



# Impact of immediately loaded implant-supported maxillary full-arch dental prostheses: a systematic review

## Abstract

Ahlam ABDUNABI<sup>1</sup>  
Martin MORRIS<sup>2</sup>   
Samer Abi NADER<sup>3</sup>  
Raphael F. de SOUZA<sup>1</sup> 

The immediate loading of implant-assisted fixed prostheses in edentulous maxillae may achieve favorable success rates with reduced treatment time. An evidence summary of clinical trials is key to recommend loading protocols in these cases. Objectives: To compare immediately loaded, fully implant-supported complete dentures to early and conventional/delayed loading in the edentulous maxillae of adult patients by a systematic review of controlled clinical trials (CCT). Methodology: CCTs reports were identified up to January 17, 2019 from Cochrane Oral Health Group's Trial register, Cochrane Central Register of controlled trials (CENTRAL), MEDLINE (Ovid), BIOSIS, EMBASE, CINAHL, Web of Science, and DARE. Two independent reviewers screened titles/abstracts and confirmed inclusion using full texts. Data were extracted and quality assessed (Cochrane Risk of Bias tool) independently and in duplicate. Study heterogeneity prevented pooling by meta-analysis. Results: Out of 1,052 candidate studies, four CCTs were included. Two trials had patient satisfaction as an outcome: (1) A randomized trial compared immediately and early loaded fixed dentures and found more satisfaction with the first after 12 months; (2) A non-randomized study found better satisfaction with immediate fixed dentures compared to conventional loading after 3 months (no more at 12 months). Regarding implant success and prosthetic complications, three trials did not report significant differences comparing immediate loading to other protocols. Conclusions: This review found weak evidence of differences between immediate load and other loading regimens, regarding patient satisfaction and maintenance events/adversities. The potential of immediate loading for favorable results in edentulous maxillae reinforces the need for well-designed RCTs, for solid clinical guidelines. Registration number: CRD42018071316 (PROSPERO database).

**Keywords:** Complete denture. Dental implant loading. Dental implantation. Health-related quality of life. Treatment outcome.

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Corresponding address:  
Raphael F. de Souza  
McGill University - Faculty of Dentistry -  
2001 McGill College Avenue - Suite 534 - Montréal -  
Québec - Canada - H3A 1G1.  
Phone: +1-514-398-4777 - Fax: +1-514-398-7220.  
e-mail: [raphael.desouza@mcgill.ca](mailto:raphael.desouza@mcgill.ca)

<sup>1</sup>McGill University, Faculty of Dentistry, Oral Health and Society, Montreal, Canada.

<sup>2</sup>McGill University, Schulich Library, Montreal, Canada.

<sup>3</sup>McGill University, Faculty of Dentistry, Restorative Dentistry, Montreal, Canada.



## Introduction

Edentulism poses a major impact on oral and general health, and on quality of life. Edentulous individuals have higher risk of systemic diseases, as pinpointed by the increased mortality rate among the edentulous elderly.<sup>1,2</sup> Impaired mastication represents a major consequence of edentulism. Even with good-quality complete dentures, masticatory performance is from 1/5 to 30% of dentate patients.<sup>3,4</sup> Besides mastication, conventional denture wearing represents a major psychological and social burden for some patients.<sup>5</sup>

Implant-assisted prostheses can tackle most of the limitations of conventional dentures, regardless of being fixed or removable. Fixed complete prostheses lead to better patient satisfaction in many cases compared to removable alternatives. This is the case when ease of hygiene is not a patient-perceived priority, which is common amongst middle-aged patients.<sup>6</sup> Primary indications for fixed prostheses include patients who cannot endure removable dentures or the feeling of being edentulous, strong gag reflex, and history of recurrent sore spots caused by dentures.<sup>7</sup> Patients with previous negative denture experience tend to perceive implant-supported fixed prostheses as their own natural teeth, leading to good self-esteem, physical and social well-being.<sup>5</sup>

Despite the focus given to the lower arch,<sup>8</sup> many edentulous patients request conversion of their maxillary dentures to implant-assisted ones. The maxillary arch poses specific challenges, including low-density bone<sup>9</sup> and limiting sinus anatomy.<sup>10</sup> Furthermore, fixed prostheses are a more intuitive choice for edentulous maxillae, given that patient satisfaction does not seem to improve much with maxillary overdentures.<sup>11</sup>

The possibility of immediate load after implant insertion can expedite an otherwise time-consuming treatment, i.e. maxillary fixed dentures. Studies have demonstrated high success rates for immediately loaded fixed prostheses in edentulous maxillae, with conventional or zygomatic implants.<sup>10,12</sup> Immediate prostheses may be more satisfying for patients than those fabricated by traditional protocols.<sup>13,14</sup>

In 2013, a systematic review of randomized clinical trials (RCT) on immediately loaded implants showed no evidence of different success rates when compared to other loading protocols.<sup>15</sup> This review, despite its high

quality, did not approach patient-reported outcomes (PRO) (e.g. satisfaction and oral health-related quality of life). Actually, PRO can be considered the main success indicator for prosthodontics.<sup>16</sup> Understanding how patients respond to different loading protocols in the edentulous maxilla is essential for developing clinical guidelines. However, there are no systematic reviews considering PROs to understand the effect of these protocols, which would be of primary relevance for clinical recommendations.<sup>17</sup>

Therefore, we present a systematic review of controlled clinical trials (CCT) comparing immediate versus early/delayed loading on implant-supported maxillary complete dentures, in terms of PROs and maintenance events/complications. This review was based on the following PICO question: in maxillary edentulous adults (P), is immediate loading (I) more effective than other loading protocols for full implant-supported prostheses (C) from the patient's perspective (O)? To reach a broad range of studies, we expanded this question to any treatment modality with complete implant support (i.e. fixed or removable).

