg test (*P*=.780; Fig. 6). The subgroup analyses resulted in a higher rate of failure for immediate loading implants than for conventional loading implants in regard to the following conditions: a nonsubmerged technique was used (RR=0.951; 95% CI, 0.907, 0.997; *P*=.037), several missing teeth (RR=0.903; 95% CI, 0.820, 0.993; *P*=.036), surgical guide used (RR=0.921; 95% CI, 0.864, 0.983; *P*=.014), and interim prostheses used for immediate loading while definitive restorations were placed in the control group (RR=0.949; 95% CI, 0.905, 0.995; *P*=.030). In the immediately loaded group, a relatively higher failure rate was identified for delayed implant (RR=0.958; 95% CI, 0.913, 1.005; *P*=.081), occlusal contact (RR=0.948; 95% CI, 0.897, 1.003; *P*=.064), single missing tooth (RR=0.957; 95% CI, 0.911, 1.006; *P*=.087), operative area not only restricted in the maxillary nonmolar or mandibular posterior region (RR=0.949; 95% CI, 0.896, 1.004; *P*=.070), and flap operations in both groups (RR=0.961; 95% CI, 0.922, 1.001; *P*=.058), without statistically significant differences (*P*>.05) (Table 4).

The change of crestal bone level was reported in all except 5 trials.[16,22,23,58,61] Most investigations used periapical radiographs except 1 using panoramic radiographs.

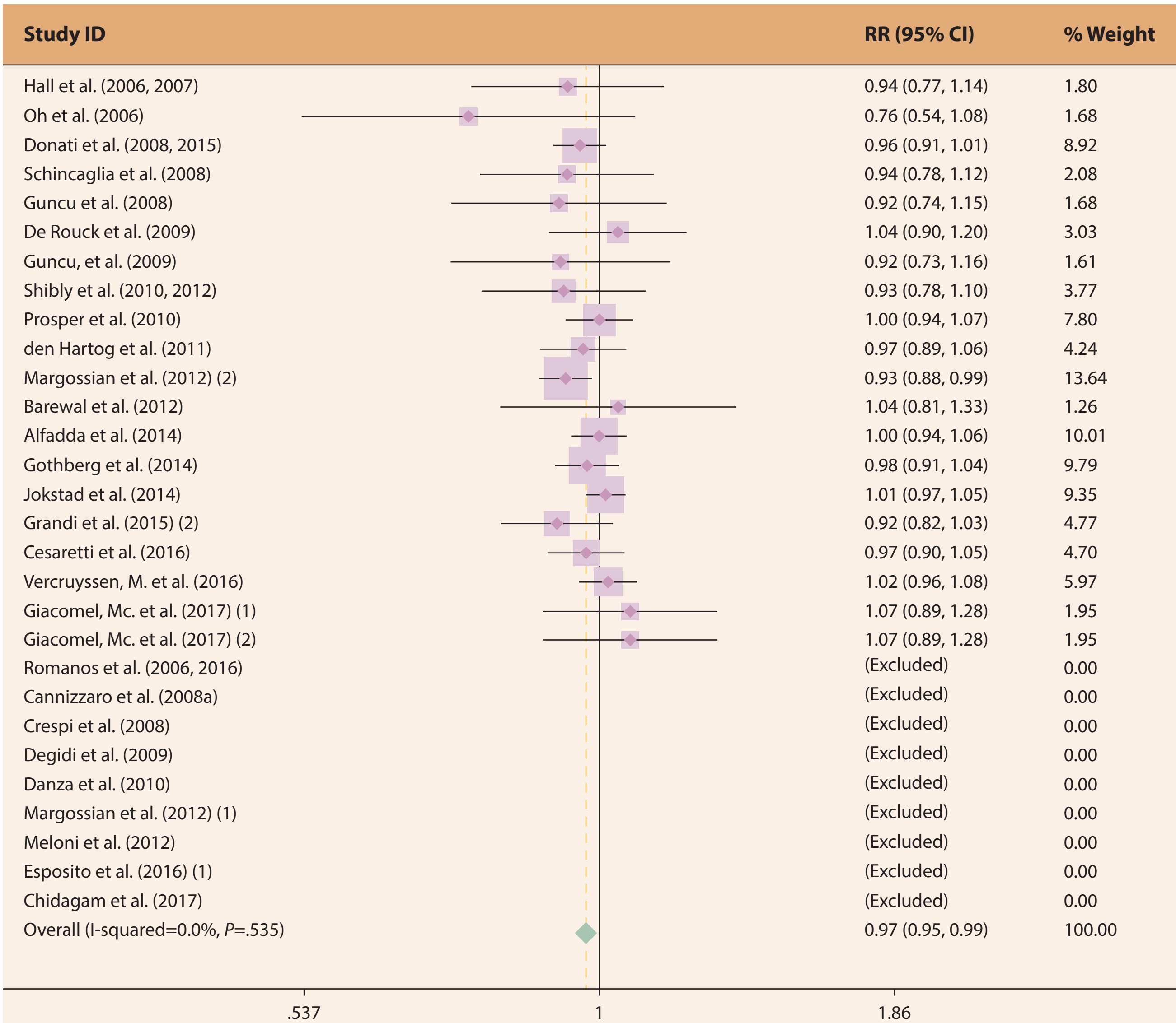

Figure 3. Forest plot of implant survival rate compared with delayed loading, for implant as statistical unit.

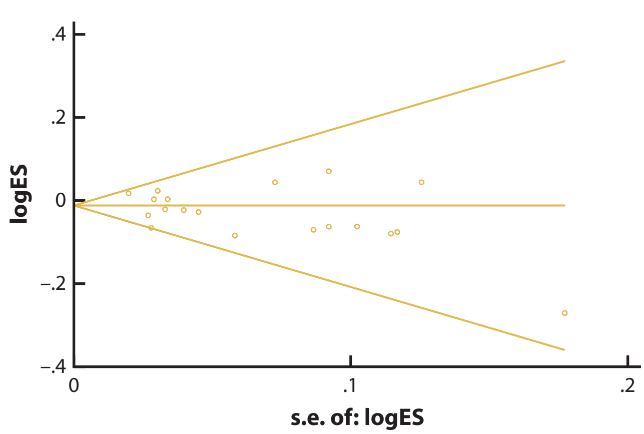

Figure 4. Funnel plot illustrating meta-analysis of implant survival rate compared with delayed loading, for implant as statistical unit.

To avoid high heterogeneity among studies, studies that used periapical radiographs to evaluate the crestal bone were combined in the independent meta-analyses. The loss of marginal bone level ranged from −1.32 mm (loss) to 0 mm in the test group and from −1.25 mm to −0.10 mm in the control group. The result shows no statistically significant differences in the crestal bone loss between the test and control groups (WMD=0.016; 95% CI, −0.052, 0.084; *P*=.645) when the data at all sites of implants were combined (Fig. 7). For any of the subgroup analyses, no statistically significant differences were found between groups, except in trials with occlusal contact (WMD=0.083; 95% CI, 0.003, 0.163; *P*=.043) and flapless operations in both groups (WMD=−0.3; 95% CI, −0.489, −0.111; *P*=.002), despite the high heterogeneity

Table 3. Results of meta-analyses on implant survival rate compared with delayed loading, for implant as statistical unit

Variable	Subgroup	N (Excluded)*	RR	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		20 (9)	0.974	0.954, 0.994	**.012**	.535	0.0
Healing method	Submerged	7 (5)	0.984	0.946, 1.023	.405	.627	0.0
	Nonsubmerged	13 (3)	0.969	0.946, 0.994	**.013**	.314	13.0
	Both	0 (1)	–	–	–	–	–
Implant time	Delay	16 (7)	0.974	0.953, 0.996	**.020**	.465	0.0
	Immediate	3 (1)	0.990	0.930, 1.055	.761	.571	0.0
	Both	1 (1)	0.915	0.817, 1.026	.129	–	–
Occlusion	Occlusion	12 (5)	0.969	0.947, 0.992	**.009**	.263	18.4
	Nonocclusion	4 (3)	0.962	0.904, 1.024	.225	.569	0.0
	NR	4 (1)	<.001	0.946, 1.057	<.001	.619	0.0
Missing teeth	Single	13 (4)	0.958	0.921, 0.998	**.038**	.826	0.0
	Several	3 (2)	0.955	0.920, 0.991	**.015**	.511	0.0
	Full	3 (0)	1.010	0.980, 1.040	.532	.881	0.0
	Any	1 (3)	<.001	0.936, 1.069	<.001	–	–
Surgery guide	Guide	8 (5)	0.953	0.920, 0.988	**.009**	.323	13.6
	Free hand	12 (4)	0.985	0.960, 1.010	.237	.68	0.0
Tooth position	Maxillary nonmolar region	4 (2)	0.951	0.877, 1.031	.221	.341	10.5
	Mandibular posterior	6 (3)	0.993	0.938, 1.050	.801	.764	0.0
	Other	10 (4)	0.972	0.951, 0.995	**.015**	.228	23.4
Surgery: test/control	Flap/flap	17 (8)	0.972	0.950, 0.994	**.015**	.664	0.0
	Flapless/flapless	2 (0)	0.957	0.885, 1.035	.276	.067	70.1
	Flapless/flap	0 (0)	–	–	–	–	–
	NR	1 (0)	1.020	0.961, 1.082	.522	–	–
First restorations: test/control	Provisional/definitive	13 (5)	0.966	0.943, 0.991	**.007**	.281	16.1
	Provisional/provisional	4 (4)	0.967	0.922, 1.013	.160	.920	0.0
	Definitive/definitive	1 (0)	1.020	0.961, 1.082	.522	–	–
	Unclear	2 (0)	1.069	0.941, 1.214	.306	<.001	0.0

Bold text indicates statistically significant differences. *Excluded: number of studies with 100% implant survival rates in both groups.

within some items (Table 5). For the study evaluating the change of marginal bone with panoramic radiography,[14,15] the differences in crestal bone loss between the 2 groups were not statistically significant (*P*>.05).

Implant stability was assessed using 2 methods: the implant stability quotient (ISQ) measured by resonance frequency analysis (RFA) with the Osstell device (Integration Diagnostics Ltd) and the implant Periotest (Siemens AG) value (PTV) with the periotest device. The Osstell was used in 7 trials. The data were reported as Figures in 2 studies,[19,57] whereas 1 reported the minimum and maximum values.[62,63] The remaining 4 studies presented the mean and standard deviation. However, 1 of them did not show the sample size.[53] Based on the last 3 studies,[16,17,64] the ISQ ranged between 69.4 and 77.1 in the test group and between 69.8 and 78.6 in the control group. Regarding the result of the meta-analysis, there was no statistically significant difference (WMD=−0.436; 95% CI, −1.469, 0.598; *P*=.409).

In the 3 studies reporting PTV,[14-16,24] the mean ranged between −1.8 and 4.07 in the test group and between −1.3 and 4.0 in control. The meta-analysis found insufficient evidence to determine whether there was a difference between immediate and delayed loading (WMD=−0.233; 95% CI, −0.707, 0.241; *P*=.335).

