IMPACT OF IMMEDIATELY LOADED IMPLANT-SUPPORTED MAXILLARY DENTAL PROSTHESES:

A SYSTEMATIC REVIEW

By

Ahlam Abdunabi
Faculty of Dentistry
Department of Prosthodontics
McGill University, Montreal
June 2018

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of M.Sc. in Dental Science.

TABLE OF CONTENTS

ABSTRACT

Background: The immediate loading of implant-assisted fixed prostheses in edentulous maxillae may achieve favorable success rates with reduced treatment time. Summarizing the evidence from clinical trials is key for recommending loading protocols for those cases.

Objectives: To compare immediately loaded implants (within 1 week) to early (between 1 week and 2 months) and delayed loaded (after two months) implants supporting full fixed maxillary prostheses.

Methods: We identified reports of CCTs up to May 22, 2018 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. We extracted data and assessed the methodological quality independently and in duplicate, using the Cochrane Risk of Bias assessment tool. Meta-analysis was not possible because of the heterogeneity among the included trials.

Results: Out of 889 candidate studies, four CCTs were included in the review. Four clinical trials met the inclusion criteria. Two trials had patient satisfaction as an outcome: (i) One randomized controlled trial (RCT) concluded that patient's satisfaction was higher in the immediate loading than the early loading group at one year; (ii) One non-randomized trial found higher satisfaction with immediate compared to conventional loading at 3 months, however, this difference no longer exists at the one year follow up. In regard to implant success and prosthesis complications, three included trials did not report significant differences comparing immediate loading to early or conventional protocols.

Conclusions: Based on the review results, there is weak evidence to determine whether immediate loading could provide better patients reported outcomes and be more efficient than other loading protocols. However, due to the potential favorable results of immediate loading for in treating edentulous cases, more well-designed clinical trials are strongly needed.

RÉSUMÉ

Contexte : La mise en charge immédiate (MCI) des prothèses fixes sur implants aux maxillaires totalement édentés peut obtenir un taux de succès élevé avec une réduction importante du temps de traitement. Un résumé des données provenues d'essais cliniques est essentiel pour recommander la mise en charge immédiate à ces cas.

Objectifs : Comparer les prothèses fixes complètes sur implants mis en charge immédiatement aux maxillaires totalement édentés de patients adultes, auxquelles chargées précocement ou traditionnellement, par milieu d'une revue systématique d'essais cliniques contrôlés (ECC).

Méthodes : Nous avons identifié rapports d'ECC jusqu'à 22 Mai 2018 à partir de : Cochrane Oral Health Group's Trial register, Cochrane Central Register of controlled trials (CENTRAL), MEDLINE (Ovid), BIOSIS, EMBASE, CINAHL, Web of Science, et DARE. Deux auteurs indépendants ont criblé les titres/résumés et confirmé l'inclusion après la lecture complète des articles pertinents. Nous avons extrait les données et évalué la qualité des ECC (outil d'évaluation du risque de biais Cochrane) de façon indépendante par deux auteurs. L'hétérogénéité des études a empêché leur combinaison par méta-analyse.

Résultats : Parmi 889 études potentielles, quatre ECC ont été inclus à cette revue. Deux essais avaient la satisfaction des patients comme critère de jugement : (i) un essai randomisé contrôlé (ERC) a comparé la MCI et la mise en charge précoce, et a trouvé plus de satisfaction avec la MCI après 1 an ; (ii) un ECC non-randomisé a trouvé que la MCI était plus satisfaisant avec la MCI que mise en charge traditionnelle aux 3 mois de suivi (mais non plus aux 12 mois). Les quatre études inclues ne fournissent pas de donnée probante qui soutient une éventuelle différence entre la MCI et les autres protocoles concernant les effets collatéraux et taux de succès des implants.

Conclusions : Cette revue a trouvé un faible niveau de preuve pour la différence entre la MCI et autres protocoles de mise en charge, à propos de la satisfaction des patients et entretien/évènements adverses. Le potentiel de la MCI pour résultats favorables sur les maxillaires totalement édentés renforce le besoin de ERCs bien conçus, pour s'obtenir recommandations cliniques solides.

ACKNOWLEDGMENTS

This research work would have been impossible without the help of several people to whom I am deeply grateful.

I would like to sincerely thank my supervisor Dr. Raphael de Souza whose expertise in Knowledge synthesis has a main role within every stage for the present thesis project, as well as my co-supervisor Dr. Samer Abi Nader for their expert advice as prosthodontists and the continuous encouragement throughout my thesis process. Many thanks to the librarian Mr. Martin Morris for his assistance in the creation of search strategies. Many thanks to Dr. Kristian Filion and Dr. Elham Emami for their detailed feedback on the protocol and the first review manuscript.

I am grateful for discussing core ideas and the support prior to my committee meetings/thesis submission from Balqees Almufleh, Entisar Abdulkader, Amina Abomriga, Tulio Nogueira, and Lojain Bassyoni.

My great appreciation to the Libyan Ministry of Health and Higher Education for providing me a master's scholarship and the funding for my thesis project. Appreciation is also extended to the Canadian Bureau for International Education for administering my scholarship throughout my stay in Canada. My appreciation to the McGill's department of graduate studies and the Network for Oral and Bone Health Research (RSBO, Réseau de recherche en santé buccodentaire et osseuse), for their excellence and poster awards.

Finally, I am most grateful to my parents, my sisters, my brothers and my beloved husband for their endless and unconditional support to pursue my studies,

Ahlam

CONTRIBUTION OF AUTHORS TO THE MANUSCRIPT

Ahlam Abdunabi: Master's candidate: conceived the study objective, prepared review protocol (1st draft), performed data collection and analysis, and wrote the thesis.

Martin Morris: Liaison Librarian, Schulich Library, McGill University, Montreal (QC), Canada: Prepared and conducted search strategies and reviewed the manuscript.

Samer Abi Nader: Associate professor, Division of Restorative Dentistry, Faculty of Dentistry, McGill University, Montreal (QC), Canada: Supervised the preparation of review protocol, participated as the third reviewer in data collection and bias assessment and reviewed the manuscript.

Raphael F de Souza: Associate professor, Division of Oral Health and Society, Faculty of Dentistry, McGill University, Montreal (QC), Canada: made major edits in the review protocol, performed data collection and analysis, modified the thesis and prepared the publication version (journal article).

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

95%CI	95% confidence interval
AA	Ahlam Abdunabi (reviewer)
BOP	bleeding on probing
CCT	controlled clinical trials
CENTRAL	Cochrane Central Register of controlled trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CL	conventional loading (also dubbed delayed loading)
CONSORT	Consolidated Standards of Reporting Trials
DARE	Database of Abstracts of Reviews of Effects
EL	early loading
EMBASE	Excerpta Medica dataBASE
FP	fixed prosthesis
IL	immediate loading
ITI	International Team for Implantology
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
MM	Martin Morris (reviewer)
OHRQoL	oral health-related quality of life
PFM	porcelain fused to metal
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols
PRO	patient-reported outcome
PROM	patient reported outcomes measure
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomized controlled trial
RFS	Raphael Freitas de Souza (reviewer)
RR	risk ratio
SAN	Samer Abi Nader (reviewer)
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SR	survival rate
VAS	visual analogue scale

1. INTRODUCTION

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

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, as common amongst middle-aged patients (6). 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 (7). 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 (5).

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

The possibility of loading implants immediately after their 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 (10, 12). Immediate prostheses may be more satisfying for patients than those fabricated by traditional protocols (13, 14).

In 2013, a systematic review of randomized clinical trials (RCT) on immediately loaded implants showed no evidence of different success rates, compared to other loading protocols (15). 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 (16). Understanding how patients respond to different loading protocols in the edentulous maxilla is of utmost importance for developing clinical guidelines. However, there is no systematic review considering PROs to understand the effect of those protocols, which would be of primary relevance for clinical recommendations (17).

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.

2. LITERATURE REVIEW

2.1. Definition of Systematic Reviews

Researchers, healthcare professionals and policy makers are overwhelmed with the amount of the published literature produced worldwide. This has led to the development of tools for knowledge synthesis, to keep those different stakeholders up-to-date in such an environment (18, 19). The main tools include different review types, e.g. narrative, scoping and systematic reviews, which strive to synthetize scientific literature according to distinct research objectives. According to Chalmers and Altman (19), a systematic review is "a review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section". Systematic reviews are meant to be as more objectively evaluative and specific than narrative reviews (20), and more specified and highly focused on a research question than scoping reviews (21). Consequently, it may provide better certainty to solve contradictions in cases where original research, reviews and editorial happened to be conflicting (18). Additionally, based on a proposed hierarchy of evidence evaluating healthcare interventions, well-prepared systematic reviews are recognized to be at the least risk of bias, providing the best evidence to guide clinical decision making (22). Even though some good systematic reviews may not yield conclusive evidence, they can identify important areas to be explored for further investigations and may also advice more accurate sample sizes where future research is needed (18).

Another advantage of systematic reviews, is the potential of summarizing the data collected from the included eligible studies into a quantitative analysis called meta-analysis. A meta-analysis improves the precision of estimates for treatment effects (18). However, it is imperative to consider the heterogeneity and biases among the included studies before

statistically pooling the results of studies estimates in order to avoid misleading systematic reviews and meta-analysis (23). To illustrate, the methodological quality of RCTs are not comparable to the methodological quality of observational studies; in turn, a meta-analysis of RCTs is not comparable to a meta-analysis of observational studies (18). A meta-analysis of RCTs should provide a very precise unbiased overall estimate of the treatment effect, while a meta-analysis of observational studies, is highly prone to be biased and confounded leading to unprecise overall estimate of treatment associations (18).