## Methodology

This review was reported according to the PRISMA guidelines (checklist available on Appendix 1).<sup>18</sup> A protocol version was published at the PROSPERO database (ID: CRD42018071316).<sup>19</sup>

### Eligibility criteria

Included studies should comply with the following criteria, grouped by design, participants, interventions, comparators and outcomes:

**Study design:** experimental studies in humans comparing immediate loading to a control group (other loading protocols). The allocation of participants to one of the groups could be random (i.e. RCT) or not (non-randomized CCT). Other designs (e.g. observational studies, one-arm trials) were not eligible.

**Participants:** Adult patients with edentulous maxillae seeking implant-supported complete dentures.

**Interventions:** Immediate-loaded, fully implant-supported complete dentures (IL): denture delivery until the 7<sup>th</sup> day following implant insertion,<sup>20</sup> regardless of being the final or interim restoration. Dentures should be fixed or removable; in the latter

case, they should receive complete support from implants. Eligible removable protocols include milled bars or telescopic attachment, given that the mucosa does not provide retention, stability or support.

**Comparators:** Similar to the intervention, but with later delivery of a maxillary denture. Comparators were divided into (1) Early Loading (EL): loading between a week and two months after implant insertion; and (2) Conventional Loading (CL, also dubbed delayed loading): loading after more than two months after implant insertion.

**Outcome measures:** Primary outcomes: general patient satisfaction with prostheses and oral health-related quality of life (OHRQoL), the most common PRO of studies on prosthodontics.<sup>16</sup> Patient satisfaction could be graded by specific questions answered on categorical or quantitative scales; OHRQoL should be tested by validated questionnaires, including: Oral Health Impact Profile (OHIP), Oral Impacts on Daily Performance (OIDP), Geriatric Oral Health Assessment (GOHAI), and Dental Impact on Daily Living (DIDL), as well as their abbreviated versions.

**Secondary outcomes:** (1) Specific patient satisfaction items, such as ease in chewing, swallowing, satisfaction with esthetics, and ease of hygiene; (2) Clinician-assessed implant-related parameters: implant success rate, marginal bone level, occurrence of mucositis and peri-implantitis, bleeding on probing (BOP), plaque index and probing depth. (3) Clinician-assessed performance of prostheses: success and survival rates, functional parameters like masticatory performance, technical complications like occlusal wear, screw loosening or fractured prosthetic components.

Due to the short-term response linked to IL and expected longevity of implant-assisted prostheses, we did not consider a particular timespan. We sought to discuss results for primary outcomes based on short-term results whenever possible, i.e. within the first three months after loading.

## Search Methods

MM, a librarian trained in systematic review searching, conducted an electronic search in MEDLINE (Ovid), PubMed, EMBASE (Ovid), BIOSIS (Ovid), Cochrane Oral Health Group's Trial register; Cochrane CENTRAL and DARE databases (the Cochrane Library 2019, issue 1), CINAHL; and Web of Science. Searches were performed on July 14, 2016, and update searches

were performed on May 22, 2018 and January 17, 2019; results were limited to researches from 1999 onwards, due to the effective introduction of IL in the 1990s. Appendix 2 shows the search strategy used for MEDLINE via Ovid, which was adapted for each database. Given the search yield, we did not apply any filter or outcome-specific term. We also screened the list of references of included studies and reviews on immediate loading. The search was restricted to articles in English.

Two authors (AA and RFS) scanned the titles and abstracts of all reports identified through the electronic searches independently. A 3<sup>rd</sup> reviewer (SAN) was contacted as required to resolve disagreements. The same authors examined full-text versions of possible inclusions independently.

## Data extraction and quality assessment

Included studies underwent data extraction and quality assessment by the same authors. We extracted data from trials based on the following characteristics:

(1) Study design: time until follow-up, sample size, study setting, sampling criteria, recruitment methods, randomization methods, randomized number, drop-outs, withdrawals and losses;

(2) Participant: age, gender, general health status (including diabetes mellitus), clinical characteristics (history of periodontitis, maxillary bone volume and density), smoking, drinking habits, other recreational drugs, occlusion during healing phase, previous experience with removable dentures, and attendance to follow-up visits;

(3) Intervention and comparators: implants (system, number, type, design, length, positioning, and insertion torque), interim prosthetic design and loading time (if applicable), and definitive prosthetic design and loading time;

(4) Outcomes: Assessment method and instrument, baseline and post-treatment scores, as well as time of data collection.

We assessed the quality of included trials by using the Cochrane Risk of Bias tool.<sup>21,22</sup> This classifies studies based on six potential sources of bias: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding (performance bias and detection bias), (4) incomplete outcome data (attrition bias), and (5) selective reporting (reporting bias), as well as (6) other sources. Each potential source was classified as low, unclear or

high. Moreover, the tool allows an overall classification of study risk of bias, i.e. any high-risk source renders the study as high risk of bias, whereas low-risk studies have all sources classified as such. Studies with any unclear source but no high-risk source were classified as moderate risk of bias.