Gingival inflammation was reported in 12 studies, and 5 indexes were used. The percentage of sites with positive bleeding on probing (BOP [%]) was reported in 5 studies. However, in 1 study,[44,45] the author without exact data stated there was no significant statistical difference between the 2 groups. In the remaining 4 trials,[17,18,24,65] BOP (%) varied from 0% to 40% in the test group and 0% to 36% in the control group. Modified sulcus bleeding index (mBI)[66] was presented in 4 trials. One[62,63] reported the change of mBI, and no significant statistical difference was shown in the Student *t* test (*P*>.05). In the other 3 studies,[20,56,61] the mean of mBI varied from 0.5 to 1.3 and from 0.67 to 1.4 in the test and control groups, respectively. Gingival index (GI)[67] was used in 2 studies.[58,64] The GI ranged from 0.29 to 0.32 in the test group and from 0.25 to 0.29 in the other group. For these 3 indexes, the result of the meta-analyses showed insufficient evidence to determine whether statistically significant differences existed.

For 2 studies reporting gingival bleeding time index (GBTI),[68] no meta-analysis was performed because the mean of 1 study[64] was 0 in both groups. However, the

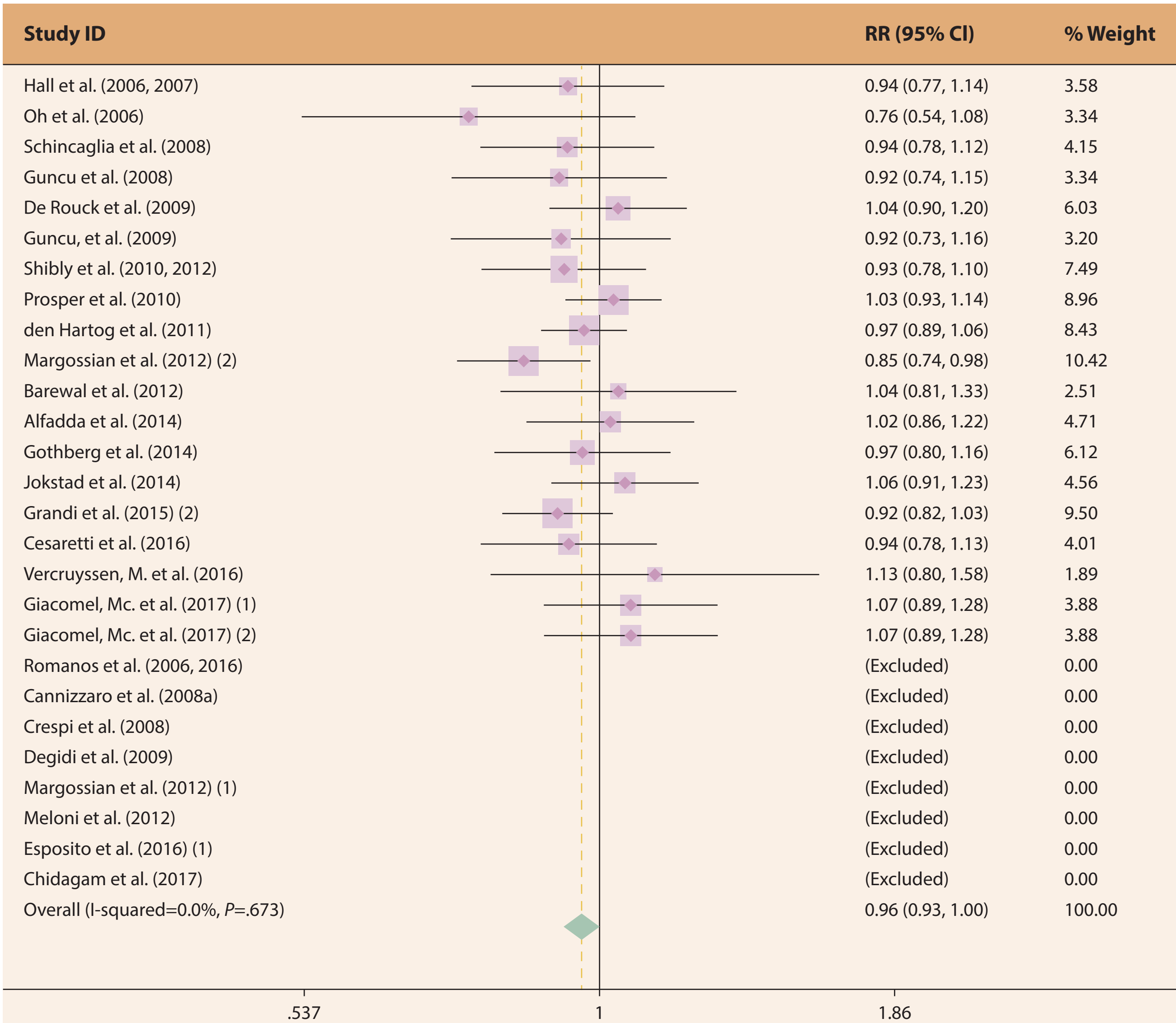

Figure 5. Forest plot of implant survival rate compared with delayed loading, for patient as statistical unit.

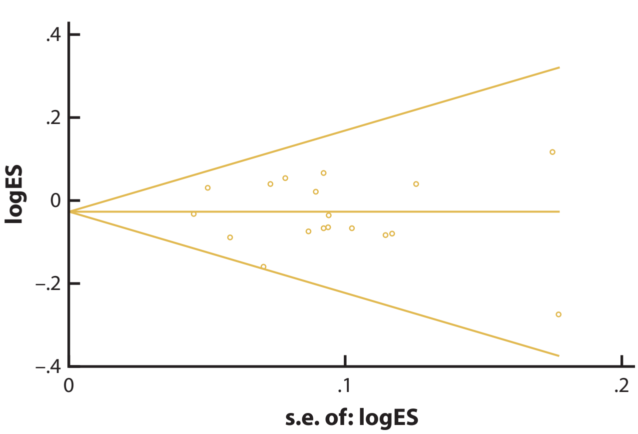

Figure 6. Funnel plot illustrating meta-analysis of implant survival rate compared with delayed loading, for patient as statistical unit.

other study[58] presented GBTI with a decreasing trend, reaching their lowest values at 12 months in both groups. Sulcus bleeding index (SBI)[69] was used in only 1 trial.[64] No statistically significant difference was found between the test and control subjects (P>.05).

For peri-implant gingival level, change in papilla, free gingiva, and keratinized mucosa were reported. For the height of papilla, 5 trials use the papilla index (PPI).[70] Three of them reported the mean, standard deviation, and sample size in both groups.[50,51,56,61] The meta-analysis, with low heterogeneity (P=.751, I^2=0.0%), presents insufficient evidence of statistically significant differences between the 2 groups (WMD=0.061; 95% CI, −0.169, 0.292; P=.602). One publication recorded the Jemt-index frequency,[17] and there was no statistically significant difference (P>.05) for the 2 procedures.

Table 4. Results of meta-analyses on implant survival rate compared with delayed loading, for patient as statistical unit

	Subgroup	N (Excluded)*	RR	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		19 (8)	0.963	0.927, 1.001	.059	.673	0.0
Healing method	Submerged	6 (4)	0.991	0.927, 1.059	.793	.729	0.0
	Nonsubmerged	13 (3)	0.951	0.907, 0.997	**.037**	.458	0.0
	Both	0 (1)	–	–	–	–	–
Implant time	Delay	15 (6)	0.958	0.913, 1.005	.081	.678	0.0
	Immediate	3 (1)	<.001	0.925, 1.081	.995	.491	0.0
	Both	1 (1)	0.915	0.817, 1.026	.129	–	–
Occlusion	Occlusion	11 (4)	0.948	0.897, 1.003	.064	.422	2.1
	Nonocclusion	4 (3)	0.962	0.904, 1.024	.225	.569	0.0
	NR	4 (1)	1.005	0.919, 1.100	.907	.623	0.0
Missing teeth	Single	12 (4)	0.957	0.911, 1.006	.087	.760	0.0
	Several	3 (2)	0.903	0.820, 0.993	**.036**	.515	0.0
	Full	3 (0)	1.053	0.941, 1.180	.367	.882	0.0
	Any	1 (2)	1.031	0.934, 1.138	.542	–	–
Surgery guide	Guide	8 (4)	0.921	0.864, 0.983	**.014**	.546	0.0
	Free hand	11 (4)	0.990	0.943, 1.038	.669	.767	0.0
Tooth position	Maxillary nonmolar region	4 (2)	0.951	0.877, 1.031	.221	.341	10.5
	Mandibular posterior	6 (3)	1.001	0.936, 1.071	.972	.711	0.0
	Other	9 (3)	0.949	0.896, 1.004	.070	.550	0.0
Surgery: test/control	Flap/flap	16 (7)	0.961	0.922, 1.001	.058	.786	0.0
	Flapless/flapless	2 (0)	0.957	0.856, 1.071	.448	.049	74.2
	Flapless/flap	0 (0)	–	–	–	–	–
	NR	1 (0)	1.125	0.799, 1.585	.500	–	–
First restorations: test/control	Provisional/definitive	12 (5)	0.949	0.905, 0.995	**.030**	.409	3.6
	Provisional/provisional	4 (3)	0.958	0.885, 1.037	.288	.877	0.0
	Definitive/definitive	1 (0)	1.125	0.799, 1.585	.500	–	–
	Unclear	2 (0)	1.069	0.941, 1.214	.306	<.001	0.0

Bold text indicates statistically significant differences. *Excluded: number of studies with 100% implant survival rates in both groups.

One[62,63] reported that papilla index at all sites, both groups combined, either remained unchanged (28.5%) or improved (63%). The other 3 studies use the height of interproximal papillae. However, 1 investigation[44,45] did not report the sample size, and the meta-analysis result of the remaining 2[56,65] showed insufficient evidence to determine the difference between the test and control procedure (WMD=0.078; 95% CI, −0.115, 0.271; *P*=.429).

Regarding free gingiva change, which was reported in 5 included studies, 3 investigations showed the recession of the mid-buccal site,[56,62,63,65] the change ranging from −0.67 mm to 0.06 mm in the test group and from −1.16 mm to −0.09 mm in the control. The meta-analysis, with high heterogeneity among trials, showed insufficient evidence with a statistically significant difference (WMD=0.204; 95% CI, −0.297, 0.704; *P*=.425). The other 2 studies measured the gingival recession from the crown margin to the gingival margin,[14,15] with a reference line connecting the highest free gingival margins of adjacent dentition.[61] Evidence of a statistically significant difference was lacking between the test and control participants regarding gingival recession (*P*>.05).

For assessing the width of the keratinized mucosa (WKM), 2 studies registered the data of the last visit.[14,15,61] The meta-analysis results found insufficient evidence to determine whether there was a statistically significant difference between the test and control groups (WMD=−0.186; 95% CI, −0.750, 0.387; *P*=.517), and 1 study reported the alteration from baseline to 1-year recall.[62,63] The mean ±standard deviation loss from definitive crown placement to 1 year was 0.83 ±1.59 mm and 1.08 ±1.31 mm for the immediate and conventional groups, respectively. There was no statistically significant difference between the 2 groups.

Probing depth (PD) was measured in 11 investigations. One,[62,63] conducted by the same authors, reported the changes of PD in the 2 loading groups, from 4 weeks after definitive crown placement to 1 year, which showed no significant statistical difference. The other 10 studies evaluated the PD on the last visit[14,15,17,18,20,24,56,58,61,64,65] and reported data as mean, standard deviation, and sample size. The meta-analysis showed no significant statistical difference in PD when comparing immediate with conventional loading technique (WMD=−0.004; 95% CI, −0.123, 0.115; *P*=.944; Fig. 8). In the analysis of subgroup, despite high heterogeneity shown in some items (nonocclusion, freehand, maxillary nonmolar region), a statistically significant difference was not found in any subgroup comparison (Table 6).