In recent years, the number of systematic reviews has obviously increased to eleven per day as cited by Bastian et al. 2010 (24). This increase intensified the need for guidelines to build a review on a well-described rationale and a hypothesis as well as a priori planned methods, and to improve complete reporting of the systematic review. For instance, both Cochrane Collaboration (25) and the Joanna Briggs Institute (26) provided detailed guidelines regarding the process of preparing and maintaining complete systematic review. One of the most recent reporting guidelines is the Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA Statement (27). In 2015, a PRISMA extension regarding the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols was published (PRISMA-P 2015) (28). It is a 17-item checklist intended to guide the report of a comprehensive protocol for the systematic review. The PRISMA guidelines serve for protocol appraisal, detecting modifying methods and selective outcome reporting, as well as improving the accuracy of completed reviews. Thus, endorsing the use of PRISMA-P2015 by all publishers, and editorials will maintain the quality of systematic reviews and meta-analysis.

2.2. Complete edentulism and its impact: Definition, epidemiology, and treatment overview

Edentulism leads to a series of problems, including impaired aesthetics and reduced ability to chew foods of different consistencies. From a broader perspective, complete tooth loss also results in poor oral health-related quality of life, due to physical and psychological discomfort, and ultimately social problems (29). Edentulous individuals often experience a disturbed self-image, are afraid of the aging process, and keep themselves isolated from the society. Anxiety/feeling insecure in public contexts is also quite common (30).

These patients require oral rehabilitation and will require some time to learn how to cope with their new prostheses (31). The decision for a specific treatment modality (e.g. different types of implant-assisted prostheses, or conventional dentures) will depend on a detailed clinical assessment matched by considering patient's perspectives and preferences (6, 7). The prescription of conventional complete dentures illustrates the complexity of decision-making for treating edentulism very well. Despite their use as the treatment of choice for many edentulous patients, conventional prostheses yield major limitations, including possible concerns regarding denture stability (3, 31). In turn, unstable dentures are a likely cause for lack of functional adaptation and social reclusion by edentulous patients (5). In order to mitigate such limitations, clinicians have employed a plethora of technical steps to improve the stability of mandibular and maxillary dentures, including impression methods and occlusal schemes (32-34). The better performance of those methods is often insufficient in some cases, including deficient alveolar bone, flabby supporting tissues or systemic diseases affecting the oral mucosa. This is even more severe when complete dentures are not sealed/seated properly, due to possible adversities, including the development of mucosal

pathological changes (e.g., cheek biting, traumatic ulcers, epulis fissuratum or denture stomatitis) (35).

Dental implants have been introduced as an effective way to enhance denture stability and have become part of the armamentarium of dentists worldwide. Implant-assisted prostheses can overcome some of the limitations of conventional dentures and thus accommodate patient expectations and needs (6, 11, 36). However, clinical expertise and judgment skills make a huge role in treatment planning and patient management. For example, the physiological, biological and functional consideration of a particular patient may lead to prefers a treatment modality over another (6, 7). Cases with impaired bone healing (e.g. high doses of radiation therapy in the orofacial region) will not be treatable by implant prosthetics (37). Patient's compliance to oral hygiene is another major determinant for decision-making; good oral hygiene renders the recommendation of more complex approaches more favorable, including fixed prostheses. Patients with prior maladaptive denture experience will also get more benefit from either implant-retained or -supported prosthesis (7). Finally, implant prosthodontics may be favorable for patients with systemic-related mucosal lesions – implants can avoid direct contact/friction between denture base and the mucosa, thus minimizing trauma (38).

2.3. Implant-assisted prostheses in the edentulous maxilla

2.3.1. Treatment planning for a successful implant assisted prosthesis

Proper patient selection mainly depends on the clinical and the medical examination to investigate for potential diseases affecting soft tissues or bone healing (39). Furthermore,

proper treatment planning must take into account patient expectations and preferences. Based on clinical examination and properly selected imaging method, the dental practitioner will evaluate tentative implant sites regarding bone volume and decide whether ridge augmentation is indicated. Due to the difference in bone density and resorption patterns between fully edentulous maxilla and mandible, treatment options tend to be different. The posterior maxilla is the less dense and short compared to the posterior mandible and is frequently affected by sinus pneumatization (40, 41). Likewise, anterior maxilla has lower bone density than the anterior mandible (41). In general, some reports state that implant survival and success rates are proportional to the amount of available bone and density at an implant location (42, 43).

In order to enhance implants success at low-density implant sites, the following approaches have been suggested:

- Positioning implants more axially (44).
- Shortening or eliminating cantilever extension (45).
- Splinting implants to promote a passive fit (45-47).
- Loading implants progressively (48).
- Narrowing occlusal tables to minimize the occlusal load (45, 49).

Recommendations for short alveolar ridges include: short textured dental implants, slightly angulated or tilted implants, and long "all-on-4" zygomatic implants (50).

In brief, the final prosthesis will be designed in compliance with the available bone substrate and a projected number of implants (43). Although less implants can be placed in edentulous mandibles (usually 4 between the mental foramens), more traditional implant schemes for

the maxillary ridge would involve 6 to 10 implants to compensate for the low bone density and unfavorable biomechanics (43). Based on the arch shape of the edentulous maxillae, 2 or 3 implants can be placed in premaxilla region. Conversely, fewer implants splinted together will promote passive fit of the prostheses, and thus distribute stress more evenly on implants and prosthetic framework (43).

2.3.2. Occlusal consideration for completely edentulous cases

Proper occlusion is vital to protect implants from overloading and deteriorating effects on peri-implant bone. Proper occlusal schemes in implantology tend to follow the same concepts used for conventional prosthodontics. For full arch fixed dentures, two occlusal schemes have been used: mutually protected, and bilateral balanced occlusion. Mutually protected occlusion is indicated when the opposing arch has natural teeth, while the bilateral balanced scheme is indicated when the opposing arch is restored by a removable denture. For cases with implant-retained overdenture, bilateral balance seems to be the most useful when the two arches are completely edentulous and achieve more axial implant loading (42, 49, 51). For cases with extreme maxillary bone resorption, either lingualized occlusion or posteriorly cross-bite have been proposed (52). A consensual aspect of those occlusal schemes refers to premature contacts/occlusal interferences, which may be especially deleterious with implant-assisted treatment modalities.

There are factors affecting the choice of occlusal scheme to achieve successful oral rehabilitation for completely edentulous cases. For example, in case the opposing dentition is either natural or mixed between natural and artificial teeth, the dentist will keep the occlusion free of functional loading and a removable prosthesis may be advised to patient with parafunctional habits. Moreover, prosthetic occlusion can be adjusted in a way that

keeps the vertical centric contacts/loading forces aligned with the long axis of the implant (49, 51, 53, 54).

Different occlusal schemes may be associated with other treatment planning approaches to mitigate overloading. Those approaches include adequate implant-prosthetic design (e.g., reduced cantilever, adequate crown/implant ratio, and different implant-abutment connection) and sufficient number, diameter, length and angulation of the implants. However, there is no scientific evidence to confirm the relative importance of those approaches (49, 51, 53).

2.3.3. Fixed full prosthesis – different designs

In 1989, Misch proposed five prosthetic options for implant prosthodontics. However, for the purpose of this review and due to different biomechanical consideration between fixed and removable prosthesis (55, 56), only studies considering the fixed prosthetic options will be considered: FP-1, FP-2, and FP-3. FP-1 refers to the fixed prosthesis that replaces crown structure; FP-2 replaces the crowns and a portion of the root; and FP-3 refers to the fixed prosthesis that replaces missing crowns and portion of alveolar process, simulating gingival architecture and color. It has been suggested that the most commonly successful implant distribution for fixed prostheses in the edentulous maxilla are: four to six splinted implants, or more than six segmentally splinted implants (43). Materials include porcelain fused to metal, zirconia and acrylic resin on a metallic framework. The latter is indicated in cases of large crown spaces because of the acrylic component advantage acting as intermediary substance between the metal and teeth. As a result, it is less prone to fracture during dynamic occlusal loading (57).

Implant-assisted prostheses can also follow different loading strategies. The 4th ITI Consensus Conference separate them into three major categories. (i) **Immediate loading** (Figure 1) represents the attachment of a prosthesis to dental implants within 1 week right after implant placement **(ii) Early loading** involves the attachment of prosthesis to dental implants after 1week and less than 2 months after the dental implant placement. With **(iii) conventional loading,** a prosthesis is attached to dental implants after a complete healing period of more than 2 months since implant placement (43). This classification can be used for a variety of cases, ranging from single crowns to full prostheses (58).