### Summary measures and statistical analysis

Most patient satisfaction and OHRQoL-related variables are continuous, and thus could be described according to their mean differences and 95% confidence interval (95%CI). Those included items answered on visual analogue scales (VAS) and summed results from Likert/ordinal scales. Similar strategies were used for other quantitative outcomes, including bone level changes. Dichotomous variables (e.g., frequency of prosthesis fracture, or occlusal wear: Yes/No) were described according to risk ratios (RR) with 95%CI. Whenever there were some issue regarding the unit of analysis for dichotomous variables (two or more event counts for the same participant), data was shown as cumulative incidence only. Inferences based on a 95%CI correspond to the

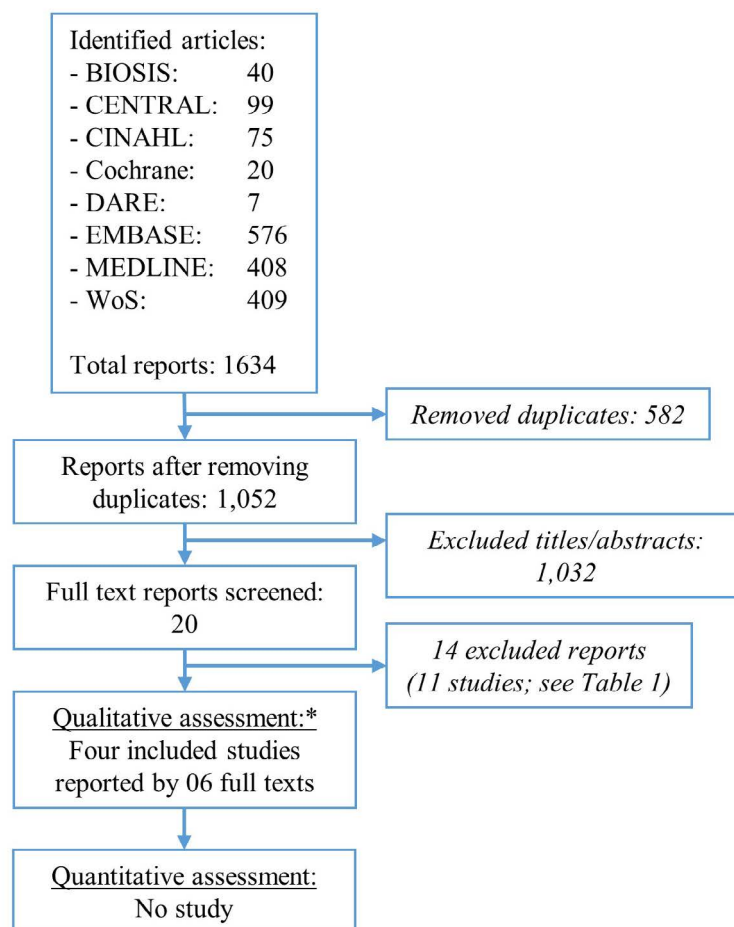
adoption of a level of significance ( $\alpha$ ) of 0.05. The RevMan 5.3 software was used for plotting quality assessment and effect measures.

If two or more trials reporting the same comparison and outcome were found, we would assess their heterogeneity. In turn, we would synthesize data by meta-analysis if applicable, giving priority to random effect models. We also planned to assess publication bias using a funnel plot, if there were sufficient studies. Please refer to our review protocol for details on planned statistical methods.<sup>23</sup>

## Results

### Search results

Figure 1 summarizes the search yield and study selection. We identified 1,052 reports by the electronic searches (duplicates excluded). Reading of titles and abstracts led to the exclusion of 98.1%, and to further appraisal of 20 full-text versions (1.9%). In turn, we included four trials reported by six manuscripts (two



**Figure 1** - Flow diagram of study selection. No study was located from other sources, including the references of screened full text reports and reviews. \*Qualitative appraisal of the body of studies (without quantitative synthesis/meta-analysis)

trials had their results published in two manuscripts each). Two of such trials provided data on patient satisfaction with received prostheses (primary outcome), whereas none assessed OHRQoL.

Eleven studies were excluded (Appendix 3).<sup>24-37</sup> Reasons included ineligible study designs (five studies) and ineligible comparator groups (five studies). A study dealt with partial edentulism, an RCT had a mixed sample with partial and complete edentulism (both arches), and another evaluated a non-eligible intervention.

**Characteristics of included studies**

The two trials evaluating patient satisfaction assessed 59 participants, with a single loss (Table 1).<sup>13,14,38</sup> Both applied nearly similar inclusion and exclusion criteria on the initial samples of 30 participants/each: edentulous maxillary arches with existing opposing occlusion, not needing augmentation procedures. Lower arches had natural teeth (complete dentition or combined with dental prostheses) or implant-assisted prosthesis. The RCT by Cannizzaro, et al.<sup>38</sup> (2008) recruited patients at an Italian private clinic from 2004 to 2005 to compare IL to EL. Follow-up extended to 12 months.<sup>38</sup> The non-randomized CCT by Peñarrocha-Oltra, et al.<sup>13,14</sup> (2013, 2014) compared IL to CL.<sup>13,14</sup> Researchers enrolled participants at a

Spanish university clinic from 2008 to 2010, treated according to patient preferences. Both studies provided provisional acrylic maxillary fixed dentures immediately after implant insertion for IL. Provisional dentures were replaced by porcelain-fused-to metal (PFM) or metal-resin bridges after nearly 3 months.

The other two included studies restricted their outcome assessment to clinical variables, and compared IL to CL. Both were conducted at university clinics and included further 64 participants (1 lost participant/arm). A non-randomized CCT in Italy compared IL on 4 to 6 implants to CL on 6 to 9 implants (loading time; IL: ≤24 h; CL: ~9 mo.).<sup>39,40</sup> Recruitment happened between September 2005 and January 2006. Participants in the IL arm wore a transitional screw-retained acrylic fixed denture with a cast metal framework and without cantilevers during 4.5 months, followed by the definitive prostheses. Both arms received similar acrylic screw-retained definitive prostheses with one-tooth long cantilevers and cast metal frameworks. An RCT in Belgium also compared IL to CL (24 h versus 3 months) on a non-variable number of six implants (surgery between February 2010 and December 2013).<sup>41</sup> Both groups received detachable acrylic prostheses with cast metal frameworks, completely supported, stabilized and retained by SynCone telescopic abutments.