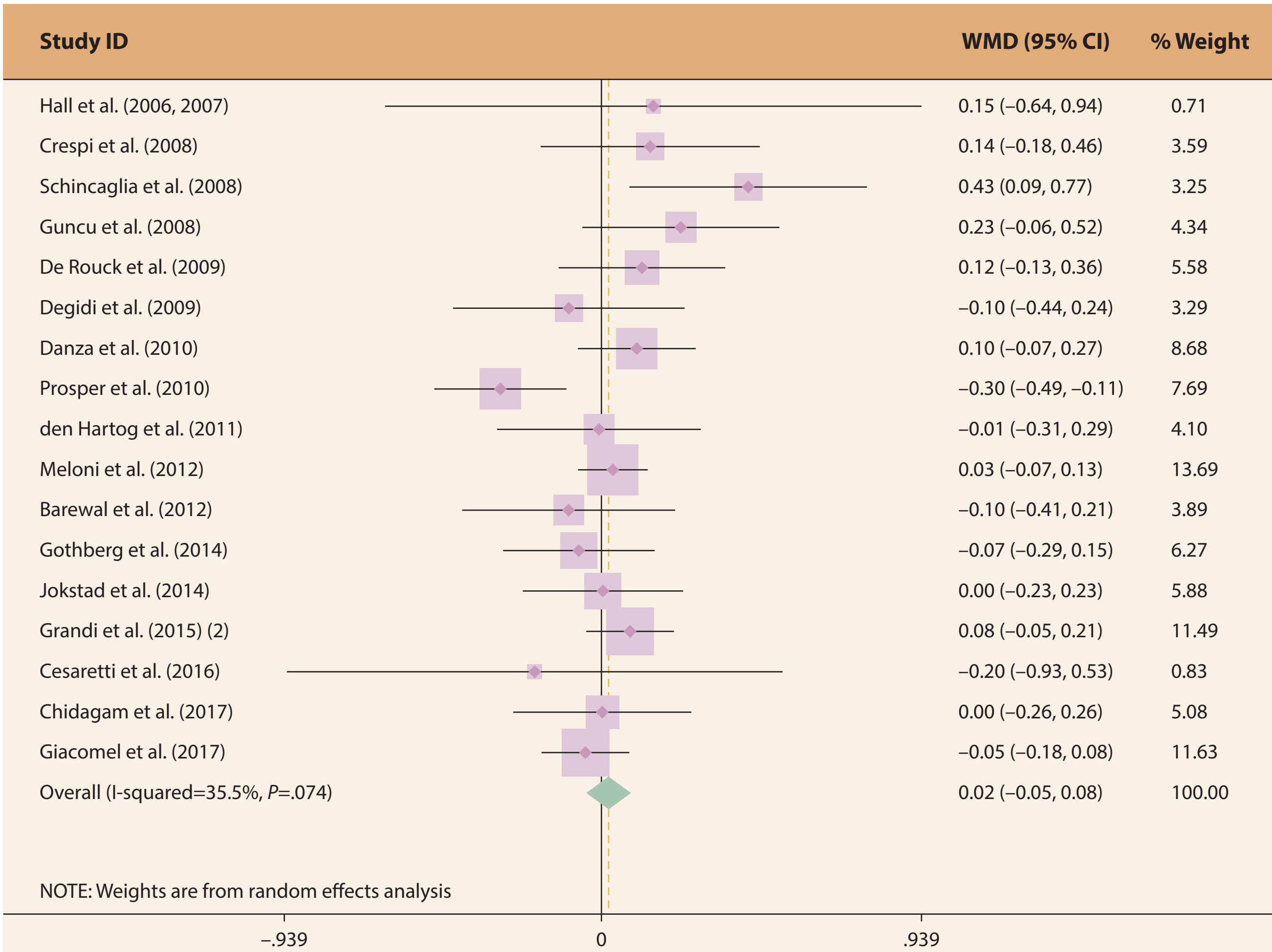

Figure 7. Forest plot of marginal bone level change compared with delayed loading.

The presence of plaque was reported in 7 trials. Three different indexes were used to assess the plaque accumulation: plaque index (PI),[71] modified plaque index (mPI),[66] and frequencies of the site with a plaque. Meta-analyses were performed for the studies by using the same indexes but without subgroup analysis being performed. For the PI, the mean change was 0.38 to 0.57 in the test group and 0.29 to 0.43 in the control group.[14,15,58,64] No statistically significant difference was observed between the test and control groups (WMD=−0.078; 95% CI, −0.101, 0.258; *P*=.963).

Three articles used mPI for assessment of plaque index, of them 2 articles stemmed from the same trial registering the mean changes[62,63] and 1 reported mPI on the last follow-up evaluation.[61] The mean change was −0.26 (decrease) in the test group and −0.14 in the control group, while mPI was 0.57 and 0.43 in the test and control groups, respectively. Again, no statistically significant difference was detected between both groups (*P*>.05). This index was reported as a frequency of the site with plaque. A meta-analysis could not be performed because the sample size was not declared in this trial.[44,45] The percentage of the site with plaque was 16% in the test group and 17% in the control group.[65]

The subjective feeling of patients was evaluated in 4 studies. The first investigation[61] showed patient satisfaction data regarding comfort level, appearance, and function. There was no statistically significant difference between the 2 groups. The second trial[65] reported patients' esthetic satisfaction, indicating on average 93% (range: 82% to 100%) for the test group and 91% (range: 80% to 96%) for the control group. The third study[16] registered the postoperative edema, pain, and use of analgesics. Immediate loading decreased the postoperative discomfort, with statistically significant differences (*P*<.05). The last one[56] showed patient satisfaction with function, esthetics, treatment procedure, and general satisfaction. The scores were high, and no statistically significant differences were found between the test and control groups.

Two methods also evaluated the survival rate of the implant, with patient and implant regarded as the

Table 5. Results of meta-analyses on marginal bone level change compared with delayed loading

	Subgroup	N	WMD	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		17	0.016	-0.052, 0.084	.645	.074	35.5
Healing method	Submerged	6	-0.050	-0.208, 0.109	.540	.074	50.3
	Nonsubmerged	11	0.048	-0.011, 0.107	.111	.422	2.1
Implant time	Delay	12	-0.002	-0.090, 0.086	.965	.025	49.8
	Immediate	3	0.111	-0.017, 0.238	.091	.976	0.0
	Mixed	2	-0.019	-0.240, 0.203	.869	.607	0.0
Occlusion	Occlusion	7	0.083	0.003, 0.163	**.043**	.244	24.3
	Nonocclusion	6	-0.063	-0.215, 0.09	.420	.122	42.4
	NR	4	-0.051	-0.155, 0.054	.343	.938	0.0
Missing teeth	Single	11	0.022	-0.079, 0.122	.672	.020	52.8
	Several	2	0.066	-0.051, 0.183	.269	.585	0.0
	Full	2	-0.080	-0.260, 0.100	.382	.877	0.0
	Any	2	0.084	-0.082, 0.250	.320	.431	0.0
Surgery guide	Guide	6	0.023	-0.136, 0.181	.779	.004	71.4
	Free hand	11	0.013	-0.056, 0.081	.721	.698	0.0
Tooth position	Maxillary nonmolar region	5	-0.039	-0.255, 0.177	.725	.044	59.2
	Mandibular posterior	5	0.099	-0.048, 0.246	.185	.057	56.4
	Other	7	0.022	-0.044, 0.089	.514	.866	0.0
Surgery: test/control	Flap/flap	16	0.036	-0.014, 0.087	.156	.566	0.0
	Flapless/flapless	1	-0.300	-0.489, -0.111	**.002**	—	—
First restorations: test/control	Provisional/definitive	11	0.026	-0.032, 0.084	.384	.018	53.6
	Provisional/provisional	5	0.024	-0.098, 0.147	.695	.727	0.0
	Unclear	1	-0.050	-0.175, 0.075	.435	—	—

Bold text indicates statistically significant differences.

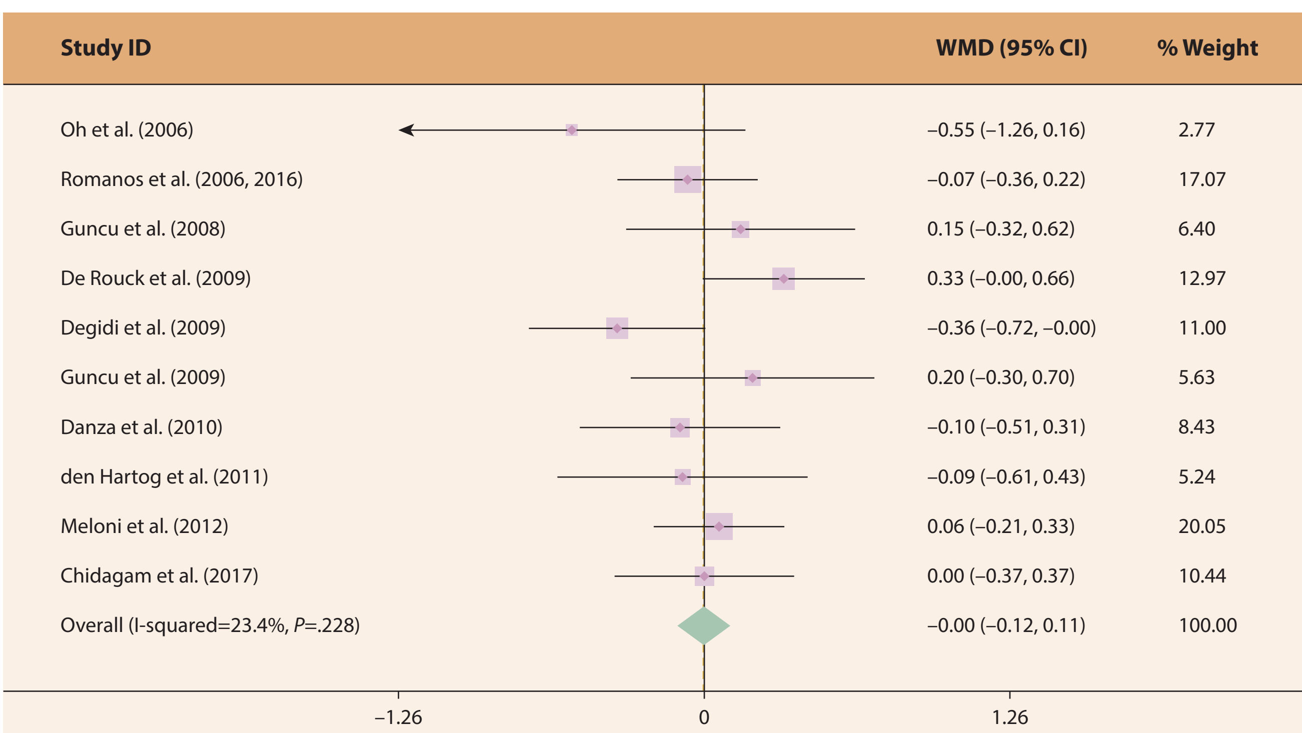

Figure 8. Forest plot of probing depth compared with delayed loading.

statistical unit. For implant as a statistical unit, the mean survival rate was 96.3% in both groups. Of the 16 included studies, there was no implant failure in 7.[12,13,19,22,26-29] The overall effect of the meta-analyses showed no statistical difference regarding the incidence of implant failure in both groups (RR=1.003; 95% CI,