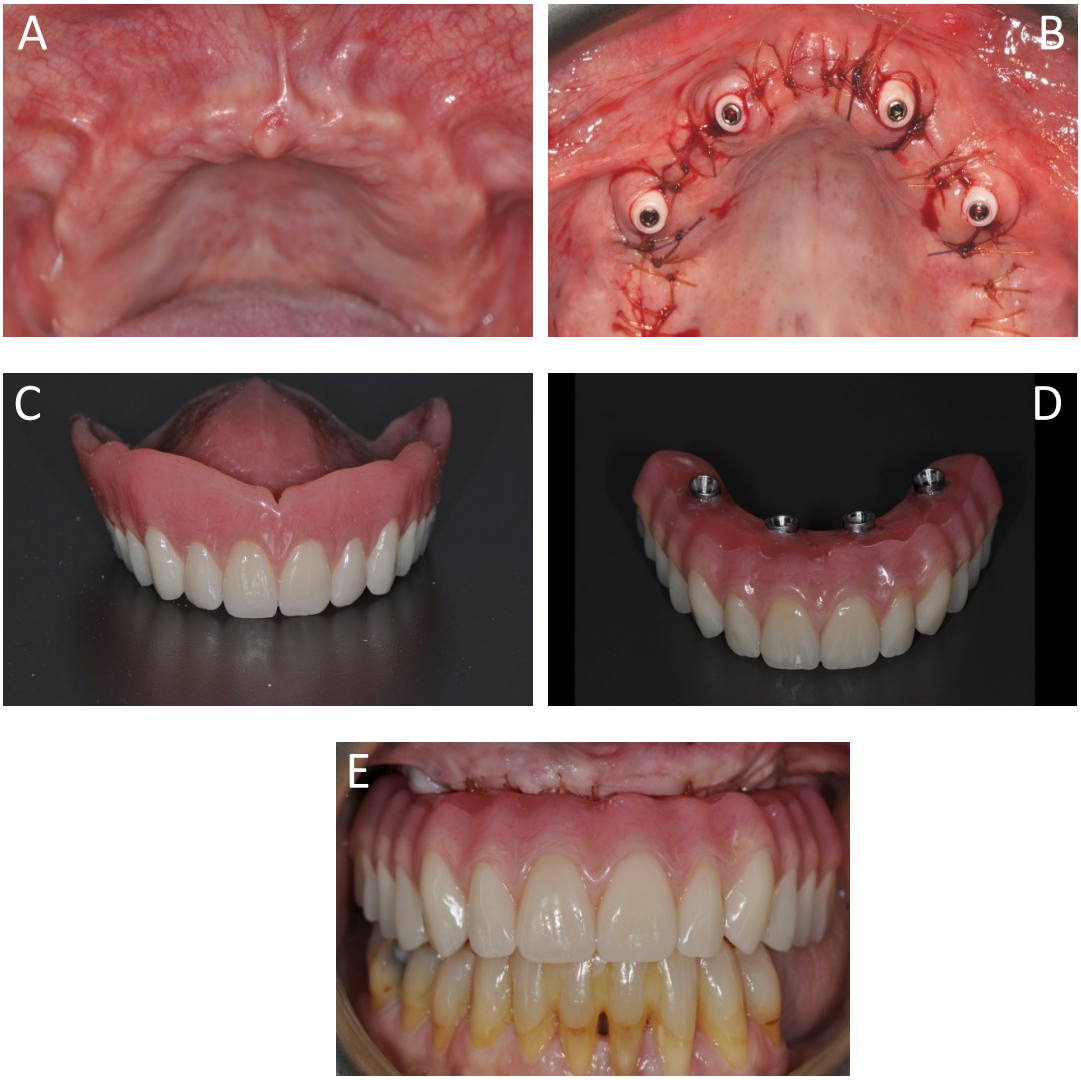

Figure 1: Representative clinical case of an immediately loaded full FP-3 in the maxillary arch, according to the all-on-4 concept (kindly provided by Dr. Samer Abi Nader and Dr. Nash Daniel, OMFS; Moncton, NB). (A) Fully edentulous maxilla; (B) four implants placed, immediate post-operative aspect; (C) existing maxillary complete denture; (D) maxillary denture converted to a provisional immediate fixed prosthesis; (E) delivered screw-retained immediate prosthesis.

It has been stated that immediate loading is contraindicated in cases with insufficient primary implant stability, implant placed simultaneously with bone augmentation, short implants, or implant or prosthetic protocols with at least six standard-size implants, in addition, proper inter-arch relationship is necessary (43).

2.3.4. Specific considerations on immediate loading

Osseointegration can be defined as the biological process of very close functional and structural adaptation of alloplastic implant in a living bone over a period of time (38). To achieve successful osseointegration, it is imperative to verify/maintain favorable patient criteria, biocompatible dental implants and adequate surgical technique (38, 43, 59, 60). Improper implant selection and traumatic surgical procedures can hamper the process and lead to failure. Once the implant is inserted, a period is required before bone healing is completed. Initial implant stability is exceedingly required upon implant insertion into the bone to enhance bone and soft tissue healing, if one opts for immediate loading (38, 43). Optimum implant insertion would be established and varies according to each particular implant design-macroscopic and microscopic implant characteristic. Minimum requirements for immediate loading on full fixed prostheses include an insertion torque of 30 Ncm and implant length of 10mm or more (43).

Initial implant stability allows for undisturbed cellular activity of bone modeling and remodeling healing process. This phenomenon has led to the hypothesis that immediate restoration of dental implants is viable as long as the initial implant stability is achieved (15, 47). Given this, the immediate loading process is highly dependent on favorable systemic and oral health condition, expertise of dental practitioners, and undisturbed bone healing using a rigid fixation of dental implants by prostheses. On some cases with atrophied

posterior alveolar bone, broad distribution of support to the underlying dental implants is not desirable. Therefore, Malo introduced “the all-on-4 concept” design whereby using slightly tipped longer implants (44).

According to another ITI consensus report (61), implant stability is understood as a lack of implant mobility immediately after replacement. Measurements of primary implant stability have included tactile sense, braking point, resonance frequency analysis, and insertion torque. At the early stage of implant osseointegration, and to keep implants stabilized, implant splinting is recommended to enhance passive fit of the dental prosthesis. Meanwhile regular follow up visits to check and maintain evenly distributed occlusion avoid occlusal overloading to the fixed prosthesis, which may lead to framework fracture and further implant failure (56).

2.4. Success criteria of the implant-supported dental prosthesis

The success criteria for dental implants have been originally based on the success of the osteointegration biological process and have separate survival and success since then. The criteria were firstly proposed by Albrektson et al. (1986), indicating that an implant is only considered successful if it is clinically stable; with no sign or symptoms of periimplantitis, pain, neuropathic injury, peri-implant radiolucency; and after the first year of loading the implant, marginal alveolar bone resorption is less than 0.2mm (62). Later on, implant success definition was revised in Pisa consensus statement (63), and the Implant Quality of Health Scale was developed by the international congress of implantologists. This scale is mainly based on the clinical evaluation of an endosseous implants using listed criteria: pain, mobility, radiographic crestal bone loss, probing depths, and peri-implant disease. The scale

classifies implants into three categories: implant success, implant survival, and implant failure. The term, implant success should include a time period of at least 1year for an implant used as a prosthodontic abutment, in addition implant survival rate will also include the linked prosthetic survival rate (63).

A systematic review found that the most frequently used criteria to assess the success criteria in implant dentistry are mostly implant related such as: implant mobility; pain; radiolucency and peri-implant bone loss (> 1.5 mm); bleeding, and probing pocket depth. It also found that the criteria used to assess success at the prosthetic level were related to the incidence of technical complications, proper functioning, and acceptable esthetics during the five-year period (64). It also found that the criteria reported to assess patient satisfaction were discomfort, satisfaction with appearance, and ability to function and chew. Research also found that most frequently criteria are mostly concerned with implant related outcomes and not considering the prosthesis implant complex as a whole nor the patient related outcomes (64).

Since then, many new technologies and concepts have been introduced to highlight new parameters of implant prosthodontic outcomes. These include prosthetics related outcomes which evaluate the whole functional efficacy of implant prosthodontics and tremendously correlates with the most important third parameter: patients centered outcomes (64-66).

2.5. Patient reported outcomes:

2.5.1. Definition and importance

There has been a recent trend and strong agreement among researchers and practitioners to include patient reported outcomes (PRO) to evaluate a treatment efficacy and impact on a patient life and his satisfaction (67, 68). A PRO means health or treatment related outcomes that is directly expressed by the patients about how they feel or function in relation to a health condition with no influence from the practioners, caregiver or a researcher (19). The tools used for gathering these outcomes "Patient reported outcomes measures" (PROMs) could be either self-administered questionnaires filled by patients or filled by practioners after interviewing the patients (69, 70). A well-designed questionnaire should be targeted either on one characteristic (unidimensional) or a group of characteristics (multidimensional), and for every characteristic there is one scale evaluating all of its aspects to be named as a construct (71, 72). A group of constructs collectively make an instrument which could be considered as a generic or condition targeted (73). Additionally, to better understand a treatment sustainability or a health condition from a patient perspective, it is important to include both short term and long-term evaluations (74). It is worth noting, that edentulism is also associated with Oral Health Related Quality of Life (OHRQoL) based on the span length and position of the tooth loss (75) for dentate patients. Another important point, an association between patient's satisfaction and patient expectations for an implant treatment have been reported (74) and this would emphasize clinicians' responsibility to provide realistic explanations to their patients prior to implant treatment. As implant dentistry tremendously get advanced, it is expected that patient attitude and expectations go higher (74). Therefore, PROs are very important area to evaluate the efficacy of implant prosthodontics and whether it met patient's expectations or not (74).

2.5.2 Improvements needed in future research

Generally, there are two groups of PRO assessments in dental research: patient satisfaction with their oral health status and OHRQoL measures. Patient satisfaction evaluates how a patient satisfied with the esthetics, function and his oral health status while OHRQoL measures evaluates the change happening on his day to day life impacted by his oral health status (76). Finding from a recent review concluded that there is a lack of standardization among the questioners used for patient-centered assessments, prohibits a meaningful comparison via a meta-analysis. For example, questioners of patient satisfaction vary in the number of the items explored ranging from three to 33 items and the rating systems, of which the most commonly rating system used the visual analogue scale (VAS). Another example, for OHRQoL measures, also variability exists from a subjective rating of pain to multiple item assessment involving scales for comfort, physical, social, and psychological effect of oral health status on OHRQoL. Of note, the timing and number of the assessment also varies considerably between studies and many have failed to provide baseline pre-treatment assessments (77). Nonetheless, it is supposed to be pre-treatment and post-treatment in order to provide prospective assessment minimizing the risk of recall bias (78). In brief, all PROMs assessment measures/instruments need to be standardized, validated and tested.

2.6. Why is this systematic review important?

In general, systematic reviews have overlooked patient-centred concerns and focused on the clinical performance of implants. In 2013, a Cochrane review examined the effects of different dental implants loading protocols (direct versus progressive; immediate versus early or conventional load; immediate/early occlusal versus non-occlusal loading) on the following

clinical outcomes: prosthetic failure, implant failure and level of peri-implant bone (79). It only found some evidence indicating a small reduction on bone loss favoring immediate loading, but the evidence was insufficient regarding other objectives. Furthermore, the authors asserted that the edentulous maxilla is often atrophied when implants are indicated, rendering bone augmentations or zygomatic implants necessary. In 2014, another systematic review compared different loading protocols, yet the results were inconclusive because of insufficient clinical studies (80). Furthermore, another systematic review published in 2015 studied the clinical efficacy of four zygomatic implants for the treatment of severely atrophied maxilla (81). It suggests that zygomatic implants have higher success rate than standard implants and may be used with immediate protocol, although no CCT compared different loading protocols for zygoma fixtures.