**Table 1-** Summary of the included study characteristics

Study ID	Cannizzaro, et al. <sup>38</sup> (2008)	Peñarrocha-Oltra, et al. <sup>13,14</sup> (2013, 2014)	Tealdo, et al. <sup>39,40</sup> (2011, 2014)	Vercruyssen, et al. <sup>41</sup> (2016)
<b>Sample size, n participants</b>	Initial : 30. IL: 15 (90 implants); EL: 15 (87 implants)	Initial: 30. IL: 15 (94 implants). CL: 15 (99 implants). IL: 1 loss	Initial: 49. IL: 34 (163 implants). CL: 15 (97 implants). 1 loss/group	Initial: 15. IL: 7 (42 implants). CL: 8 (48 implants).
<b>Outcome variable and instrument</b>	(1) Overall patient satisfaction on 5-point Likert scale  (2) Frequency, clinical complications: damaged prostheses, peri-implant adversities, lost implants, mucosal lesions	(1) Overall patient satisfaction (100-mm VAS)  (2) Patient appraisal of aesthetics, chewing, speech, comfort, self-esteem and hygiene (100-mm VAS)	(1) prosthodontic survival  (3) marginal bone level (4) prosthetic complications	Short-term implant failure rate
<b>Data collection timeline</b>	Up to 12 months. Patient satisfaction collected at 12-mo. (no baseline data)	Baseline, 3-mo. ,and 12-mo. follow-up	Baseline, 1-, 2-, 3-, and 6-y follow-up	Up to 3 months
<b>Implants: n, insertion torque</b>	n (patients): 5 (IL: 5, EL: 7); 6 (IL: 6, EL : 5); 7 (IL: 3, EL: 2) ; 8(1/arm). Torque >48 Ncm	n: 6-8 per patient. Torque >35 Ncm	n IL, mean: 4.6; range: 4 to 8. N CL: mean: 6.5 range: 6 to 9. Torque ≥40 Ncm	6 per patient. No data on torque
<b>Implant system</b>	Tapered Swiss Plus (Zimmer Dental, Carlsbad, CA, USA); diameter: 3.7 to 4.8 mm; length: 10, 12 and 14 mm	Kohno SP (Sweden & Martina SpA, Padova, Italy)	Osseotite and Osseotite NT (Biomet 3i); diameter: 4 mm	Ankylos (Dentsply Implants, Molndal, Sweden); diameter: 3.5 or 4.5 mm; length: 9.5 to 14 mm

None of the four trials used grafting or other ridge augmentation procedures before implant insertion. Participants in CL or EL wore conventional complete dentures relined with soft materials before insertion of definitive prostheses.

### Methodological quality of the trials

All the four trials showed some potential source of bias classified as “high risk”. Figure 2 summarizes the quality assessment of the four included trials. Appendix 4 details the methodological quality assessment of individual trials.

Sequence generation was adequate for Canizzaro, et al.<sup>38</sup> (2008) and Vercruyssen, et al.<sup>41</sup> (2016), whereas only the first was explicit regarding the use of allocation concealment. The other CCTs [Peñarocha-Oltra, et al.<sup>13,14</sup> (2013, 2014) and Tealdo, et al.<sup>39,40</sup> (2011, 2014)] were preference trials; therefore, they were classified at high risk for selection bias-related criteria.

All trials had high risk for performance bias as a limitation — patients cannot be treated blindly, and no

study described any approach to prepare prostheses in a way that could mitigate this source of bias. Two trials performed a blind outcome assessment,<sup>13,14,38</sup> whereas other two study reports provided no data on blinding for eligible outcomes.<sup>39-41</sup>

Incomplete outcome data was a minor concern for the four trials. Two trials reported a comprehensive series of outcomes in a way that consistently leads to “low risk” classification for selective reporting.<sup>13,14,38</sup> There was no study protocol for any of the studies, thus selective reporting was unclear for the other two trials.<sup>39-41</sup>

Finally, other potential sources of bias included between-group imbalances regarding: (1) the final prosthesis provided by one of the studies, i.e. Toronto-type acrylic prostheses, IL: 4 (27%); EL: 9 (60%) participants;<sup>38</sup> and (2) number of implants, i.e. IL received less implants/maxillary denture than the CL group.<sup>39,40</sup> One of the preference trials is very unlikely affected by other biases,<sup>13,14</sup> and we could not determine whether sponsorship would influence results of an RCT.<sup>41</sup>

	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)	Other bias
Canizzaro, et al. (2008)	+	+	-	+	+	+	-
Peñarocha-Oltra, et al. (2013-2014)	-	-	-	+	+	+	+
Tealdo, et al. (2011-2014)	-	-	-	?	+	?	-
Vercruyssen, et al. (2015)	+	?	-	?	+	?	?

**Figure 2-** Risk of bias summary for included studies: evaluations on risk of bias concerning each potential source and type of bias. A + signifies that the corresponding approach to minimize bias was probably done (adequately described) for a given study, whereas a - discloses an evident limitation in controlling bias. A question mark underscores that the study provides insufficient description for judging a given approach as adequate or not



Effect of interventions

Table 2 summarizes the main findings of the four included trials, according to each outcome.