Table 6. Results of meta-analyses on probing depth compared with delayed loading

Variable	Subgroup	N	WMD	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		10	-0.004	-0.123, 0.115	.944	.228	23.4
Healing method	Submerged	5	0.047	-0.102, 0.196	.540	.376	5.4
	Nonsubmerged	5	-0.094	-0.291, 0.104	.352	.179	36.4
Implant time	Delay	9	-0.054	-0.182, 0.073	.406	.512	0.0
	Immediate	1	0.330	-0<.001, 0.660	.050	—	—
Occlusion	Occlusion	6	-0.029	-0.196, 0.138	.733	.605	0.0
	Nonocclusion	4	0.021	-0.148, 0.191	.805	.047	62.3
Missing teeth	Single	8	0.022	-0.116, 0.159	.758	.130	37.5
	Several	1	-0.070	-0.358, 0.218	.634	—	—
	Any	1	-0.100	-0.509, 0.309	.632	—	—
Surgery guide	Guide	5	-0.092	-0.271, 0.088	.316	.765	0.0
	Free hand	5	0.064	-0.094, 0.223	.427	.082	51.7
Tooth position	Maxillary nonmolar region	4	-0.052	-0.263, 0.158	.625	.020	69.6
	Mandibular posterior	5	0.035	-0.119, 0.189	.655	.874	0.0
	Posterior	1	-0.100	-0.509, 0.309	.632	—	—
Surgery: test/control	Flap/flap	9	0.011	-0.109, 0.132	.854	.306	15.3
	Flapless/flapless	1	-0.550	-1.264, 0.164	.131	—	—
First restorations: test/control	Provisional/definitive	6	0.104	-0.052, 0.260	.192	.346	10.8
	Provisional/provisional	4	-0.155	-0.339, 0.029	.099	.633	0.0

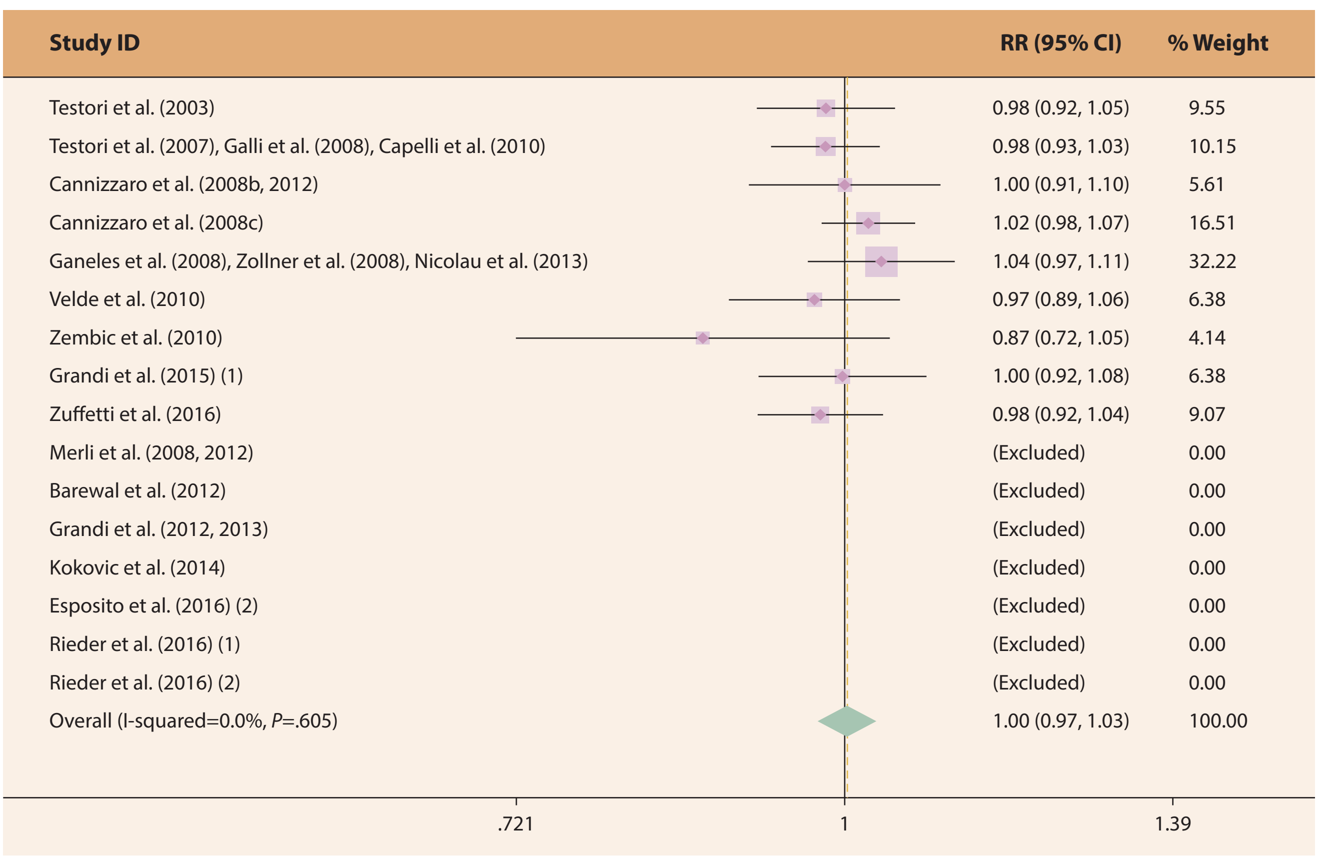

Figure 9. Forest plot of implant survival rate compared with early loading, for implant as statistical unit.

0.974, 1.032; *P*=.851; Fig. 9). No publication bias was detected with the Begg test (*P*=.111; Fig. 10). The subgroup analysis also resulted in no statistically significant differences between the immediate and early loading groups, with acceptably low heterogeneity among studies (*P*>.1; I^2<50%) (Table 7).

For patient as a statistical unit, the mean survival rate was 94.6% and 95.9% in the immediate loading and the

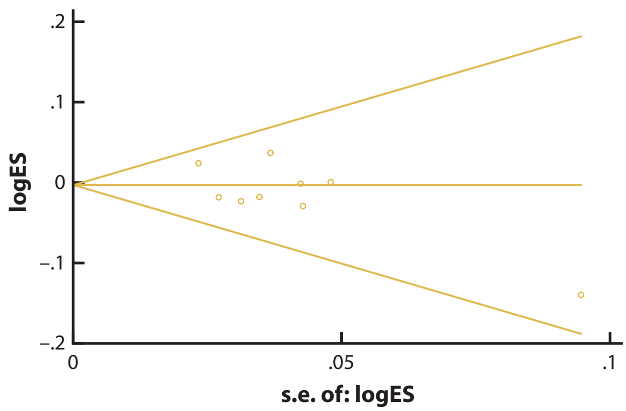

Figure 10. Funnel plot illustrating meta-analysis of implant survival rate compared with early loading, for implant as statistical unit.

early loading groups, respectively. In 7 of the 15 included trials, the survival rate of implants was 100%. The results of the meta-analysis of the remaining 8 studies are presented in Figure 11. The meta-analysis resulted in the same survival rate in both the groups (RR=0.984; 95% CI, 0.937, 1.033; *P*=.516). No publication bias was detected by the Begg test (*P*=.312) (Fig. 12). In the subgroup analyses, also no statistically significant difference was shown in the implant survival rate of either group (*P*>.05) (Table 8).

The change of crestal bone level was reported in all trials, except 2.[22,29] All 13 investigations used periapical radiographs for bone loss evaluation. One study did not register the standard deviation,[72] so the remaining 12 were combined in the meta-analysis. The loss of marginal bone level ranged from −1.60 mm (loss) to −0.12 mm in the test group and from −1.54 mm to −0.17 mm in the controls. The result shows no statistically significant difference in crestal bone loss between the test and control groups (WMD=0.02; 95% CI, −0.138, 0.178; *P*=.809) when combining the data at all sites of implants (Fig. 13). For any of the subgroup analysis, no statistically significant difference was found between groups, except in trials that did not report definitive immediate occlusion (WMD=0.400; 95% CI, 0.240, 0.560; *P*<.001) and when interim prostheses were used for immediate loading while directly definitive restorations were used for early loading (WMD=0.240; 95% CI, 0.015, 0.465; *P*=.036) (Table 9).

The Osstell device was used in 5 trials for testing implants' stability. One reported data as Figures,[19] and one showed the results by comparing cylindrical implants with tapered ones.[72] The remaining 3 studies presented data as mean, standard deviation, and sample size.[5,28,46,73] The mean varied from 66.10 to 82.97 in the test group and from 70.40 to 81.14 in the control group. The meta-analysis results reported that there was no sufficient evidence to support the significant statistical difference between the 2 groups (WMD=−0.805; 95% CI, −3.309, 1.699; *P*=.529).

Gingival inflammation was registered in 5 studies, and 2 indexes were used: modified sulcus bleeding index (mBI)[66] and peri-implant mucositis. Two methods also evaluated the peri-implant mucositis. Patients and implants were regarded as a statistical unit. For patient as a statistical unit, the rates were 2.5% and 0.8% in the test and control groups, respectively.[22,26,27,52,74] The meta-analysis for the 4 studies showed the same rate of peri-implant mucositis in both groups, with no significant difference observed between immediate and early loading (RR=1.922; 95% CI, 0.417, 8.866; *P*=.402). For implant as a statistical unit, the peri-implant mucositis rate was 3.2% in the test and 1.5% in the control group. The meta-analysis for the 4 studies[5,22,46,52,74] with low heterogeneity found insufficient evidence to determine whether differences existed between both groups (RR=1.845; 95% CI, 0.562, 6.056; *P*=.313). Modified sulcus bleeding index (mBI)[66] was presented in 1 trial,[28] which showed no significant statistical difference between the 2 groups (*P*>.05).

For patient and implant as the statistical unit, the rates of peri-implantitis were 0 and 0.5% in the immediately loaded group and 2.6% and 2.3% in the early loaded group. According to the results of meta-analysis, evidence of a statistically significant difference was lacking in either method.

As for peri-implant soft tissue, the pink esthetic score (PES),[75] gingival recession, and attached mucosa height were registered. PES, consisting of 7 soft-tissue parameters, was used for the assessment in 1 trial.[29] No statistically significant difference was found between the immediately and early loaded groups in terms of the overall effect (*P*=.124). Gingival recession outcomes were reported in 2 studies.[4,42,43,74] The meta-analysis was associated with low heterogeneity, and there was insufficient evidence to determine whether a statistically significant difference existed between the test and control subjects (WMD=−0.145; 95% CI, −0.330, 0.040; *P*=.124). For the height of attached mucosa, only 1 study reported the data at different time periods.[59] No statistically significant difference was found between the test and control groups at 3, 6, 12, and 18 months (*P*>.05).

Plaque index was reported in 2 trials. In 1 study,[28] the mPI[66] was registered for the test and control groups at 1 and 5 years after loading. No statistically significant difference was shown at either time period (*P*>.05). The plaque control record (PCR)[76] was used in another trial,[73] where only the percentage of plaque accumulation was reported.