The disease-centered focus observed in the abovementioned systematic reviews leaves an important gap in knowledge. Patient-reported outcomes, including patient satisfaction and oral health-related quality of life, can be considered the main success indicators for almost all oral prosthetic interventions (16). Immediate loading is a very important tool in oral rehabilitation, given its potential to minimize treatment time without jeopardizing long-term success. Therefore, my review aims to evaluate whether immediate, early and delayed loading protocols are comparable in treating edentulous maxillary cases. This included different clinical indications such as atrophied maxillae with no augmentations procedures, and different prosthetic modifications able to promote the treatment success, prosthesis longevity and patient satisfaction. Given distinct treatment strategies as well patient-perceived and clinical needs, this review does not include partial prostheses (49, 51).

3. OBJECTIVE:

The main objective of the systematic review in the present thesis is to compare immediately loaded implants (within 1 week) to early (between 1 week and 2 months) and delayed loaded (after two months) implant-supported maxillary prostheses.

To guide the systematic review for the present thesis, the following main research questions were formulated:

1) In adult patients with fully edentulous maxillae seeking implant-supported maxillary prostheses, what is the impact of immediately loading prosthetic technique on patients reported outcomes compared to other loading techniques?

2) Does immediate loading influence implant-related outcomes and clinical performance of implant-supported maxillary prostheses in comparison to early or conventional loading techniques?

4. METHODS

This review was reported according to the PRISMA guidelines (checklist available on Appendix Figure 1) (27). A protocol version was published at the PROSPERO database (ID: CRD42018071316) (82).

4.1. Eligibility criteria

Included studies should comply with a series of criteria, grouped by design, participants, interventions, comparators and outcomes, as follows:

- ***Study design:*** We included experimental studies in human participants that compared immediate loading (experimental group) 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 fixed complete dentures.
- ***Interventions:*** Immediately-loaded implant-supported maxillary prostheses (IL): we considered loading as immediate when the prosthesis is delivered within the first week following implant placement (83), regardless of being the final or interim restoration.
- ***Comparators:*** Similar to the intervention, but with later delivery of implant-supported maxillary prostheses. Loading protocols were divided into (43) (i) Early Loading (EL): loading between a week and two months after implant insertion; and (ii) Conventional Loading (CL, also dubbed delayed loading): loading after more than two months after implants insertion, aiming at complete bone healing before function.

Given the similarities in treatment planning and indication for removable prostheses with complete support provided by implants, trials reporting on them were included. Eligible implant-support removable modalities included prostheses supported by milled bars or telescopic attachment, as long as the mucosa does not participate in retention, stability and support.

- Outcome measures:

Primary outcomes: these outcomes comprise the most common PRO of studies on prosthetic treatment of edentulism (16): general patient satisfaction with prostheses and oral health-related quality of life (OHRQoL). Patient satisfaction could be graded by specific questions answered on categorical or quantitative scales, and OHRQoL should be tested by validated questionnaires (e.g. OHIP, OIDP, GOHAI, DIDL, and its abbreviated versions).

Secondary outcomes: (i) Specific patient satisfaction items, such as ease of chewing, swallowing, satisfaction with esthetics, and ease of hygiene; (ii) 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 from a reference point. (iii) Clinician-assessed performance of prostheses: success and survival rates, functional parameters like masticatory performance, technical complications like occlusal wear, screw loosening or fracture of the 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. However, we sought to discuss observed results for primary outcomes based on short-term results whenever possible, i.e. within the first three months following functional loading.

4.2. Search Methods

One of the authors (MM), a librarian trained in systematic review searching, conducted an electronic search in the following databases: MEDLINE via Ovid, PubMed, EMBASE via Ovid, BIOSIS via Ovid, Cochrane Oral Health Group's Trial register; The Cochrane Collaboration's CENTRAL and DARE databases (the Cochrane library 2018, issue 5), CINAHL; and Web of Science. Searches were performed on July 14, 2016, and update searches were performed on May 22, 2018; results were limited from 1999 due to the effective introduction of immediate loading in the 90s. Appendix Table 1 presents the search strategy used for MEDLINE via Ovid, composed by terms representing our interventions of interest, eligible participants (population), and comparators. Given the search yield, we did not apply any filter or outcome-specific term. MeSH terms and free text words were combined for the search using Boolean operators, and the search was adapted for each database. We also screened the list of references of included studies and reviews on immediate loading. The search was restricted to English-language articles.

Two review authors (AA and RFS) scanned the titles and abstracts of all reports identified through the electronic searches independently. The third reviewer (SAN) was contacted as required to resolve disagreements. The same authors examined full-text versions of possible inclusions independently, without disagreement.

4.3. Data extraction and quality assessment

Included studies underwent data extraction and quality assessment by the same two reviewers, and the 3rd reviewer to resolve disagreements. The reviewers specially designed the data extraction forms for the review.

We extracted data from included trials based on the following groups of characteristics:

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

(ii) Participant: age, gender, general health status (diabetes mellitus), clinical characteristics (history of periodontitis, maxillary bone volume and density), smoking, occlusion pattern during healing phase, previous experience with removable denture, and attendance to follow-up visits;

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

(iv) Outcomes: Assessment method and type of 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 (25, 84). 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 risk of bias for the studies, i.e. any high-risk source renders the study as at high risk of bias, whereas low risk studies need to have all sources classified as such. Studies merging low risk and unclear sources are classified as at moderate risk of bias.

4.4. 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 will be 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 was some issue regarding the unit of analysis for dichotomous variables (two or more event counts for the same participant), data was presented as cumulative incidence only.

Data from included studies underwent narrative synthesis. If we had found two or more trials reporting same comparison and outcome, we would assess their heterogeneity. In turn, we would synthetize data by meta-analysis if applicable, giving priority to random effect models. We also planned to assess publication bias using a funnel plot, if we had sufficient studies (85). The RevMan 5.3 software was used for plotting quality assessment and effect measures.

5. RESULTS

5.1. Search results

Figure 2 summarizes the search yield and study selection. We identified 889 reports by the electronic searches (duplicates excluded). Reading of titles and abstracts led to the exclusion of 870 reports (97.9%) and further appraisal of 20 full-text versions (2.2%). In turn, we included four trials reported by six manuscripts. Two of such studies provided data on patient satisfaction with received prostheses (primary outcome), whereas three delved into implant and prosthetic maintenance events/complications (secondary outcomes).

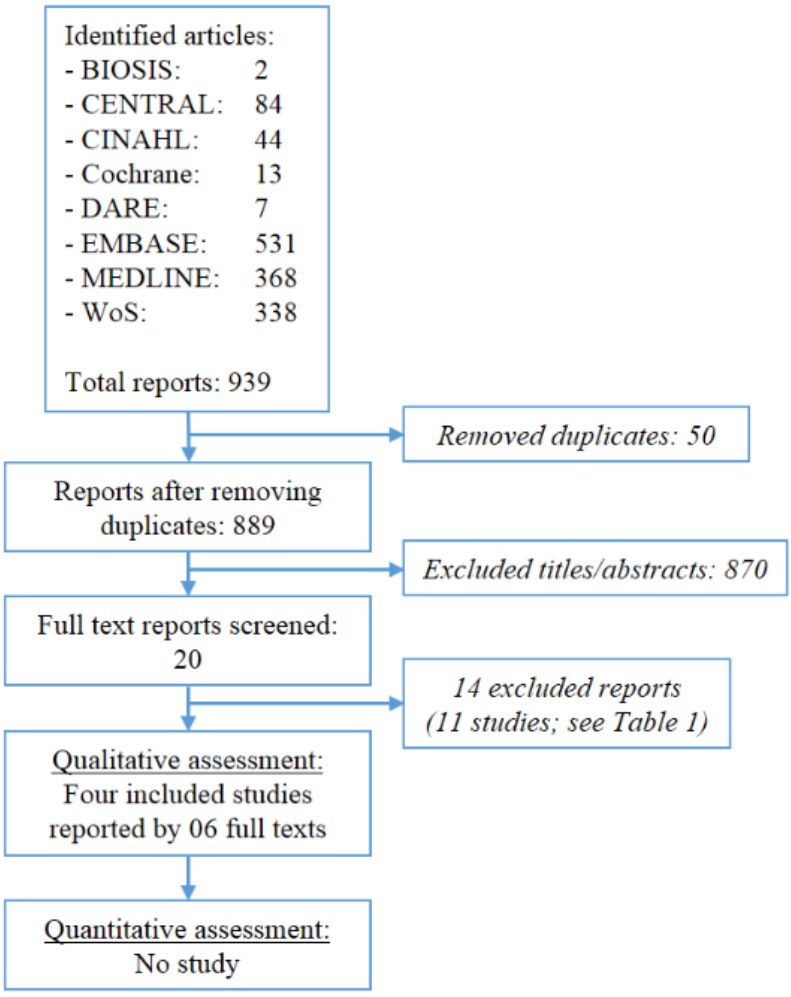

Figure 2: Flow diagram of study selection. No study was located from other sources.

Fourteen reports corresponding to 11 studies were excluded. Most frequent reasons involved study design (five studies were not clinical trials) and no eligible comparator group (five studies). One study dealt with partial edentulism (ineligible participants), an RCT had a mixed sample with partial and complete edentulism of both arches, and another evaluated a non-eligible intervention.

Table 1: Excluded studies after full-text assessment and reasons.