Primary outcomes

IL versus EL: Cannizzaro, et al.<sup>38</sup> (2008) performed a single assessment at the 12-month follow-up by asking whether patients were satisfied with overall treatment, indicated on a 5-point Likert scale. The RR of having participants more satisfied with IL after 12 months was 2.20 (95%CI: 1.01 to 4.79).

IL versus CL: Peñarrocha-Oltra, et al.<sup>13,14</sup> (2013,

2014) quantified overall patient satisfaction on a 100-mm VAS. The average value after 3 months was 35 mm higher for the IL arm (95%CI: 26 to 44 mm). Such difference recedes after 12-months follow-up (mean difference: 0; 95%CI: -6 to 6 mm).

Secondary outcomes

A single trial reported specific patient satisfaction items, by questions answered on a 100 mm-VAS.<sup>13,14</sup> At 3 months, mean differences between IL and CL for separate items were (in mm; positive values favor IL): esthetics: 20, 95%CI: 9 to 32; chewing: 48, 95%CI: 33 to 63; speech: 25, 95%CI: 12 to 38; comfort:

Table 2- Summary of outcome data from included studies (NR: not reported)

Study	Patient satisfaction	Implant failure and survival rate (SR)	Peri-implant bone level (mm)*	Maxillary Prostheses, SR	Prosthetic complications**
<b>IL versus EL:</b>					
Cannizzaro, et al. <sup>38</sup> (2008)	"Completely satisfied" answer, 12 mo. (n): - IL: 11 (73%) - EL: 5 (33%)	Failed Implants, 12 mo. (n/ total): - IL: 1/90, SR = 98.8% - EL: 3/87, SR = 96.5%	- Baseline, IL: 0.1(0.1); NR EL: 0.1 (0.1) - 12 mo., IL: 0.7 (0.2); EL: 0.8 (0.2)		IL, Total: 8  - Ulcers by provisional: 1  - Fractured provisional: 2 - Fractured final prosthesis: 1 - Masticatory/TMJ problem: 2 - Peri-implant complications: 2 EL, total: 5 - Fractured provisional: 2 - Masticatory/TMJ problem: 1 - Peri-implant complications: 1 - Esthetics: 1
<b>IL versus CL:</b>					
Peñarrocha-Oltra, et al. <sup>13,14</sup> (2013, 2014)	100-mm VAS, mean (SD) for IL and CL: - Baseline: 45 (18) and 48 (17) - 3 mo.: 85 (11) and 50 (13) - 12 mo.: 90 (7) and 90 (10)	Failed Implants, 12 mo. (n/ total): - IL: 3/94, SR = 96.8% - CL: 1/99, SR = 99.0%	Baseline, both groups: 0.2  -12 mo., IL: 0.6 (0.2); CL: 0.6 (0.3)	- 100% both arms (12 mo.)	- IL, Total: 8 (4 loose screws, 1 tooth fracture, 3 mucositis)  - CL, Total: 8 (3 mucositis; 5 ulcers)
Tealdo, et al. <sup>39,40</sup> (2011, 2014)	NR	Failed Implants, 12 mo. (n/ total): - IL: 10/163, SR = 93.9% - CL: 4/97, SR = 95.9%  No failed implant between 12 and 72 mo.	Baseline, both groups: 0.5 - 12 mo., IL: 1.3 (0.8); CL: 1.9 (0.8) - 24 mo., IL: 1.5 (0.9); CL: 2.2 (0.9)  - 36 mo., IL: 1.6 (0.9); CL: 2.3 (1.1) - 72 mo., IL: 1.6 (1.2); CL: 2.4 (1.4)	- 100% both arms (72 mo.)  - Success rate: IL: 82.4%, CL: 73.3% (72 mo.)	- IL, Total: 9 (4 minor fractures, 2 major fractures, 3 loose screws)  - CL, Total: 9 (3 minor fractures; 1 major fracture; 5 loose screws)
Vercruyssen, et al. <sup>41</sup> (2016)	NR	Failed Implants, 3 mo. (n/ total): - IL: 0/42, SR = 100% - DL: 1/48, SR = 97.9%	NR	NR	NR

\* Distance between most coronal portion implant-bone contact area and coronal margin of implant collar; \*\* At the longest follow-up period/ total n comprises prosthetic complications + others

53, 95%CI: 39 to 67; self-esteem: 33, 95%CI: 21 to 45; ease of cleaning: -6, 95%CI: -19 to 7; treatment duration: 40, 95%CI: 32 to 48. At 12 mo., mean differences were: esthetics: -9, 95%CI: -17 to -1; chewing: 1, 95%CI: -6 to 8; speech: 3, 95%CI: -4 to 10; comfort: -2, 95%CI: -8 to 4; self-esteem: 0, 95%CI: -7 to 7; ease of cleaning: -2, 95%CI: -12 to 8; treatment duration: 8, 95%CI: -5 to 21.

The total n of studied implants were: (IL) 299; (CL) 244; and (EL) 87. There was no evidence that implant survival was different with IL or other protocols. Data comparing IL to EL comes from a single trial<sup>38</sup> and observed a 1-year RR of 0.32 (95%CI: 0.03 to 3.04) with IL. A single study comparing IL to CL<sup>41</sup> observed a RR of 0.38 (95%CI: 0.02 to 9.08) up to 3 months, and two heterogeneous trials found similar RR after 12 months: 3.16 (95%CI: 0.33 to 29.84);<sup>13,14</sup> 1.49 (95%CI: 0.48 to 4.61).<sup>39,40</sup> The latter study observed no implant failure between 12 and 72 months.