For subjective assessment, patients were asked to fill in a questionnaire with a visual analog scale (VAS) in 1 study.[59] There were no statistically significant differences in speech, function, esthetics, and self-confidence after loading with interim prostheses (6 weeks). A statistical difference was found between the

Table 7. Results of meta-analyses on implant survival rate compared with early loading, for implant as statistical unit

Variable	Subgroup	N (Excluded)*	RR	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		9 (7)	1.003	0.974, 1.032	.851	.605	0.0
Healing method	Submerged	9 (6)	1.003	0.974, 1.032	.851	.605	0.0
	Nonsubmerged	0 (1)	—	—	—	—	—
Implant time	Delay	2 (2)	1.026	0.965, 1.092	.408	.180	44.4
	Immediate	0 (1)	—	—	—	—	—
	Early	0 (1)	—	—	—	—	—
	Both	7 (3)	0.988	0.962, 1.015	.372	.590	0.0
Occlusion	Occlusion	4 (1)	0.990	0.952, 1.030	.611	.227	30.9
	Nonocclusion	5 (4)	1.009	0.971, 1.049	.646	.479	0.0
	NR	0 (2)	—	—	—	—	—
Missing teeth	Single	3 (4)	1.027	0.972, 1.085	.343	.658	0.0
	Several	3 (1)	0.955	0.903, 1.010	.104	.408	0.0
	Full	1 (0)	1.024	0.979, 1.072	.301	—	—
	Any	2 (2)	0.979	0.940, 1.019	.296	.91	0.0
Surgery guide	Guide	2 (3)	1.009	0.970, 1.051	.652	.265	19.4
	Free hand	7 (4)	1.001	0.966, 1.037	.963	.581	0.0
Tooth position	Posterior	3 (2)	1.011	0.954, 1.072	.712	.136	49.8
	Maxillary incisors	0 (2)	—	—	—	—	—
	Maxillary	1 (0)	1.024	0.979, 1.072	.301	—	—
	Any	5 (3)	0.985	0.956, 1.016	.349	.989	0.0
Surgery: test/control	Flap/flap	4 (5)	0.968	0.930, 1.007	.107	.534	0.0
	Flapless/flapless	2 (1)	1.018	0.977, 1.061	.396	.649	0.0
	Flapless/flap	1 (0)	0.971	0.893, 1.055	.485	—	—
	Unclear	2 (1)	1.025	0.967, 1.085	.408	.198	39.7
First restorations: test/control	Provisional/definitive	0 (1)	—	—	—	—	—
	Provisional/provisional	9 (6)	1.003	0.974, 1.032	.851	.605	0.0

*Excluded: number of studies with 100% implant survival rates in both groups.

test and control groups regarding pain, comfort, or overall satisfaction scores at any time point (*P*>.05). Another trial[5,46] showed no statistically significant difference when patients who preferred immediate versus early loading were compared after 3 months and 4 years of loading.

DISCUSSION

The results showed that immediate loading represented a higher risk of implant failure than delayed loading, while presenting no difference in marginal bone level change or probing depth. When compared with early loading, immediate loading achieved similar implant survival rates and marginal bone level change.

This systematic review included 39 RCTs, with a total of 1868 patients and 3746 implants, that compared immediate loading versus early or delayed loading in patients rehabilitated with a fixed prosthesis. Six of the studies had less than 1 year of follow-up duration.[5,22,23,25,29,46,61] Esposito et al[30] reported on a relatively short period (4 months to 1 year), but the time was sufficient to determine the impact of loading on the establishment of osseointegration as the first several months of immediate or early loading is the key period for osseointegration. As the influence of the loading method on the outcomes after osseointegration is reduced, it is reasonable to include these 6 trials.

Compared with conventional loading, immediately loaded implants had a statistically significant lower survival rate (implant as statistical unit), and this finding was similar to the result reported in previously published systematic reviews of fixed restorations.[33,34] The survival rate in the immediate group showed no significant difference, although it was relatively lower with patients considered as the statistical unit. The discrepancy caused by the statistical unit can be explained thus: the patient unit increases the implant failure rate to some extent as the failure of a multiunit prosthesis may be caused by the loss of only 1 implant. Additionally, this method has decreased the relative sample size of implant-supported fixed prostheses for meta-analysis.

No statistically significant difference in MBL was shown in the overall effects of the meta-analysis when immediate loading was compared with the delayed protocol. This was also consistent with previously published systematic reviews.[30,35,36] This result indicated that different loading protocols behaved similarly after osseointegration because only successful treatments were included in the meta-analysis. Sanz-Sanchez et al[33] reported statistically significant lower bone loss in the immediate loading group than that in the conventionally

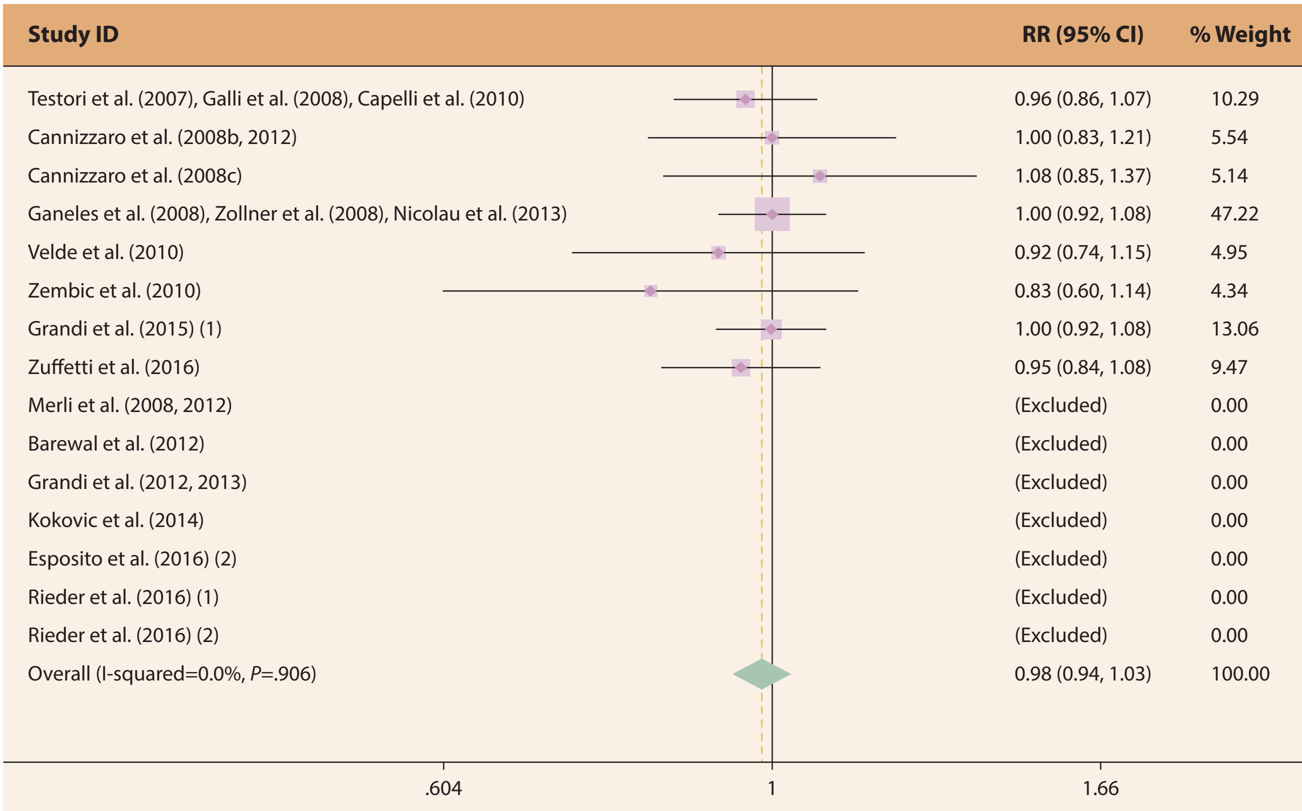

Figure 11. Forest plot of implant survival rate compared with early loading, for patient as statistical unit.

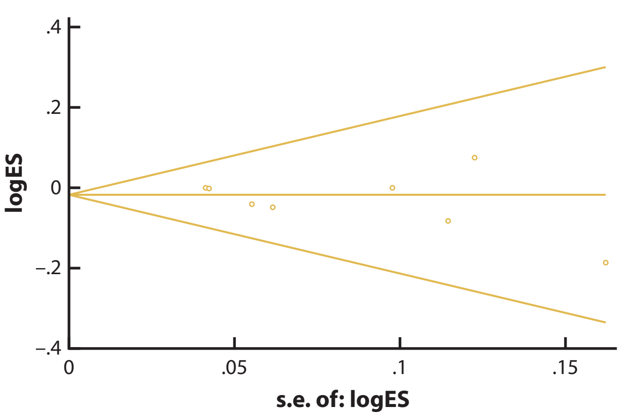

Figure 12. Funnel plot illustrating meta-analysis of implant survival rate compared with early loading, for patient as statistical unit.

loaded group. These discrepancies may be explained by previous systematic reviews combining both fixed and removable implant-supported prostheses,[30,31,33,34,36] while the current meta-analysis focused on only fixed restorations. Additionally, the Cochrane review made comparisons at 4 to 12 months after loading,[30] while the others assessed data at the last visit.[31,33,34,36] The present review used the latter method. Because the MBL change is irreversible, it is reasonable to use the most recent data because of the longer follow-up time.

In the subgroup analyses, the lower survival rate of implants was observed in the immediately loaded implants with items listed previously. Types of loading, tooth position, and unit number of prostheses caused the different outcomes between the test and control groups by influencing stabilization during the osseointegration period. Micromotion might hinder the proliferation of osteoblasts and lead to the formation of fibrous tissues at the bone-implant interface.[77,78] Nonocclusal patterns reduced the masticatory force on immediately loaded implants, while cross-arch stabilization could be obtained from complete-arch restorations. It was concluded that controlled occlusal loads for complete-arch prostheses and nonocclusal loads for short-span prostheses and single-tooth replacements were important factors for a successful outcome.[79] However, a systematic review, based on 10 RCTs, concluded that immediately and conventionally loaded single-implant crowns were clinically equal regarding implant survival, marginal bone loss, papilla height, and the recession of midfacial peri-implant mucosa.[80] A similar conclusion was also drawn by Moraschini and Barboza[81] on single posterior mandibular implants. For partially edentulous situations, Schrott et al[82] concluded that there was no statistically significant difference in implant survival rate among immediate, early, or delayed loading. The result of another meta-analysis concluded that the differences in

Table 8. Results of meta-analyses on implant survival rate compared with early loading, for patient as statistical unit

Variable	Subgroup	N (Excluded)*	RR	95% CI	*P*	Heterogeneity *P*	Heterogeneity I^2 (%)
Overall		8 (7)	0.984	0.937, 1.033	.516	.906	0.0
Healing method	Submerged	0 (1)	—	—	—	—	—
	Nonsubmerged	8 (6)	0.984	0.937, 1.033	.516	.906	0.0
Implant time	Delay	2 (2)	0.993	0.920, 1.071	.847	.491	0.0
	Immediate	0 (1)	—	—	—	—	—
	Early	0 (1)	—	—	—	—	—
	Both	6 (3)	0.974	0.918, 1.034	.395	.813	0.0
Occlusion	Occlusion	4 (1)	0.963	0.855, 1.085	.535	.574	0.0
	Nonocclusion	4 (4)	0.989	0.938, 1.044	.688	.856	0.0
	NR	0 (2)	—	—	—	—	—
Missing teeth	Single	2 (5)	0.999	0.921, 1.083	.976	.986	0.0
	Several	2 (1)	0.878	0.726, 1.060	.176	.589	0.0
	Full	1 (0)	1.077	0.847, 1.369	.545	—	—
	Any	3 (1)	0.987	0.928, 1.050	.687	.711	0.0
Surgery guide	Guide	2 (3)	1.000	0.848, 1.180	1.000	.344	0.0
	Free hand	6 (4)	0.982	0.933, 1.034	.489	.867	0.0
Tooth position	Posterior	3 (2)	0.980	0.910, 1.056	.594	.448	0.0
	Maxillary incisors	0 (2)	—	—	—	—	—
	Maxillary	1 (0)	1.077	0.847, 1.369	.545	—	—
	Any	4 (3)	0.977	0.923, 1.035	.429	.902	0.0
Surgery: test/control	Flap/flap	4 (5)	0.956	0.898, 1.018	.163	.614	0.0
	Flapless/flapless	2 (1)	1.037	0.890, 1.208	.641	.629	0.0
	Flapless/flap	1 (0)	0.920	0.735, 1.151	.466	—	—
	Unclear	1 (1)	1.000	0.922, 1.084	.998	—	—
First restorations: test/control	Provisional/definitive	0 (1)	—	—	—	—	—
	Provisional/provisional	8 (6)	0.984	0.937, 1.033	.516	.906	0.0

*Excluded: number of studies with 100% implant survival rates in both groups.