Study	**Reason**
Agnini et al. 2014 (86)	No comparator group
Aires and Berger 2002 (87)	Not a clinical trial
Alves et al. 2010 (88)	Not a clinical trial
Aparicio et al. 2010 (89)	No comparator group
Busenlechner et al. 2016 (90, 91)	Not a clinical trial
Babbush et al. 2013 (92)	Not a clinical trial, no comparator group
Calandriello and Tomatis 2005 (36)	No comparator group
Esposito et al. 2016 (93, 94)	Participants cannot be considered
Esposito et al. 2018 (95)	Comparator cannot be considered
Nordin et al. 2004, 2007 (96, 97)	Not a clinical trial, intervention cannot be considered
Zhou et al. 2009 (98)	Participants cannot be considered

5.2. Characteristics of included studies

The two trials evaluating patient satisfaction assessed 59 participants, with a single loss (Table 2) (13, 14, 99).

Both applied nearly similar inclusion and exclusion criteria on initial samples of 30 participants/each: volunteers with edentulous maxillary arches with existing opposing occlusion, not needing augmentation procedures. Mandibular arches possessed natural teeth

(complete dentition or combined with dental prostheses) or implant-assisted prosthesis. The RCT by Canizzaro et al. recruited patients at an Italian private clinic from 2004 to 2005 to compare IL to EL. Follow-up extended to 12 months (99). The non-randomized CCT Penarrocha-Oltra et al. compared IL to CL (13, 14). 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 approximately 3 months. In general, participants received at least five implants in the maxillae (mostly received between 6 and 8; no between-arm difference).

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 with 2 lost participants (1 in the IL arm). A non-randomized CCT conducted in Italy compared IL on 4 to 6 implants to CL on 6 to 9 implants (loading time; IL: ≤24 h; CL: ~9 mo.) (100, 101). 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 mo., 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 mo.) on a non-variable number of 6 implants (102). Participants underwent implant surgery between February 2010 and December 2013. Both groups received detachable acrylic prostheses with cast metal frameworks, completely supported, stabilized and retained by SynCone telescopic abutments.

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

Table 2: Summary of the included studies' characteristics.

Study ID	Canizzaro et al. 2008 (99)	Penarrocha-Oltra et al. 2013-2014 (13, 14)	Tealdo et al. 2011-2014 (100, 101)	Vercruyssen et al. 2015 (102)
Sample size, n participants	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).
Outcome variable and instrument	(i) Overall patient satisfaction on 5-point Likert scale (ii) Frequency, clinical complications: damaged prostheses, peri-implant adversities, lost implants, mucosal lesions	(i) Overall patient satisfaction (100-mm VAS) (ii) Patient appraisal of aesthetics, chewing, speech, comfort, self-esteem and hygiene (100-mm VAS)	(i) prosthodontic survival (ii) failed implants and survival (iii) marginal none level (iv) prosthetic complications	Short-term implant failure rate
Data collection timeline	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
Implants: n, insertion torque	n (patients): 5 (IL: 5, EL: 7); 6 (IL: 6, EL : 5); 7 (IL: 3, EL: 2) ; 8(1/arm). Torque > 48Ncm	n: 6-8 per patient. Torque > 35Ncm	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
Implant system	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

5.3. Methodological quality of the trials

All the four trials presented some potential source of bias classified as “high risk”. Figure 3 summarizes the quality assessment of the four included trials. Appendix Table 2 details the methodological quality assessment of individual trials.

Sequence generation was adequate for Canizzaro et al. (99) and Vercruyssen et al. (102), whereas only the first was explicit regarding the use of allocation concealment. The other CCTs (Penarocha-Oltra et al. (13, 14) and Tealdo et al. (100, 101)) 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, given that patients cannot be treated blindly as a limitation of the operative protocol. Moreover, no study describes any approach to prepare prostheses in a way that could mitigate such source of bias. Two trials strived to conduct blind outcome assessment (13, 14, 99), whereas reports of the other two studies provide no information on blinding for outcomes of interest (100, 101).

Incomplete outcome data was a minor concern for all inclusions, leading to a “low risk” classification. Two of the trials report a comprehensive series of outcomes in a way that consistently leads to “low risk” classification for selective reporting (13, 14, 99). We found no study protocol for any of the studies, thus selective reporting was unclear for the other two trials (100, 101).

Finally, other potential sources of bias included between-group imbalances regarding: (i) the final prosthesis provided by one of the studies, i.e. Toronto-type acrylic prostheses, IL: 4 (27%); EL: 9 (60%) participants (99); and (ii) number of implants, i.e. IL received less implants/maxillary denture than the CL group (100, 101). One of the preference trials is very

unlikely affected by other biases (13, 14), and we could not determine whether sponsorship would influence results of an RCT (102).

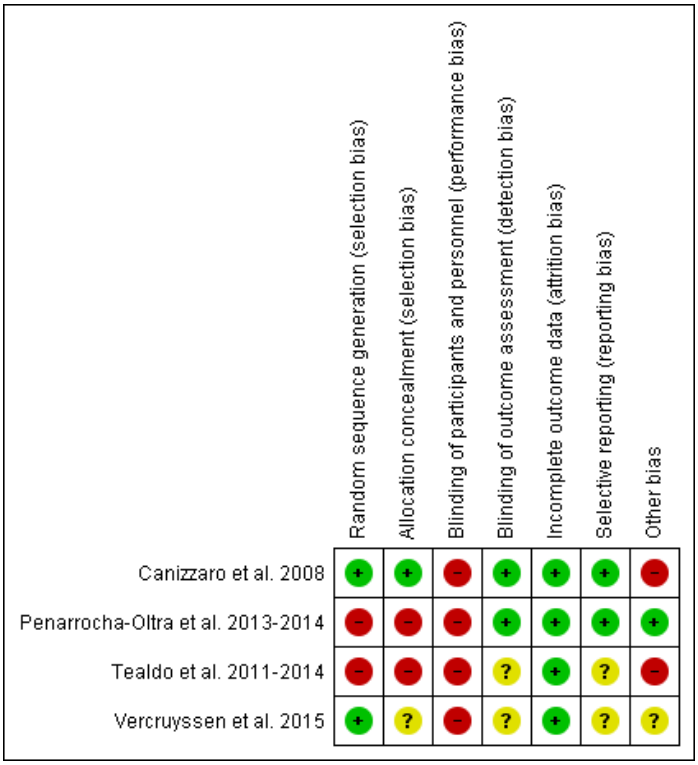

Figure 3: Risk of bias summary for included studies: judgments about risk of bias concerning each potential source and type of bias. A + signifies that the corresponding approach to minimize bias was probably done (adequately described) for a given study, whereas a - discloses an evident limitation in controlling bias. A question mark underscores that the study provides insufficient description for judging a given approach as adequate or not.

5.4. Effect of Interventions

Table 3 summarizes the main findings of the four included trials, according to each outcome.

Primary Outcomes

Two studies reported general patient satisfaction with prostheses as an outcome variable (13, 14, 99), whereas none assessed OHRQoL.

- *IL versus EL:* The RCT by Canizzaro el al. (99) 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 number of completely satisfied participants was IL: 11 (73%), and EL: 5 (33%) (assessed n: 15/arm). Thus, 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:* Penarrocha-Oltra et al. (13, 14) quantified overall patient satisfaction on a 100-mm VAS. The average value on 3 months was 35 mm higher for the IL arm (95%CI: 26 to 44 mm). Such difference recedes at the 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 (13, 14). 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: 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.

Altogether, a total number of 299 implants were immediately loaded, 244 implants received delayed loading and 87 were early loaded. The implant survival is identified as the percentage of number of implants still functioning in the oral cavity at the follow up visits. In all included trials comparing immediate loading to delayed loading, the test group appears to be comparable at one year with respect to the implant survival rate (13, 14, 100-102). Comparing IL to EL, the Canizzaro et al. RCT also showed comparable outcome between immediate and

early loading protocol (99), although the implant failure rate was 0.32 times that observed with EL. Comparing IL to CL seems to be contradicting, one RCT comparing IL to CL (102) observed a RR of 0.38 (95%CI: 0.02 to 9.08) at 3 months of follow-up. In addition, one non-randomised CCT (13, 14) reveals a risk ratio of 3.16 (95%CI: 0.33 to 29.84) on one year follow up, while another non-randomized CCT (100, 101) found a risk ratio of 1.49 (95%CI: 0.48 to 4.61). Both trials found comparable rates at the one year follow up favouring the conventional loading

Results show no significant difference regarding peri-implant bone level comparing IL to EL and CL. One Compared to EL, i.e. 0.55 (0.22) mm of resorption, mean changes at 12 mo. were similar for IL: 0.62 (0.25) mm of bone loss (99) – mean difference: 0.07 (95%CI: -0.10 to 0.24). Differences in bone level between IL and CL were very small; at 12 mo., mean differences were 0.0 (95%CI) for Penarrocha-Oltra et al. (13, 14) and -0.60 (95%CI: -1.10, -0.10) for Tealdo et al. (100, 101). The difference found by latter study was significant and reached -0.80 mm at 72 mo. (95%CI: -1.64 to 0.04).

Finally, it seems that the IL groups had higher cumulative incidence of prosthetic complications compared to both delayed and early loading groups on the short term and one year-long term. Cumulative rates of mechanical failures for separate studies were:

- Penarrocha-Oltra et al. (13, 14), IL: 62.5%; CL: 0%.
- Tealdo et al. (100, 101), IL: 50%; CL: 50%.
- Canizzaro et al. (99), IL: 50%; EL: 25%.

Most of those failures were related to the provisional prostheses provided to the participants in the IL groups.

Table 3: 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**
IL versus EL:					
Canizzaro et al. (99)	"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); EL: 0.1 (0.1) - 12 mo., IL: 0.7 (0.2); EL: 0.8 (0.2)	NR	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
IL versus CL:					
Penarrocha-Oltra et al. (13, 14)	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. (100, 101)	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. (102)	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.

6. DISCUSSION

6.1. Summary of main results

A recent growing interest in the literature on the subject of immediately loaded dental implants and its impact on patients seeking rehabilitations for edentulous maxillae is evident given that the oldest included report was published in 2008 (99), whereas the majority of observational studies on IL were conducted in 2005 (103), thus suggesting a shift towards CCTs in recent years.