Results show no evident difference regarding peri-implant bone level observed by radiographs comparing IL to EL and CL. Compared to EL, mean changes after 12 mo. were similar for IL:<sup>38</sup> – mean difference: 0.07 mm (95%CI: -0.10 to 0.24). Mean differences in bone level between IL and CL were very small at 12 months, ranging from 0.0 mm (95%CI: -0.18, 0.18)<sup>13,14</sup> to -0.60 mm (95%CI: -1.10, -0.10).<sup>39,40</sup> The latter difference was significant, and reached -0.80 mm after 72 months (95%CI: -1.64 to 0.04).

Finally, it seems that the IL groups had higher cumulative incidence of prosthetic complications compared to the other groups on the short term and one year-long term. Cumulative rates of mechanical failures for separate studies were: Peñarrocha-Oltra, et al.<sup>13,14</sup> (2013, 2014), IL: 62.5%; CL: 0%; Tealdo, et al.<sup>39,40</sup> (2011, 2014), IL: 50%; CL: 50%; Canizzaro, et al.<sup>38</sup> (2008), IL: 50%; EL: 25%. Most of those failures occurred with provisional prostheses in IL.

## Discussion

Despite the impact of IL for the management of edentulous maxillae, this review included a small number of CCTs. A recent growing interest in the literature on the subject is evident given the year of the oldest included report (i.e. 2008).<sup>38</sup> This contrasts with the wide proportion of observational studies on IL found in 2005,<sup>42</sup> thus suggesting a recent shift towards CCTs.

Comparisons between IL and comparators show that patients may be more satisfied when they receive a functional fixed denture, regardless of when. Evidence is minor, but IL was more satisfying than EL in a single RCT after 1 year.<sup>38</sup> However, that trial evaluated satisfaction as a secondary outcome and performed a simple assessment. An imbalance in the types of prostheses delivered to the two groups may also have contributed to post-treatment differences. Therefore, as tempting it is to suggest a long-term effect of IL on patient satisfaction, this finding should be interpreted carefully. A trial comparing IL to CL showed similar treatment effect after 3 months;<sup>13,14</sup> this is intuitive, given that participants still had relined conventional dentures in the CL group. Results for satisfaction are similar at 12 months though, suggesting that results may not differ at that point. Patients may get used with existing fixed dentures and provide similar responses after few months. In other words, patients may undergo a response shift and reach similar perception of received prostheses regardless of initial experiences.<sup>43</sup>

In general, findings suggest that IL is effective compared to EL and CL, although evidence is not enough for solid clinical recommendations. Clinician-reported outcomes show no evident difference in survival rates for implants and prostheses. Failures tend to be quite rare. Other complications show no difference, although a synthesis of the four trials was unviable. Bone loss was not different when IL was compared to other protocols. A trial observed a lower complication rate with IL compared to CL, possibly caused by different prosthetic configurations/n of implants rather than the loading protocol itself.

All studies provided treatment with standard dental implants, thus evidence from CCTs is absent for zygomatic implants. Their potential safety and effectiveness make them a very interesting subject for future trials, as found by observational studies.<sup>10,44,45</sup>

Trial participants represent average edentulous patients regarding age and gender, who can receive standard implants without ridge augmentation. No data can be extrapolated to patients with severely atrophied maxillae, who may need bone augmentation procedures (e.g. onlay bone grafts and sinus lifting) or zygomatic implants. Furthermore, most inclusions refer to IL versus CL, with a single trial with EL as a comparator.

Three out of the four included trials were conducted



at university clinics. This may not be a major issue given that specialists normally provide tested interventions. However, it is arguable whether results are exactly the same expect for routine patients without research involvement. For instance, potential participants may refrain to participate given potential concerns regarding randomization.<sup>32</sup> The inclusion of preference trials may mitigate such issues, by rendering study participants closer to real patients, with freedom to deliberate on which treatment they will receive.<sup>46,47</sup>

The paucity of studies makes any assumption regarding specific clinical conditions unclear. For example, one cannot infer whether different results are expected because of different occlusal schemes or antagonist arch. The same could not be done for certain adverse conditions that could contra-indicate IL, e.g. severe parafunction, smoking, and high risk of periodontal disease.<sup>48,49</sup>

In summary, all included studies could be classified as high risk of bias for varying reasons. Amongst design-related issues, the inclusion of preference trials deserves comments, given their important drawback: higher risk of selection bias.<sup>50</sup> Those trials cannot implement sequence generation methods able to minimize selection bias. Blinding also was a major limitation, given that blinding the participants and care providers is not possible for the tested comparisons. In general, studies were careful when reporting the numbers of non-adherent participants.

Given the long-lasting recommendation of trial registration and contemporaneity of included trials, the absence of published protocols was surprising. Trial registration has been a persisting recommendation of guidelines for trial protocols<sup>51</sup> and final reports.<sup>52</sup>

One of the main limitation of this review is the low number of included studies. A scarcity of RCTs was foreseeable and approached by widening eligibility criteria to preference trials and other non-randomized CCTs. However, even this approach resulted in a considerably low number of trials. Summed to the finding of only two trials reporting our primary outcomes, this review is further limited to the non-comparability of different questionnaires for patient satisfaction. Studies were also underpowered (modest sample sizes) for categorical outcomes. Major clinical heterogeneity also proscribes meta-analysis and thus contributes to the power-related issue. Our search strategy attempted to approach a wide series of potential sources for better sensitivity. Although we

were initially limited to reports written in English, our search did not found non-English studies. Thus, language cannot be considered as a limitation of this review.