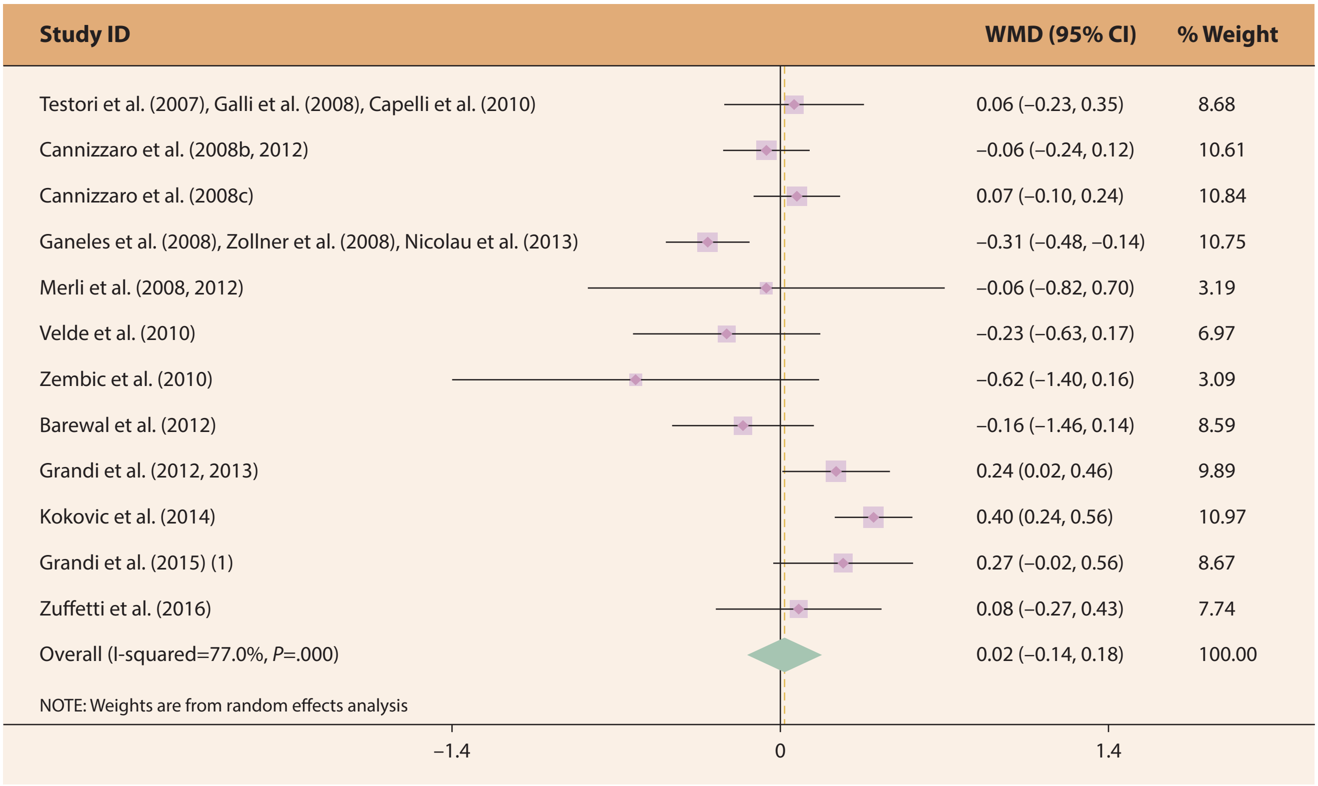

Figure 13. Forest plot of marginal bone level change compared with early loading.

Table 9. Results of meta-analyses on marginal bone level change compared with early loading

Variable	Subgroup	N	WMD	95% CI	P	Heterogeneity P	Heterogeneity I^2 (%)
Overall		12	0.020	-0.138, 0.178	.809	<.001	77.0
Healing method	Submerged	0	—	—	—	—	—
	Nonsubmerged	12	0.020	-0.138, 0.178	.809	<.001	77.0
Implant time	Delay	4	-0.065	-0.476, 0.345	.755	<.001	92.2
	Mixed	8	0.076	-0.035, 0.187	.178	.248	22.7
Occlusion	Occlusion	5	-0.064	-0.201, 0.073	.361	.256	24.8
	Nonocclusion	6	0.049	0.189, 0.286	.689	.001	75.1
	NR	1	0.400	0.240, 0.560	<.001	—	—
Missing teeth	Single	5	0.105	-0.154, 0.365	.426	.001	79.5
	Several	3	-0.105	-0.569, 0.359	.657	.025	73.0
	Full	1	0.07	-0.099, 0.239	.416	—	—
	Any	3	-0.084	-0.368, 0.200	.562	.033	70.7
Surgery guide	Guide	5	0.045	-0.214, 0.305	.732	.001	78.0
	Free hand	7	0.000	-0.196, 0.196	.998	.001	73.3
Tooth position	Posterior	5	-0.133	-0.519, 0.252	.498	<.001	90.2
	Maxillary	1	0.070	-0.099, 0.239	.416	—	—
	Any	6	0.095	-0.029, 0.219	.132	.312	15.8
Surgery: test/control	Flap/flap	6	0.095	-0.136, 0.326	.421	.004	71.3
	Flapless/flapless	3	0.008	-0.114, 0.131	.892	.582	0.0
	Flapless/flap	1	-0.230	-0.625, 0.165	.254	—	—
	Unclear	2	-0.040	-0.579, 0.499	.885	<.001	93.0
First restorations: test/control	Provisional/definitive	1	0.240	0.015, 0.465	**.036**	—	—
	Provisional/provisional	11	-0.006	-0.176, 0.165	.947	<.001	77.7

Bold text indicates statistically significant differences.

occlusal loading might not have significant effects on implant survival rate and marginal bone loss.[83] A consensus meeting, based on systematic reviews, reported no increased risk of implant loss in immediate loading with occlusal contact or complete-arch fixed restorations and a lower implant survival rate and less marginal bone level change in the test group.[33,84] In regard to tooth position, a potential problem of installing implants in poor-quality bone is the difficulty in obtaining adequate primary implant stability.[77,85,86] Relatively lower survival rate in immediate loading groups was also caused by the delayed implant, implant guide plate, and flap surgery. This could be explained by the predictable clinical outcomes with conventionally standardized therapy. Another statistically significant difference was shown in marginal bone level as compared with delayed loading, depending on the occlusal contact of immediately loaded implants (WMD=0.083; 95% CI, 0.003, 0.163; P=.043).

The implant survival rate might be influenced by many other elements including insertion torque, implant surface and design modifications, bone density, alveolar ridge augmentation, load, infection, and smoking.[20,77,79,86-97] However, comparing the outcomes between the test and control groups was impossible based on the RCTs included in this article because the related data were obtained in an inconsistent manner.

According to the results of the current meta-analysis, immediate and early loaded implants were equally successful regarding implant survival and marginal bone loss. Zhang et al[34] reported that both immediate and early loading had a negative impact on the formation of implant-connective tissue interface, which resulted in similar outcomes in these 2 protocols. In subgroup analyses, no statistically significant differences were shown in primary or secondary outcomes, which indicates that these factors might not influence the clinical results of early or immediately loaded implants.

For single-implant-supported crowns, a previous systematic review concluded that no significant differences were found on implant survival rate and marginal bone loss at 1 or 3 years between the 2 loading protocols.[98] For flapless placement in 2 groups, another systematic review[99] was consistent with the present findings in that no statistical differences were found in implant survival rate, marginal bone level change, or complications between the 2 protocols; however, the authors included studies reporting the survival rate of patients rehabilitated with overdentures. For tooth position, Schrott et al[82] reported a similar result of meta-analysis that immediate loading presented no difference in implant survival rate for patients with extended edentulous sites in the posterior zone when compared with early or delayed loading.

The results presented in this systematic review must be regarded with caution. Although 39 studies that were designated as RCTs were included, only 16 of them reported the procedures for both random sequence generation and allocation concealment, which suggests potential selection bias. Additionally, in 20 RCTs, the measurement of correlative parameters was not performed by calibrated investigators in a blinded fashion (Fig. 2). In regard to other biases, some information such as sample size[18,44,45,53] was not available through the published articles or e-mail requests.

In addition to the biases listed, several elements may have influenced the results of the comparison. When the implant was considered as a statistical unit, the meta-analysis resulted in a statistically significant lower survival rate in immediately loaded implants than in the conventionally loaded implants. However, the 100% survival rate of implants in 9 of the 29 included trials, excluded from the meta-analysis, might overestimate the failure risk of the immediately loaded implants. Additionally, implant stability, gingival inflammation, peri-implantitis, peri-implant gingival level change, and subjective feeling of patients in the included studies were assessed by using different methods and indexes. Therefore, insufficient evidence, with the same index, could be found to determine whether there was a significant difference between the test and control groups. Also, RFA measurement at the time of implant placement is not sufficiently accurate to determine implant stability and osseointegration during immediate loading.[100] The way by which the MBL was assessed is often influenced by the precision of the radiographic and measurement technique.[101,102] Experienced operators, strict inclusion, and exclusion criteria of patients mentioned in most of the RCTs included could have improved the clinical outcomes of immediate loading. De Bruyn et al[3] also concluded that appropriate indication selection was key to achieving predictable outcomes.

CONCLUSIONS

Based on the finding of this systematic review and meta-analysis of randomized controlled clinical trials, the following conclusions were drawn:

1. When compared with early loading, immediate loading could achieve comparable implant survival rates and marginal bone level change.
2. However, when comparing immediately versus conventionally loaded protocols, the results of the current meta-analysis showed a higher risk of failure in the test group while presenting no difference in marginal bone level change and probing depth.
3. As to other secondary outcomes, the evidence was insufficient to determine the difference, which indicates more high-quality RCTs reported according to the CONSORT guidelines are needed.