In the included studies, comparisons between IL and EL or CL suggest that patients receiving immediate full fixed prosthesis were more satisfied than patients on other groups. While the evidence is inconclusive, IL was more satisfying than EL in one RCT (99). This RCT assessed patient satisfaction as a secondary outcome which was assessed after one year. Delivering different prosthesis to the two groups may also have contributed to the differences in post-treatment outcomes. Therefore, as tempting as it may be to suggest a long-term effect of IL on patient satisfaction, this finding should be interpreted carefully. One non-randomized clinical trial comparing IL to CL demonstrated a similar treatment effect at 3 months after implant placement (13, 14); this was expected given that participants in the IL group were given fixed prosthesis, whereas participants in the CL were given conventional dentures. Results for patient satisfaction are similar on `1. though, suggesting that results may not differ at that time point. Patients may get used with existing fixed dentures and provide similar responses after few months, regardless of having to endure a period with conventional dentures or not. In other words, patients may undergo a response shift after few months and reach similar perception of received prostheses regardless of initial experiences (104).

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

All studies provided treatment with standard implants. Evidence is even scarcer for zygomatic implants, given the absence of included trials. Their potential safety and effectiveness make them a very interesting subject for future trials, as found by observational studies (10, 105, 106).

6.2. Overall completeness and applicability of evidence

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. only 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 (93). 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 (107, 108).

The paucity of studies makes any assumption regarding different clinical conditions unclear. For example, one cannot infer whether different results are expected consequent to different occlusal conditions – edentulous or dentate mandible, different occlusal schemes and prosthetic veneering/framework materials. Trials do not provide separate effect data on adverse cases; trials could have done it by applying restrictive eligibility criteria or performing subgroup analysis. Adverse conditions include severe parafunction, smoking, improper bone healing conditions, and high-risk of periodontal disease, which are often described as contra-indications for IL (109, 110).

6.3. Quality of the evidence

In summary, all included studies could be classified as at high risk of bias for varying reasons. The design of included trials was a major issue in this review. Firstly, preference trials possess an important drawback: higher risk of selection bias (111). This review had two of such trials, which could not implement sequence generation methods able to minimize selection bias. Other concerns related to that source of bias refer to concealed allocation, reported by a single study.

Given that blinding of participants and care providers is not possible for the tested comparisons, one must see that as an inherent limitation rather than lack of quality. Blinding of outcome assessors was possible, however, and reported for some trials. In general, studies were careful regarding the handling of withdrawals and losses; i.e. numbers of non-adherent participants were very low and well reported.

Given the long-lasting recommendation of trial registration and contemporaneity of included trials, the unavailability of published protocols was surprising. Trial registration has been a persisting recommendation of guidelines for trial protocols (112) and final reports (113).

Publication bias remains unclear given the low number of trials comparing IL to other protocols in the edentulous maxilla. The number of inclusions precludes the assessment of that source of bias (85).

6.4. Potential biases in the review process

One of the main limitation of this review is the low number of included studies. A paucity of RCTs was foreseeable and approached by widening eligibility criteria to preference trials and other non-randomized CCT designs. However, even this approach resulted in a considerably low number of trials, mostly for patient satisfaction. Summed to the finding of only two trials reporting our primary outcomes, this review is further limited to the non-comparability of different measurement instruments for patient satisfaction. In general, studies were also underpowered (modest sample sizes) and could not detect clinically significant differences 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 find non-English studies. Thus, language cannot be considered as a limitation of this review.

6.5. Agreements and disagreements with other studies or reviews

This systematic review adds novelty by its patient-centered focus, which is uncommon in other reviews. However, it is noteworthy that previous reviews found akin results for clinician/disease-centered outcomes. Esposito et al. observed comparable survival/success rates for different loading

methods. That review considered clinical performance exclusively and missed four of our six included reports given its last update's timing (15). Finally, we extended eligibility criteria to include preference trials, different of that review. Further three recent systematic reviews on IL's clinical outcomes (114-116) found a single CCT (99).

Other reviews did not find CCTs comparing immediately loaded zygomatic implants to other loading protocols on similar fixtures either (117, 118).

6.6. Implications for future research

Future trials are fundamental to compare IL to other traditional approaches to load implants in the edentulous maxilla and should consider zygomatic fixtures. Given the specific patient profile (standard patients can cope well with conventional dentures), and associated cost/complexity of the intervention, recruitment in an RCT can be quite slow. Thus, a collaboration among clinical and research experts in the field of oral implantology is strongly recommended to conduct larger multicenter RCTs. Such tentative trial(s) should use standardized tools for preliminary clinical evaluations and the outcome measurements at several recall visits – baseline up to at least 12 months but focusing on short-term follow-up. Focus on patient-reported outcomes seems imperative in future studies, given their fundamental importance for clinical guidelines/recommendations (17).

Following reporting guidelines, including SPIRIT and CONSORT, will lead to more transparent and comprehensive research methods. Trial registration in public databases (e.g. clinicaltrials.gov) must be seem as needed to achieve further transparency.

6.7. Implication for clinical practice

The selection of IL instead of CL or EL must rest on solid practitioner's skills to provide such treatment and patient preferences. Evidence provides some support for the use of IL with standard implants as an effective way to rehabilitate fully edentulous maxillae, for cases where no augmentation method is used. Patients seem at least as satisfied with IL, and clinical complications may be comparable. Such favorable results, however, are associated with a careful decision based on several favorable clinical characteristics (e.g., favorable ridge anatomy). Comparative evidence on cases with unfavorable features remains scant.

7. CONCLUSION

This review found weak evidence on the comparative performance of IL versus other loading regimens (CL and EL) for providing full fixed 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 treatment of adult patients with edentulous maxillary arches with IL must be the subject of future clinical trials. Recommended design includes multicenter RCTs with at least 1 year of follow-up to examine patient-reported outcomes while providing data on short-term survival/success rates.

8. REFERENCES

1. Cunha-Cruz J, Hujoel PP, Nadanovsky P. Secular trends in socio-economic disparities in edentulism: USA, 1972-2001. J Dent Res. 2007;86(2):131-6.
2. Emami E, de Souza RF, Kabawat M, Feine JS. The impact of edentulism on oral and general health. Int J Dent. 2013;2013:498305.
3. Cunha TR, Della Vecchia MP, Regis RR, Ribeiro AB, Muglia VA, Mestriner W, Jr., et al. A randomised trial on simplified and conventional methods for complete denture fabrication: masticatory performance and ability. J Dent. 2013;41(2):133-42.
4. Michael CG, Javid NS, Colaizzi FA, Gibbs CH. Biting strength and chewing forces in complete denture wearers. J Prosthet Dent. 1990;63(5):549-53.
5. Trulsson U, Engstrand P, Berggren U, Nannmark U, Branemark PI. Edentulousness and oral rehabilitation: experiences from the patients' perspective. Eur J Oral Sci. 2002;110(6):417-24.
6. Feine JS, de Grandmont P, Boudrias P, Brien N, LaMarche C, Tache R, et al. Within-subject comparisons of implant-supported mandibular prostheses: choice of prosthesis. J Dent Res. 1994;73(5):1105-11.
7. Emami E, Michaud PL, Sallaleh I, Feine JS. Implant-assisted complete prostheses. Periodontology 2000. 2014;66(1):119-31.
8. Thomason JM, Kelly SA, Bendkowski A, Ellis JS. Two implant retained overdentures--a review of the literature supporting the McGill and York consensus statements. J Dent. 2012;40(1):22-34.
9. Preoteasa E, Melescanu-Imre M, Preoteasa CT, Marin M, Lerner H. Aspects of oral morphology as decision factors in mini-implant supported overdenture. Rom J Morphol Embryol. 2010;51(2):309-14.
10. Coppede A, de Mayo T, de Sa Zamperlini M, Amorin R, de Padua A, Shibli JA. Three-year clinical prospective follow-up of extrasinus zygomatic implants for the rehabilitation of the atrophic maxilla. Clin Implant Dent Relat Res. 2017;19(5):926-34.
11. de Albuquerque Junior RF, Lund JP, Tang L, Larivee J, de Grandmont P, Gauthier G, et al. Within-subject comparison of maxillary long-bar implant-retained prostheses with and

without palatal coverage: patient-based outcomes. Clin Oral Implants Res. 2000;11(6):555-65.

12. Hopp M, de Araujo Nobre M, Malo P. Comparison of marginal bone loss and implant success between axial and tilted implants in maxillary All-on-4 treatment concept rehabilitations after 5 years of follow-up. Clin Implant Dent Relat Res. 2017;19(5):849-59.
13. Penarrocha-Oltra D, Covani U, Aparicio A, Ata-Ali J, Penarrocha-Diago M, Penarrocha-Diago M. Immediate versus conventional loading for the maxilla with implants placed into fresh and healed extraction sites to support a full-arch fixed prosthesis: nonrandomized controlled clinical study. Int J Oral Maxillofac Implants. 2013;28(4):1116-24.
14. Penarrocha-Oltra D, Penarrocha-Diago M, Canullo L, Covani U, Penarrocha M. Patient-reported outcomes of immediate versus conventional loading with fixed full-arch prostheses in the maxilla: a nonrandomized controlled prospective study. Int J Oral Maxillofac Implants. 2014;29(3):690-8.
15. Esposito M, Grusovin MG, Maghaireh H, Worthington HV. Interventions for replacing missing teeth: different times for loading dental implants. Cochrane Database Syst Rev. 2013(3):CD003878.
16. de Souza RF, Ahmadi M, Ribeiro AB, Emami E. Focusing on outcomes and methods in removable prosthodontics trials: a systematic review. Clin Oral Implants Res. 2014;25(10):1137-41.
17. Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69(3):548-56.
18. Egger M, Davey-Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. London: BMJ Publishing Group; 2008.
19. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: Wiley; 2008.
20. Teagarden JR. Meta-Analysis: Whither Narrative Review? Pharmacotherapy. 1989;9(5):274-84.
21. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19-32.

22. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs. 2003;12(1):77-84.
23. Huque M, editor Experiences with meta-analysis in NDA submissions. Proceedings of the Biopharmaceutical Section of the American Statistical Association; 1988.
24. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
25. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Available from: http://handbook-5-1.cochrane.org/.
26. Aromataris E, Munn Z. Joanna Briggs Institute Reviewer's Manual. Adelaide: The Joanna Briggs Institute; 2017. Available from: https://reviewersmanual.joannabriggs.org/.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
28. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
29. Hugo FN, Hilgert JB, Da Luz Rosário de Sousa M, Cury JA. Oral status and its association with general quality of life in older independent-living south-Brazilians. Community Dent Oral Epidemiol. 2009;37(3):231-40.
30. Fiske J, Davis D, Frances C, Gelbier S. The emotional effects of tooth loss in edentulous people. British Dent J. 1998;184(2):90.
31. Allen PF, McMillan AS. A review of the functional and psychosocial outcomes of edentulousness treated with complete replacement dentures. J Can Dent Assoc. 2003;69(10):662.
32. Gahan MJ, Walmsley AD. The neutral zone impression revisited. Br Dent J. 2005;198(5):269-72.
33. Shirani M, Mosharraf R, Shirany M. Comparisons of patient satisfaction levels with complete dentures of different occlusions: a randomized clinical trial. J Prosthodont. 2014;23(4):259-66.

34. Jayaraman S, Singh BP, Ramanathan B, Pazhaniappan Pillai M, MacDonald L, Kirubakaran R. Final-impression techniques and materials for making complete and removable partial dentures. Cochrane Database Syst Rev. 2018;4:CD012256.
35. Carlsson GE. Clinical morbidity and sequelae of treatment with complete dentures. J Prosthet Dent. 1998;79(1):17-23.
36. Calandriello R, Tomatis M. Simplified treatment of the atrophic posterior maxilla via immediate/early function and tilted implants: A prospective 1-year clinical study. Clin Implant Dent Relat Res. 2005;7 Suppl 1:S1-12.
37. Curi MM, Condezo AFB, Ribeiro K, Cardoso CL. Long-term success of dental implants in patients with head and neck cancer after radiation therapy. Int J Oral Maxillofac Surg. 2018;47(6):783-8.
38. Zarb GA, Hobkirk J, Eckert S, Jacob R. Prosthodontic Treatment for Edentulous Patients-E-Book: Complete Dentures and Implant-Supported Prostheses. St. Louis: Elsevier Health Sciences; 2013.
39. Chen ST, Beagle J, Jensen SS, Chiapasco M, Darby I. Consensus statements and recommended clinical procedures regarding surgical techniques. Int J Oral Maxillofac Implants. 2009;24 Suppl:272-8.
40. Atwood DA, Coy WA. Clinical, cephalometric, and densitometric study of reduction of residual ridges. J Prosthet Dent. 1971;26(3):280-95.
41. Cawood JI, Howell RA. Reconstructive preprosthetic surgery. I. Anatomical considerations. Int J Oral Maxillofac Surg. 1991;20(2):75-82.
42. Zitzmann NU, Marinello CP. Treatment plan for restoring the edentulous maxilla with implant-supported restorations: removable overdenture versus fixed partial denture design. J Prosthet Dent. 1999;82(2):188-96.
43. Wismeijer D, Buser D, Belser U. ITI Treatment Guide, Vol 4: Loading Protocols in Implant Dentistry. Berlin: Quintessence; 2010.
44. Paulo M, Bo R, Miguel N. All-on-4 Immediate-Function Concept with Brånemark System® Implants for Completely Edentulous Maxillae: A 1-Year Retrospective Clinical Study. Clinical Implant Dentistry and Related Research. 2005;7(s1):s88-s94.

45. 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(1):153-87.
46. 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(5):610-21.
47. Hugo DB, Stefanie R, Pär-Olov Ö, Jan C. Immediate loading in partially and completely edentulous jaws: a review of the literature with clinical guidelines. Periodontol 2000. 2014;66(1):153-87.
48. Khorshid HE, Hamed HA, Aziz EA. The effect of two different immediate loading protocols in implant-supported screw-retained prostheses. Implant Dent [Internet]. 2011; 20(2):[157-66 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/992/CN-00800992/frame.html.
49. Kim Y, Oh TJ, Misch CE, Wang HL. Occlusal considerations in implant therapy: clinical guidelines with biomechanical rationale. Clin Oral Implants Res. 2005;16(1):26-35.
50. Agliardi EL, Romeo D, Panigatti S, de Araujo Nobre M, Malo P. Immediate full-arch rehabilitation of the severely atrophic maxilla supported by zygomatic implants: a prospective clinical study with minimum follow-up of 6 years. Int J Oral Maxillofac Surg. 2017;24:24.
51. Koyano K, Esaki D. Occlusion on oral implants: current clinical guidelines. J Oral Rehabil. 2015;42(2):153-61.
52. Reitz JV. Lingualized occlusion in implant dentistry. Quintessence Int. 1994;25(3):177-80.
53. Rilo B, da Silva JL, Mora MJ, Santana U. Guidelines for occlusion strategy in implant-borne prostheses. A review. Int Dent J. 2008;58(3):139-45.
54. Gowd MS, Shankar T, Ranjan R, Singh A. Prosthetic consideration in implant-supported prosthesis: A review of literature. J Int Soc Prev Community Dent.. 2017;7(Suppl 1):S1.
55. Misch CE. Bone classification, training keys to implant success. Dent Today. 1989;8(4):39-44.
56. Gowd MS, Shankar T, Ranjan R, Singh A. Prosthetic Consideration in Implant-supported Prosthesis: A Review of Literature. J Int Soc Prev Community Dent. 2017;7(Suppl 1):S1-s7.
57. Misch CE. Dental Implant Prosthetics-E-Book: Elsevier Health Sciences; 2014.

58. Nkenke E, Fenner M. Indications for immediate loading of implants and implant success. Clin Oral Implants Res. 2006 Oct;17(Suppl 2):19-34.
59. Yamada J, Kori H, Tsukiyama Y, Matsushita Y, Kamo M, Koyano K. Immediate loading of complete-arch fixed prostheses for edentulous maxillae after flapless guided implant placement: a 1-year prospective clinical study. Int J Oral Maxillofac Implants. 2015;30(1):184-93.
60. Zarb GA, Albrektsson T. Consensus report: towards optimized treatment outcomes for dental implants. J Prosthet Dent. 1998;80(6):641.
61. Neukam FW, Flemmig TF, 3 WG. Local and systemic conditions potentially compromising osseointegration: Consensus report of Working Group 3. Clin Oral Implants Res. 2006;17(S2):160-2.
62. Albrektsson T, Zarb G, Worthington P, Eriksson A. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. Int J Oral Maxillofac Implants. 1986;1(1):11-25.
63. Misch CE, Perel ML, Wang H-L, Sammartino G, Galindo-Moreno P, Trisi P, et al. Implant success, survival, and failure: the International Congress of Oral Implantologists (ICOI) pisa consensus conference. Implant Dent. 2008;17(1):5-15.
64. Papaspyridakos P, Chen C-J, Singh M, Weber H-P, Gallucci G. Success criteria in implant dentistry: a systematic review. J Dent Res. 2012;91(3):242-8.
65. Ketabi M, Deporter D, Atenafu EG. A Systematic Review of Outcomes Following Immediate Molar Implant Placement Based on Recently Published Studies. Clin Implant Dent Relat Res. 2016;18(6):1084-94.
66. Lambert FE, Weber H-P, Susarla SM, Belser UC, Gallucci GO. Descriptive analysis of implant and prosthodontic survival rates with fixed implant–supported rehabilitations in the edentulous maxilla. J Periodontol. 2009;80(8):1220-30.
67. Allen PF. Assessment of oral health related quality of life. Health Qual Life Outcomes. 2003;1(1):40.
68. Marshall S, Haywood K, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: a structured review. J Eval Clin Pract.. 2006;12(5):559-68.

69. Marquis P, Caron M, Emery M-P, Scott JA, Arnould B, Acquadro C. The role of health-related quality of life data in the drug approval processes in the US and Europe. Pharm Med. 2011;25(3):147-60.
70. Bottomley A, Jones D, Claassens L. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. Eur J Cancer. 2009;45(3):347-53.
71. Pugliese P, Perrone M, Nisi E, Garufi C, Giannarelli D, Bottomley A, et al. An integrated psychological strategy for advanced colorectal cancer patients. Health Qual Life Outcomes. 2006;4:9-.
72. Kuliś D, Arnott M, Greimel ER, Bottomley A, Koller M. Trends in translation requests and arising issues regarding cultural adaptation. Expert Rev Pharmacoecon Outcomes Res. 2011;11(3):307-14.
73. Fayers PM, Machin D. Quality of life: the assessment, analysis and interpretation of patient-reported outcomes. Chichester: John Wiley & Sons; 2013.
74. Yao J, Tang H, Gao X-L, McGrath C, Mattheos N. Patients' expectations from dental implants: a systematic review of the literature. Health Qual Life Outcomes. 2014;12(1):153.
75. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes. 2010;8(1):126.
76. Newsome PR, McGrath C. Patient-centred measures in dental practice: 1. An overview. Dental update. 2006;33(10):596-600.
77. McGrath C, Lam O, Lang N. An evidence-based review of patient-reported outcome measures in dental implant research among dentate subjects. J Clin Periodontol. 2012;39(s12):193-201.
78. Locker D, Jokovic A, Clarke M. Assessing the responsiveness of measures of oral health-related quality of life. Community Dent Oral Epidemiol. 2004;32(1):10-8.
79. Esposito M, Grusovin Maria G, Maghaireh H, Worthington Helen V. Interventions for replacing missing teeth: different times for loading dental implants. Cochrane Database of Systematic Reviews [Internet]. 2013; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003878.pub5/abstract.