This systematic review innovates by its patient-centered focus, which is uncommon in other reviews. However, it is notable that previous reviews found akin results for clinician/disease-centered outcomes. Esposito, et al.<sup>15</sup> (2013) found similar survival and success rates for different loading methods. That review only considered clinical performance, and missed four of our six included reports given its last update timing.<sup>15</sup> Finally, we extended the eligibility criteria to include preference trials, different from that review. Further three recent systematic reviews on IL's clinical outcomes<sup>53-55</sup> found a single CCT.<sup>38</sup> Other reviews did not find CCTs comparing immediately loaded zygomatic implants to other loading protocols on similar fixtures either.<sup>56,57</sup>

Future trials are fundamental to compare IL to other loading approaches in the edentulous maxilla, and should consider zygomatic fixtures. Given that many patients can cope well with maxillary conventional dentures, and that the cost/complexity of IL may be quite high, recruitment in such trials can be quite slow. Multicenter RCTs can overcome those issues and timely reach a good sample size. Such tentative trial(s) should use standardized tools for outcome assessment at several recall visits —baseline up to at least 12 months, but focusing on short-term follow-up. Focus on patient-reported outcomes is imperative, given their fundamental role for clinical guidelines/recommendations.<sup>17</sup> The use of reporting guidelines (e.g. SPIRIT and CONSORT) will lead to more transparent and comprehensive research methods, as well as trial registration in public databases (e.g. clinicaltrials.gov).

## Conclusions

This review found modest evidence on the comparative performance of IL versus other loading regimens (CL and EL) for providing fully implant-supported maxillary dental prostheses. A limited number of trials suggest that patient satisfaction may be at least as good with IL, and show no major discrepancies regarding clinical complications.

The selection of IL instead of CL or EL must rest on

solid practitioner's skills to provide such treatment and patient preferences. Evidence supports effective use of IL for fixed full prostheses on standard implants, given that no augmentation method is used. Patients seem at least as satisfied with IL, and clinical complications may be comparable. Comparative evidence on cases with unfavorable clinical features remains scant.

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## Appendix 1 - PRISMA checklist



## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1,2
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2,4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	App. Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8,9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8,9, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10, Fig 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12, Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, App. Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16,17
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

**Appendix 2-** Systematic review search strategy in Medline (Ovid), composed by terms representing our interventions of interest, eligible participants (population), and comparators. MeSH terms and free text words were combined for the search using Boolean operators

Search date: 17/01/2019 Note: CL was not included because it is anticipated to be the common comparator.	
Intervention and Comparison	1. exp Dental Implants/ 2. exp Dental Implantation/ 3. exp Dental Prosthesis, Implant-Supported/ 4. ((osseintegrat* adj3 implant\$) and (dental* or oral*)).ti,ab,kf. 5. (((overdenture* or crown* or bridge* or prosthes?s or restoration*) adj5 (dental* or oral*)) and implant*).ti,ab,kf. 6. "implant supported dental prosthesis".ti,ab,kf. 7. ("blade implant*" and (dental* or oral*)).ti,ab,kf. 8. ((endosseous adj5 implant*) and (dental* or oral*)).ti,ab,kf. 9. ((dent* or oral* or zygomatic or axial or tilted) adj5 implant*).ti,ab,kf. 10. or/1-9 11. ((early or immediate*) adj3 (loaded or loading or restoration or rehabilitat*)).ti,ab,kf.
Population	12. exp Maxilla/ 13. maxilla*.ti,ab,kf. 14. ((zygomatic or alveolar or palatine) adj process*).ti,ab,kf. 15. or/12-14 16. exp Mandible/ 17. (mandible* or mandibular*).ti,ab,kf. 18. Jaw, Edentulous/ 19. (edentulous* or edentate or edentulism).ti,ab,kf. 20. 18 or 19
Outcomes	Not included
Filters	None
Final search	21. 10 and 11 and 15 and 20 22. 11 and 15 and 20

**Appendix 3-** Excluded studies after full-text assessment and reasons

Study	Reason
Agnini, et al. <sup>24</sup> (2014)	No comparator group
Aires and Berger <sup>25</sup> (2002)	Not a clinical trial
Alves, et al. <sup>26</sup> (2010)	Not a clinical trial
Aparicio, et al. <sup>27</sup> (2010)	No comparator group
Busenlechner, et al. <sup>28,29</sup> (2016)	Not a clinical trial
Babbush, et al. <sup>30</sup> (2013)	Not a clinical trial, no comparator group
Calandriello and Tomatis <sup>31</sup> (2005)	No comparator group
Esposito, et al. <sup>32</sup> (2016); Mitsias, et al. <sup>33</sup> (2018)	Participants cannot be considered
Esposito, et al. <sup>34</sup> (2018)	Comparator cannot be considered
Nordin, et al. <sup>35,36</sup> (2004, 2007)	Not a clinical trial, intervention cannot be considered
Zhou, et al. <sup>37</sup> (2009)	Participants cannot be considered



**Appendix 4-** Detailed risk of bias assessment according to the Cochrane Risk of Bias tool. Author's judgement refers to the classification scale for risk of bias (low/unclear/high); Support for judgment will contain a critical appraisal leading to each closed-ended answer, including quotes that led to judgement