REFERENCES

1. Branemark PI, Hansson BO, Adell R, Breine U, Lindstrom J, Hallen O, et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. Scand J Plast Reconstr Surg Suppl 1977;16:1-132.
2. Strub JR, Jurdzik BA, Tuna T. Prognosis of immediately loaded implants and their restorations: a systematic literature review. J Oral Rehabil 2012;39:704-17.
3. De Bruyn H, Raes S, Ostman PO, Cosyn J. Immediate loading in partially and completely edentulous jaws: a review of the literature with clinical guidelines. Periodontol 2000 2014;66:153-87.
4. Galli F, Capelli M, Zuffetti F, Testori T, Esposito M. Immediate non-occlusal vs. early loading of dental implants in partially edentulous patients: a multicentre randomized clinical trial. Peri-implant bone and soft-tissue levels. Clin Oral Implants Res 2008;19:546-52.
5. Cannizzaro G, Leone M, Torchio C, Viola P, Esposito M. Immediate versus early loading of 7-mm-long flapless-placed single implants: a split-mouth randomised controlled clinical trial. Eur J Oral Implantol 2008;1:277-92.
6. Schnitman PA, Wohrle PS, Rubenstein JE. Immediate fixed interim prostheses supported by two-stage threaded implants: methodology and results. J Oral Implantol 1990;16:96-105.
7. Schnitman PA, Wohrle PS, Rubenstein JE, DaSilva JD, Wang NH. Ten-year results for Branemark implants immediately loaded with fixed prostheses at implant placement. Int J Oral Maxillofac Implants 1997;12:495-503.
8. Assad AS, Hassan SA, Shawky YM, Badawy MM. Clinical and radiographic evaluation of implant-retained mandibular overdentures with immediate loading. Implant Dent 2007;16:212-23.
9. Romeo E, Chiapasco M, Lazza A, Casentini P, Ghisolfi M, Iorio M, et al. Implant-retained mandibular overdentures with ITI implants. Clin Oral Implants Res 2002;13:495-501.
10. Cannizzaro G, Leone M, Esposito M. Immediate versus early loading of two implants placed with a flapless technique supporting mandibular bar-retained overdentures: a single-blinded, randomised controlled clinical trial. Eur J Oral Implantol 2008;1:33-43.
11. Crespi R, Capparé P, Gherlone E, Romanos GE. Immediate versus delayed loading of dental implants placed in fresh extraction sockets in the maxillary esthetic zone: A clinical comparative study. Int J Oral Maxillofac Implants 2008;23:753-8.
12. Merli M, Moscatelli M, Mariotti G, Piemontese M, Nieri M. Immediate versus early non-occlusal loading of dental implants placed flapless in partially edentulous patients: a 3-year randomized clinical trial. J Clin Periodontol 2012;39:196-202.
13. Merli M, Merli A, Bernardelli F, Lombardini F, Esposito M. Immediate versus early non-occlusal loading of dental implants placed flapless in partially edentulous patients. One-year results from a randomised controlled trial. Eur J Oral Implantol 2008;1:207-20.
14. Romanos GE, Aydin E, Locher K, Nentwig GH. Immediate vs. delayed loading in the posterior mandible: a split-mouth study with up to 15 years of follow-up. Clin Oral Implants Res 2016;27:e74-9.
15. Romanos GE, Nentwig GH. Immediate versus delayed functional loading of implants in the posterior mandible: a 2-year prospective clinical study of 12 consecutive cases. Int J Periodontics Restorative Dent 2006;26:459-69.
16. Cannizzaro G, Leone M, Consolo U, Ferri V, Esposito M. Immediate functional loading of implants placed with flapless surgery versus conventional implants in partially edentulous patients: a 3-year randomized controlled clinical trial. Int J Oral Maxillofac Implants 2008;23:867-75.
17. Degidi DM, Nardi D, Piattelli A. Immediate versus one-stage restoration of small-diameter implants for a single missing maxillary lateral incisor: A 3-year randomized clinical trial. J Periodontol 2009;80:1393-8.
18. Danza M, Tortora P, Quaranta A, Perrotti V, Vozza I, Piattelli A. Randomised study for the 1-year crestal bone maintenance around modified diameter implants with different loading protocols: a radiographic evaluation. Clin Oral Investig 2010;14:417-26.
19. Barewal RM, Stanford C, Weesner TC. A randomized controlled clinical trial comparing the effects of three loading protocols on dental implant stability. Int J Oral Maxillofac Implants 2012;27:945-56.
20. Meloni SM, De Riu G, Pisano M, De Riu N, Tullio A. Immediate versus delayed loading of single mandibular molars. One-year results from a randomised controlled trial. Eur J Oral Implantol 2012;5:345-53.
21. Jokstad A, Alkumru H. Immediate function on the day of surgery compared with a delayed implant loading process in the mandible: a randomized clinical trial over 5 years. Clin Oral Implants Res 2014;25:1325-35.
22. Esposito M, Siormpas K, Mitsias M, Bechara S, Trullenque-Eriksson A, Pistilli R. Immediate, early (6 weeks) and delayed loading (3 months) of

single implants: 4-month post-loading from a multicenter pragmatic randomised controlled trial. Eur J Oral Implantol 2016;9:249-60.
23. Vercruyssen M, Cox C, Naert I, Jacobs R, Teughels W, Quirynen M. Accuracy and patient-centered outcome variables in guided implant surgery: a RCT comparing immediate with delayed loading. Clin Oral Implants Res 2016;27:427-32.
24. Chidagam P, Gande V, Yadlapalli S, Venkata R, Kondaka S, Chedalawada S. Immediate versus delayed loading of implant for replacement of missing mandibular first molar: a randomized prospective six years clinical study. J Clin Diagn Res 2017;11:ZC35-9.
25. Giacomel M, Camati P, Souza J, Deliberador T. Comparison of marginal bone level changes of immediately loaded implants, delayed loaded non-submerged implants, and delayed loaded submerged implants: a randomized clinical trial. Int J Oral Maxillofac Implants 2017;32:661-6.
26. Grandi T, Garuti G, Guazzi P, Tarabini L, Forabosco A. Survival and success rates of immediately and early loaded implants: 12-month results from a multicentric randomized clinical study. J Oral Implantol 2012;38:239-49.
27. Grandi T, Guazzi P, Samarani R, Grandi G. A 3-year report from a multicentre randomised controlled trial: immediately versus early loaded implants in partially edentulous patients. Eur J Oral Implantol 2013;6:217-24.
28. Kokovic V, Jung R, Feloutzis A, Todorovic VS, Jurisic M, Hämmerle CH. Immediate vs. early loading of SLA implants in the posterior mandible: 5-year results of randomized controlled clinical trial. Clin Oral Implants Res 2014;25:e114-9.
29. Rieder D, Eggert J, Krafft T, Weber H-P, Wichmann M, Heckmann S. Impact of placement and restoration timing on single-implant esthetic outcome-a randomized clinical trial. Clin Oral Implants Res 2016;27:e80-6.
30. Esposito M, Grusovin MG, Maghaireh H, Worthington HV. Interventions for replacing missing teeth: different times for loading dental implants. Cochrane Database Syst Rev 2013:CD003878. Accessed March 28, 2013.
31. Kern JS, Kern T, Wolfart S, Heussen N. A systematic review and meta-analysis of removable and fixed implant-supported prostheses in edentulous jaws: post-loading implant loss. Clin Oral Implants Res 2016;27:174-95.
32. Engelhardt S, Papacosta P, Rathe F, Ozen J, Jansen JA, Junker R. Annual failure rates and marginal bone-level changes of immediate compared to conventional loading of dental implants. A systematic review of the literature and meta-analysis. Clin Oral Implants Res 2015;26:671-87.
33. Sanz-Sanchez I, Sanz-Martin I, uero E, Sanz M. Clinical efficacy of immediate implant loading protocols compared to conventional loading depending on the type of the restoration: a systematic review. Clin Oral Implants Res 2015;26:964-82.
34. Zhang S, Wang S, Song Y. Immediate loading for implant restoration compared with early or conventional loading: A meta-analysis. J Craniomaxillofac Surg 2017;45:793-803.
35. Chrcanovic BR, Albrektsson T, Wennerberg A. Immediately loaded non-submerged versus delayed loaded submerged dental implants: a meta-analysis. Int J Oral Maxillofac Surg 2015;44:493-506.
36. Suarez F, Chan HL, Monje A, Galindo-Moreno P, Wang HL. Effect of the timing of restoration on implant marginal bone loss: a systematic review. J Periodontol 2013;84:159-69.
37. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
38. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
39. Esposito M, Grusovin MG, Willings M, Coulthard P, Worthington HV. The effectiveness of immediate, early, and conventional loading of dental implants: a Cochrane systematic review of randomized controlled clinical trials. Int J Oral Maxillofac Implants 2007;22:893-904.
40. Weber HP, Morton D, Gallucci GO, Roccuzzo M, Cordaro L, Grutter L. Consensus statements and recommended clinical procedures regarding loading protocols. Int J Oral Maxillofac Implants 2009;24(Suppl):180-3.
41. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
42. Testori T, Galli F, Capelli M, Zuffetti F, Esposito M. Immediate nonocclusal versus early loading of dental implants in partially edentulous patients: 1-Year results from a multicenter, randomized controlled clinical trial. Int J Oral Maxillofac Implants 2007;22:815-22.
43. Capelli M, Esposito M, Zuffetti F, Galli F, Fabbro M, Testroi T. A 5-year report from a multicentre randomised clinical trial: immediate non-occlusal versus early loading of dental implants in partially edentulous patients. Eur J Oral Implantol 2010;3:209-19.
44. Donati M, Scala V, Raimondo R, Speroni S, Testi M, Berglundh T. Marginal bone preservation in single-tooth replacement: a 5-year prospective clinical multicenter study. Clin Implant Dent Relat Res 2015;17:425-34.
45. Donati M, Scala V, Billi M, Dino B, Torrisi P, Berglundh T. Immediate functional loading of implants in single tooth replacement: a prospective clinical multicenter study. Clin Oral Implants Res 2008;19:740-8.
46. Cannizzaro G, Felice P, Leone M, Ferri V, Viola P, Esposito M. Immediate versus early loading of 6.5 mm-long flapless-placed single implants: a 4-year after loading report of a split-mouth randomised controlled trial. Eur J Oral Implantol 2012;5:111-21.
47. Ganeles J, Zöllner A, Jackowski J, Ten Bruggenkate C, Beagle J, Guerra F. Immediate and early loading of Straumann implants with a chemically modified surface (SLActive) in the posterior mandible and maxilla: 1-Year results from a prospective multicenter study. Clin Oral Implants Res 2008;19:1119-28.
48. Zöllner A, Ganeles J, Korostoff J, Guerra F, Krafft T, Brägger U. Immediate and early non-occlusal loading of Straumann implants with a chemically modified surface (SLActive) in the posterior mandible and maxilla: Interim results from a prospective multicenter randomized-controlled study. Clin Oral Implants Res 2008;19:442-50.
49. Nicolau P, Korostoff J, Ganeles J, Jackowski J, Krafft T, Neves M, et al. Immediate and early loading of chemically modified implants in posterior jaws: 3-year results from a prospective randomized multicenter study. Clin Implant Dent Relat Res 2013;15:600-12.
50. Shibly O, Patel N, Albandar JM, Kutkut A. Bone regeneration around implants in periodontally compromised patients: a randomized clinical trial of the effect of immediate implant with immediate loading. J Periodontol 2010;81:1743-51.
51. Shibly O, Kutkut A, Patel N, Albandar JM. Immediate implants with immediate loading vs. conventional loading: 1-year randomized clinical trial. Clin Implant Dent Relat Res 2012;14:663-71.
52. Grandi T, Guazzi P, Samarani R, Tohme H, Khoury S, Sbricoli L, et al. Immediate, early (3 weeks) and conventional loading (4 months) of single implants: preliminary data at 1 year after loading from a pragmatic multicenter randomised controlled trial. Eur J Oral Implantol 2015;8:115-26.
53. Margossian P, Mariani P, Stephan G, Margerit J, Jorgensen C. Immediate loading of mandibular dental implants in partially edentulous patients: a prospective randomized comparative study. Int J Periodontics Restorative Dent 2012;32:e51-8.
54. Alfadda SA. A randomized controlled clinical trial of edentulous patients treated with immediately loaded implant-supported mandibular fixed prostheses. Clin Implant Dent Relat Res 2014;16:806-16.
55. Cannizzaro G, Torchio C, Leone M, Esposito M. Immediate versus early loading of flapless-placed implants supporting maxillary full-arch prostheses: a randomised controlled clinical trial. Eur J Oral Implantol 2008;1:127-39.
56. Den Hartog L, Raghoebar GM, Stellingsma K, Vissink A, Meijer HJA. Immediate non-occlusal loading of single implants in the aesthetic zone: A randomized clinical trial. J Clin Periodontol 2011;38:186-94.
57. Göthberg C, André U, Gröndahl K, Ljungquist B, Thomsen P, Slotte C. Immediately loaded implants with or without abutments supporting fixed partial dentures: 1-year results from a prospective, randomized, clinical trial. Clin Implant Dent Relat Res 2014;16:487-500.
58. Güncü GN, Tözüm TF, Güncü MB, Yamalik N, Tümer C. A 12-month evaluation of nitrite oxide metabolism around immediate and conventionally loaded dental implants. Implant Dent 2009;18:27-37.
59. Velde T, Sennerby L, Bruyn H. The clinical and radiographic outcome of implants placed in the posterior maxilla with a guided flapless approach and immediately restored with a provisional rehabilitation: a randomized clinical trial. Clin Oral Implants Res 2010;21:1223-33.
60. Esposito M, Ardebili Y, Worthington HV. Interventions for replacing missing teeth: different types of dental implants. Cochrane Database Syst Rev 2014:CD003815. Accessed July 22, 2014.
61. Oh TJ, Shotwell JL, Billy EJ, Wang HL. Effect of flapless implant surgery on soft tissue profile: a randomized controlled clinical trial. J Periodontol 2006;77:874-82.
62. Hall JAG, Payne AGT, Purton DG, Torr B. A randomized controlled clinical trial of conventional and immediately loaded tapered implants with screw-retained crowns. Int J Prosthodont 2006;19:17-9.
63. Hall JAG, Payne AGT, Purton DG, Torr B, Duncan WJ, De Silva RK. Immediately restored, single-tapered implants in the anterior maxilla: Prosthodontic and aesthetic outcomes after 1 year. Clin Implant Dent Relat Res 2007;9:34-45.
64. Güncü MB, Aslan Y, Tümer C, Güncü GN, Uysal S. In-patient comparison of immediate and conventional loaded implants in mandibular molar sites within 12 months. Clin Oral Implants Res 2008;19:335-41.
65. Rouck T, Collys K, Wyn I, Cosyn J. Instant provisionalization of immediate single-tooth implants is essential to optimize esthetic treatment outcome. Clin Oral Implants Res 2009;20:566-70.
66. Mombelli A, van Oosten MA, Schurch E Jr, Land NP. The microbiota associated with successful or failing osseointegrated titanium implants. Oral Microbiol Immunol 1987;2:145-51.
67. Loe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand 1963;21:533-51.