80. Papaspyridakos P, Chun-Jung C, Sung-Kiang C, Weber H-P. Implant Loading Protocols for Edentulous Patients with Fixed Prostheses: A Systematic Review and Meta-Analysis. Int J Oral Maxillofac Implants. 2014;29:256-70 15p.
81. Wang F, Monje A, Lin G-H, Wu Y, Monje F, Wang H-L, et al. Reliability of four zygomatic implant-supported prostheses for the rehabilitation of the atrophic maxilla: a systematic review. Int J Oral Maxillofac Implants. 2015;30(2):293-8..
82. Abdunabi A, Morris M, Abi Nader S, de Souza R. Impact of immediate loaded implant-supported fixed dental prostheses on edentulous maxillae: a systematic review. PROSPERO. 2018;2018:CRD42018071316. Aavailable at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD.
83. Tonetti M, Palmer R, Working Group 2 of the VEWoP. Clinical research in implant dentistry: study design, reporting and outcome measurements: consensus report of Working Group 2 of the VIII European Workshop on Periodontology. J Clin Periodontol. 2012;39 Suppl 12:73-80.
84. 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.
85. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
86. Agnini A, Agnini AM, Romeo D, Chiesi M, Pariente L, Stappert CF. Clinical investigation on axial versus tilted implants for immediate fixed rehabilitation of edentulous arches: preliminary results of a single cohort study. Clin Implant Dent Relat Res. 2014;16(4):527-39.
87. Aires I, Berger J. Immediate placement in extraction sites followed by immediate loading: a pilot study and case presentation. Implant Dent. 2002;11(1):87-94.
88. Alves CC, Correia AR, Neves M. Immediate implants and immediate loading in periodontally compromised patients-a 3-year prospective clinical study. Int J Periodontics Restorative Dent. 2010;30(5):447-55.
89. Aparicio C, Ouazzani W, Aparicio A, Fortes V, Muela R, Pascual A, et al. Immediate/Early loading of zygomatic implants: clinical experiences after 2 to 5 years of follow-up. Clin Implant Dent Relat Res. 2010;12 Suppl 1:e77-82.

90. Busenlechner D, Mailath-Pokorny G, Haas R, Furhauser R, Eder C, Pommer B, et al. Graftless Full-Arch Implant Rehabilitation with Interantral Implants and Immediate or Delayed Loading-Part II: Transition from the Failing Maxillary Dentition. Int J Oral Maxillofac Implants. 2016;31(5):1150-5.
91. Busenlechner D, Mailath-Pokorny G, Haas R, Furhauser R, Eder C, Pommer B, et al. Graftless Full-Arch Implant Rehabilitation with Interantral Implants and Immediate or Delayed Loading-Part I: Reconstruction of the Edentulous Maxilla. Int J Oral Maxillofac Implants. 2016;31(4):900-5.
92. Babbush CA, Kanawati A, Brokloff J. A new approach to the All-on-Four treatment concept using narrow platform NobelActive implants. J Oral Implantol. 2013;39(3):314-25.
93. 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(3):249-60.
94. Mitsias M, Siormpas K, Pistilli V, Trullenque-Eriksson A, Esposito M. Immediate, early (6 weeks) and delayed loading (3 months) of single, partial and full fixed implant supported prostheses: 1-year post-loading data from a multicentre randomised controlled trial. Eur J Oral Implantol. 2018;11(1):63-75.
95. Esposito M, Davo R, Marti-Pages C, Ferrer-Fuertes A, Barausse C, Pistilli R, et al. Immediately loaded zygomatic implants vs conventional dental implants in augmented atrophic maxillae: 4 months post-loading results from a multicentre randomised controlled trial. Eur J Oral Implantol. 2018;11(1):11-28.
96. Nordin T, Graf J, Frykholm A, Hellden L. Early functional loading of sand-blasted and acid-etched (SLA) Straumann implants following immediate placement in maxillary extraction sockets. Clinical and radiographic result. Clin Oral Implants Res. 2007;18(4):441-51.
97. Nordin T, Nilsson R, Frykholm A, Hallman M. A 3-arm study of early loading of rough-surfaced implants in the completely edentulous maxilla and in the edentulous posterior maxilla and mandible: results after 1 year of loading. Int J Oral Maxillofac Implants. 2004;19(6):880-6.

98. Zhou W, Han C, Yunming L, Li D, Song Y, Zhao Y. Is the osseointegration of immediately and delayed loaded implants the same?--comparison of the implant stability during a 3-month healing period in a prospective study. Clin Oral Implants Res. 2009;20(12):1360-6.
99. 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;9 Suppl 1(2):127-39.
100. Tealdo T, Bevilacqua M, Menini M, Pera F, Ravera G, Drago C, et al. Immediate versus delayed loading of dental implants in edentulous maxillae: a 36-month prospective study. Int J Prosthodont. 2011;24(4):294-302.
101. Tealdo T, Menini M, Bevilacqua M, Pera F, Pesce P, Signori A, et al. Immediate versus delayed loading of dental implants in edentulous patients' maxillae: a 6-year prospective study. Int J Prosthodont. 2014;27(3):207-14.
102. 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(4):427-32.
103. Attard NJ, Zarb GA. Immediate and early implant loading protocols: a literature review of clinical studies. J Prosthet Dent. 2005;94(3):242-58.
104. Ring L, Hofer S, Heuston F, Harris D, O'Boyle CA. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. Health Qual Life Outcomes. 2005;3:55.
105. Bedrossian E, Rangert B, Stumpel L, Indresano T. Immediate function with the zygomatic implant: a graftless solution for the patient with mild to advanced atrophy of the maxilla. Int J Oral Maxillofac Implants. 2006;21(6):937-42.
106. Hirsch JM, Ohrnell LO, Henry PJ, Andreasson L, Branemark PI, Chiapasco M, et al. A clinical evaluation of the Zygoma fixture: one year of follow-up at 16 clinics. J Oral Maxillofac Surg. 2004;62(9 Suppl 2):22-9.
107. Marcus SM, Stuart EA, Wang P, Shadish WR, Steiner PM. Estimating the causal effect of randomization versus treatment preference in a doubly randomized preference trial. Psychol Methods. 2012;17(2):244-54.
108. Sidani S, Fox M, Epstein DR. Contribution of treatment acceptability to acceptance of randomization: an exploration. J Eval Clin Pract. 2017;23(1):14-20.

109. Bahat O, Sullivan RM. Parameters for successful implant integration revisited part II: algorithm for immediate loading diagnostic factors. Clin Implant Dent Relat Res. 2010;12 Suppl 1:e13-22.
110. Bahat O, Sullivan RM. Parameters for successful implant integration revisited part I: immediate loading considered in light of the original prerequisites for osseointegration. Clin Implant Dent Relat Res. 2010;12 Suppl 1:e2-12.
111. Archer S, Forshaw MJ. Using a randomised controlled trial (RCT) methodology in CAM research with gynaecological cancer patients: A commentary on the perks and pitfalls. Complement Ther Clin Pract. 2015;21(1):11-8.
112. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
113. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7(3):e1000251.
114. Gallucci GO, Morton D, Weber HP. Loading protocols for dental implants in edentulous patients. Int J Oral Maxillofac Implants. 2009;24 Suppl:132-46.
115. Papaspyridakos P, Chen CJ, Chuang SK, Weber HP. Implant loading protocols for edentulous patients with fixed prostheses: a systematic review and meta-analysis. Int J Oral Maxillofac Implants. 2014;29 Suppl:256-70.
116. Strub JR, Jurdzik BA, Tuna T. Prognosis of immediately loaded implants and their restorations: a systematic literature review. J Oral Rehabil. 2012;39(9):704-17.
117. Candel-Marti E, Carrillo-Garcia C, Penarrocha-Oltra D, Penarrocha-Diago M. Rehabilitation of atrophic posterior maxilla with zygomatic implants: review. J Oral Implantol. 2012;38(5):653-7.
118. Tuminelli FJ, Walter LR, Neugarten J, Bedrossian E. Immediate loading of zygomatic implants: A systematic review of implant survival, prosthesis survival and potential complications. Eur J Oral Implantol. 2017;10 Suppl 1:79-87.

APPENDICES

Appendix Figure 1: PRISMA checklist.

Appendix Table 1: Systematic review search in Medline.

Appendix Table 2: Risk of bias assessment of the included studies.

PRISMA 2009 Checklist

Appendix Figure 1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**i**
ABSTRACT			
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.	**iv-v; French: vi-vii**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**01-02**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**18**
METHODS			
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.	**19**
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.	**19-20 (ref. 19)**
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.	**21**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Appendix 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).	**21**
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.	**21-22**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**22-23**
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.	**22**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**23**
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.	**23**

PRISMA 2009 Checklist

Appendix Figure 1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
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).	**23, 37**
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**
RESULTS			
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.	**24-25, 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.	**25-27, 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).	**29-30, Fig. 2; App Table 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.	**30-33, 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).	**(See #19)**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**n/a**
DISCUSSION			
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).	**34-36**
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).	**37-39**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**39-41**
FUNDING			
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.	**viii**

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**.

Appendix Table 1. Systematic review search strategy in Medline (Ovid).

Search date	**May 22, 2018** **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 Table 2. 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.

STUDY ID: Canizzaro et al. 2008 [IL compared to EL]		
Source of Bias	**Judgment**	**Support for judgement**
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".

STUDY ID: Penarrocha-Oltra et al. 2013 & 2014 [IL compared to CL]		
Source of Bias	**Judgment**	**Support for judgement**
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 se- lection 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.

STUDY ID: Vercruyssen et al. 2016 (IL compared to CL)		
Source of Bias	**Judgment**	**Support for judgement**
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.
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).

STUDY ID: Tealdo et al. 2016 & 2011 (IL compared to CL)		
Source of Bias	**Judgment**	**Support for judgement**
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.