<b>STUDY ID: Canizzaro, et al.<sup>38</sup> (2008) [IL compared to EL]</b>		
<b>Source of Bias</b>	<b>Judgment</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low	Quote: "A computer generated restricted randomization list was used to create two groups with equal numbers of patients by one of the authors, who was not involved in patient recruitment or treatment and had access to the randomization list stored in a password-protected portable computer"
Allocation concealment (selection bias)	Low	Quote: "After all implants were inserted..., the envelope containing the randomization code was opened and the operator knew whether the patient would have the implants immediately loaded or loaded after 2 months" Quote: "The randomized codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially only after all the implants were inserted, therefore treatment allocation was concealed to the investigator in charge of enrolling and treating the patients included in the trial."
Blinding of participants and personnel (performance bias)	High	N/A for participants and personnel.
Blinding of outcome assessment (detection bias)	Low	Quote: "Independent dentists who were not aware of patient allocation evaluated implant stability, including ISQ values ... and marginal bone levels changes..." Quote: "A biostatistician... analyzed the data, without knowing the group allocation."
Incomplete outcome data (attrition bias)	Low	No dropout or loss to follow-up, all participants were included in the statistical analysis.
Selective reporting (reporting bias)	Low	A comprehensive set of clinical outcomes was reported, as well as patient satisfaction -- unlikely selective reporting.
Other bias	High	Type of prosthetic treatment is imbalanced in the two groups, with possible influence on patient satisfaction: Toronto-type acrylic prostheses, IL: 4 (27%); EL: 9 (60%); other participants received PFM (less provided needed for the upper lip, i.e. better ridge anatomy). Recruitment happened in clinical practice (probably as part of routine care), unlikely conflict of interest. Quote: "Patients were recruited and treated in one Italian private practice" and "No commercial support of any form has been received by the investigators".
<b>STUDY ID: Peñarrocha-Oltra, et al.<sup>13,14</sup> (2013, 2014) [IL compared to CL]</b>		
<b>Source of Bias</b>	<b>Judgment</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High	Non-randomized sequence Quote: "A clinical prospective controlled nonrandomized study was performed at the Oral Surgery Unit".
Allocation concealment (selection bias)	High	Open allocation sequence Quote: "15 consecutive patients fulfilling the selection criteria were treated following a conventional loading protocol (control group) until July 2009... The next 15 consecutive patients fulfilling the inclusion criteria were, therefore, treated with this protocol (test group)."
Blinding of participants and personnel (performance bias)	High	N/A for participants and personnel.
Blinding of outcome assessment (detection bias)	Low	Blind outcome assessor Quote: "All data were collected by a single trained clinician (DP), who was not the surgeon or the prosthodontist, following a pre-established protocol."
Incomplete outcome data (attrition bias)	Low	One drop-out (test group); reason unlikely to be related to intervention. Some unloaded implants in both groups, with similar numbers and reasons and no change in assigned intervention. Quote: "One patient belonging to the test group failed to attend the scheduled recall visits because of personal reasons and was excluded from the study." "Sixteen implants—nine in the test group and seven in the control group, all of which were placed in molar regions—did not achieve the minimum insertion torque of 35 Ncm and were excluded from analysis, left submerged, and loaded conventionally."
Selective reporting (reporting bias)	Low	Most implant and prosthetic success criteria were reported, including adverse events.
Other bias	Low	Unlikely bias from other sources.
<b>STUDY ID: Vercruyssen, et al.<sup>41</sup> (2016) (IL compared to CL)</b>		
<b>Source of Bias</b>	<b>Judgment</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low	Possibly done, but no explanation of method. Quote: "For the allocation, a computerized random number generator was used."
Allocation concealment (selection bias)	Unclear	No detail on how the random numbers were applied (e.g. an open list or generated immediately before each intervention).
Blinding of participants and personnel (performance bias)	High	N/A for participants and personnel.

Continued on the next page



Continued from previous page

Blinding of outcome assessment (detection bias)	Unclear	No specific information regarding outcome of interest.
Incomplete outcome data (attrition bias)	Low	Quote: "one implant from the delayed treatment group was lost before prosthesis installment due to non-integration."
Selective reporting (reporting bias)	Unclear	Specific set of clinician-reported outcomes and short-term patient-reported outcome assessment (pain/discomfort and general health-related quality of life). No data on key outcomes used in oral implantology.
Other bias	Unclear	Oral implants were delivered free of charge by DENTSPLY Implants (Molndal, Sweden). Stereolithographic guides were delivered free of charge by the Materialise Dental Company (Leuven, Belgium).
<b>STUDY ID: Tealdo, et al.<sup>39,40</sup> (2011, 2014) (IL compared to CL)</b>		
<b>Source of Bias</b>	<b>Judgment</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High	Participants were allocated according to their preferences to one of the interventions.
Allocation concealment (selection bias)	High	Open allocation. Quote: "The patients in the test group were selected for treatment with the immediate loading protocol because of both their expectations and demand for immediate, fixed implant prostheses; they sought to avoid the use of a transitional complete denture. On the other hand, the patients in the control group were willing to accept wearing a complete denture for a short time interval, and this cohort was composed of older patients relative to the test group."
Blinding of participants and personnel (performance bias)	High	N/A for participants and personnel.
Blinding of outcome assessment (detection bias)	Unclear	No blinding mentioned. Quote: "Subjects were seen by a dental hygienist every 4 months for the first year. At each follow-up visit, prostheses were removed and implants and abutments were evaluated individually for tenderness, swelling, and mobility."
Incomplete outcome data (attrition bias)	Low	Low number of dropouts (n=1/group), but reasons are unclear. Few losses due to reasons unlikely associated with protocol. Quote: "At the 6-year follow-up, 2 patients had dropped out. One patient with 4 implants in the test group died, and 1 patient in the control group with 7 implants relocated."
Selective reporting (reporting bias)	Unclear	Study focuses on implants' clinical performance, and do not report relevant patient-reported outcomes.
Other bias	High	Different number of implants may confound the effect of immediate versus delayed loading.