68. Nowicki D, Vogel RI, Melcer S, Deasy MJ. The gingival bleeding time index. J Periodontol 1981;52:260-2.
69. Muhlemann HR, Son S. Gingival sulcus bleeding–a leading symptom in initial gingivitis. Helv Odontol Acta 1971;15:107-13.
70. Jemt T. Regeneration of gingival papillae after single-implant treatment. Int J Periodontics Restorative Dent 1997;17:326-33.
71. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
72. Testori T, Bianchi F, Fabbro M, Szmukler-Moncler S, Francetti L, Weinstein R. Immediate non-occlusal loading vs. early loading in partially edentulous patients. Pract Proced Aesthet Dent 2003;15:787-94; quiz 96.
73. Zembic A, Glauser R, Khraisat A, Hammerle CH. Immediate vs. early loading of dental implants: 3-year results of a randomized controlled clinical trial. Clin Oral Implants Res 2010;21:481-9.
74. Zuffetti F, Esposito M, Galli F, Capelli M, Grandi G, Testori T. A 10-year report from a multicentre randomised controlled trial: immediate non-occlusal versus early loading of dental implants in partially edentulous patients. Eur J Oral Implantol 2016;9:219-30.
75. Furhauser R, Florescu D, Benesch T, Haas R, Mailath G, Watzek G. Evaluation of soft tissue around single-tooth implant crowns: the pink esthetic score. Clin Oral Implants Res 2005;16:639-44.
76. O'Leary TJ, Drake RB, Naylor JE. The plaque control record. J Periodontol 1972;43:38.
77. Javed F, Romanos GE. The role of primary stability for successful immediate loading of dental implants. A literature review. J Dent 2010;38:612-20.
78. Roberts WE, Smith RK, Zilberman Y, Mozsary PG, Smith RS. Osseous adaptation to continuous loading of rigid endosseous implants. Am J Orthod 1984;86:95-111.
79. Aparicio C, Rangert B, Sennerby L. Immediate/early loading of dental implants: a report from the Sociedad Espanola de Implantes World Congress consensus meeting in Barcelona, Spain, 2002. Clin Implant Dent Relat Res 2003;5:57-60.
80. Benic GI, Mir-Mari J, Hammerle CH. Loading protocols for single-implant crowns: a systematic review and meta-analysis. Int J Oral Maxillofac Implants 2014;29 Suppl:222-38.
81. Moraschini V, Porto Barboza E. Immediate versus conventional loaded single implants in the posterior mandible: a meta-analysis of randomized controlled trials. Int J Oral Maxillofac Surg 2016;45:85-92.
82. Schrott A, Riggi-Heiniger M, Maruo K, Gallucci GO. Implant loading protocols for partially edentulous patients with extended edentulous sites–a systematic review and meta-analysis. Int J Oral Maxillofac Implants 2014;29 Suppl:239-55.
83. Chrcanovic BR, Albrektsson T, Wennerberg A. Immediate nonfunctional versus immediate functional loading and dental implant failure rates: a systematic review and meta-analysis. J Dent 2014;42:1052-9.
84. Schwarz F, Sanz-Martin I, Kern JS, Taylor T, Schaer A, Wolfart S, et al. Loading protocols and implant supported restorations proposed for the rehabilitation of partially and fully edentulous jaws. Camlog Foundation Consensus Report. Clin Oral Implants Res 2016;27:988-92.
85. Chow J, Hui E, Liu J, Li D, Wat P, Li W, et al. The Hong Kong Bridge Protocol. Immediate loading of mandibular Branemark fixtures using a fixed provisional prosthesis: preliminary results. Clin Implant Dent Relat Res 2001;3:166-74.
86. Chung S, McCullagh A, Irinakis T. Immediate loading in the maxillary arch: evidence-based guidelines to improve success rates: a review. J Oral Implantol 2011;37:610-21.
87. Collaert B, De Bruyn H. Immediate functional loading of TiOblast dental implants in full-arch edentulous maxillae: a 3-year prospective study. Clin Oral Implants Res 2008;19:1254-60.
88. De Bruyn H, Christiaens V, Doornewaard R, Jacobsson M, Cosyn J, Jacquet W, et al. Implant surface roughness and patient factors on long-term peri-implant bone loss. Periodontol 2000 2017;73:218-27.
89. Schincaglia GP, Rubin S, Thacker S, Dhingra A, Trombelli L, Ioannidou E. Marginal bone response Around immediate- and delayed-loading implants supporting a LOCATOR-retained mandibular overdenture: a randomized controlled study. Int J Oral Maxillofac Implants 2016;31:448-58.
90. Al-Nawas B, Krummenauer F, Buchter A, Kleinheinz J, Neukam F, Petrin G, et al. Multicenter randomized clinical trial: early loading of implants in maxillary bone. Clin Implant Dent Relat Res 2013;15:625-36.
91. Greenstein G, Cavallaro J. Implant insertion torque: its role in achieving primary stability of restorable dental implants. Compend Contin Educ Dent 2017;38:88-95; quiz 6.
92. Douglas de Oliveira DW, Lages FS, Lanza LA, Gomes AM, Queiroz TP, Costa Fde O. Dental implants with immediate loading using insertion torque of 30 Ncm: a systematic review. Implant Dent 2016;25:675-83.
93. Schincaglia GP, Marzola R, Giovanni GF, Chiara CS, Scotti R. Replacement of mandibular molars with single-unit restorations supported by wide-body implants: immediate versus delayed loading. A randomized controlled study. Int J Oral Maxillofac Implants 2008;23:474-80.
94. Shibli JA, Piattelli A, Iezzi G, Cardoso LA, Onuma T, de Carvalho PS, et al. Effect of smoking on early bone healing around oxidized surfaces: a prospective, controlled study in human jaws. J Periodontol 2010;81:575-83.
95. Atieh MA, Alsabeeha N, Duncan WJ. Stability of tapered and parallel-walled dental implants: A systematic review and meta-analysis. Clin Implant Dent Relat Res 2018;20:634-45.
96. Tettamanti L, Andrisani C, Bassi MA, Vinci R, Silvestre-Rangil J, Tagliabue A. Immediate loading implants: review of the critical aspects. Oral Implantol (Rome) 2017;10:129-39.
97. Morton D, Pollini A. Evolution of loading protocols in implant dentistry for partially dentate arches. Periodontol 2000 2017;73:152-77.
98. Pigozzo MN, Rebelo da Costa T, Sesma N, Lagana DC. Immediate versus early loading of single dental implants: A systematic review and meta-analysis. J Prosthet Dent 2018;120:25-34.
99. Xu L, Wang X, Zhang Q, Yang W, Zhu W, Zhao K. Immediate versus early loading of flapless placed dental implants: a systematic review. J Prosthet Dent 2014;112:760-9.
100. Atieh MA, Alsabeeha NH, Payne AG. Can resonance frequency analysis predict failure risk of immediately loaded implants? Int J Prosthodont 2012;25:326-39.
101. Borg E, Grondahl K, Persson LG, Grondahl HG. Marginal bone level around implants assessed in digital and film radiographs: in vivo study in the dog. Clin Implant Dent Relat Res 2000;2:10-7.
102. Shin YK, Han CH, Heo SJ, Kim S, Chun HJ. Radiographic evaluation of marginal bone level around implants with different neck designs after 1 year. Int J Oral Maxillofac Implants 2006;21:789-94.
103. Prosper L, Crespi R, Valenti E, Capparé P, Gherlone E. Five-year follow-up of wide-diameter implants placed in fresh molar extraction sockets in the mandible: immediate versus delayed loading. Int J Oral Maxillofac Implants 2010;25:607-12.
104. Cesaretti G, Botticelli D, Renzi A, Rossi M, Rossi R, Lang NP. Radiographic evaluation of immediately loaded implants supporting 2-3 units fixed bridges in the posterior maxilla: a 3-year follow-up prospective randomized controlled multicenter clinical study. Clin Oral Implants Res 2016;27:399-405.

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