CLINICAL ORAL SCIENCE AND DENTISTRY

RESEARCH ARTICLE ISSN 2688-7428 Open Access

Clinical Outcome of Immediate vs. Early/conventional Loading of Dental Implants with fixed Prosthetic in RCT- a Systematic Literature Review and Meta-Analysis

Mercede Ghorbanirad Rasmussen*

*Dentist and Implantologist DDS, MSc. Master of science in oral implantology / Clinic Owner at Smile Clinic, Denmark.

Received date: January 05, 2025, **Accepted date:** January 11, 2025, **Published date:** January 15, 2025.

***Corresponding Author:** Dr. Mercede Ghorbanirad Rasmussen, Dentist and Implantologist DDS, MSc. Master of science in oral implantology / Clinic Owner at Smile Clinic, Denmark.

Abstract

Introduction

In this study, clinical outcomes between various loading protocols for dental implants were explored. Specifically, immediate loading of dental implants was compared to both delayed (conventional) and early loading in terms of clinical outcomes like marginal bone loss and survival rates. Currently, there is no consensus within existing literature regarding which dental loading protocol is most effective and leads to the best patient outcomes. Therefore, the aim of the study was to investigate original randomized controlled trials (RCTs), interpreting their findings on the use of immediate, early, and delayed loading techniques for dental implants.

Material and Methods

A systematic literature review was conducted in an attempt to answer the following research question: Which dental implant loading protocol – immediate, early, or conventional – results in the least marginal bone loss and highest survival rate. The Medline database was searched

for relevant peer-reviewed published within the last 20 years, with inclusion criteria specifying these articles were original RCTs and using a Split Mouth research design. The articles also had to investigate quantitative measures or clinical outcomes like marginal bone loss and survival rate of dental implants.

Results

A total of eight peer-reviewed journal articles were identified in the systematic literature review. The articles were published between 2008 and 2019, with the studies enrolling 240 total participants who received 537 implants. For immediate loading, the average marginal bone loss was 0.98 mm, with a 95.3% survival rate for 102 participants throughout 265 implants. For early loading, the average marginal bone loss was 0.67 mm, with a 98% survival rate for 36 participants throughout 89 implants. Finally, for conventional or delayed loading, the average marginal bone loss was 1.4 mm, with a 100% survival rate for 66 participants throughout 142 implants.

The results of the meta-analysis in comparison of MBL at 1 year, between IL and EL showed fixed standard mean difference in MBL as 0.46 [0.17; 0.76] at 95% CI, (P=0.06), and for the IL and CL showed a fixed standard mean difference of -0.22 [- 0.48; 0.05] at 95% CI,(P=0.35). The differences were not statistically significant (P>0.05).

Conclusion

The results of this literature review showed that there was no statistically significant differences in terms of MBL for IL group compared to either CL group or EL group. However, the CL protocol offered the highest survival rate with 100%, and the EL group with 98% was at the second place in terms of survival rate. IL group with the survival rate of 95.3% comes at the third place. Nevertheless, 95.3% survival rate for the IL group is considered as a high survival rate. Hence the result of current study provides evidence supporting the use of immediate loading protocol for the dental implants.

Introduction

Immediate loading of the dental implants has become more and more popular within the last two decades in dental community, due to the benefits it provides to both clinicians and the patients, regarding shorter treatment time, satisfying the aesthetic needs of the patients and the comfort it provides to the patients regarding reducing the number of the surgeries. This systematic review compares the clinical outcomes of the immediate loading of dental implants with delayed (conventional) or early loading of dental implants.

In order to attain proper osseointegration, the conventional approach involves submerging implants without any load (Chen et al., 2019). This should occur for three to four months in the mandible, while for the maxilla, the delayed loading should continue for six to eight months (Chen et al., 2019; De Bruyn et al., 2014; Strub et al., 2012). Nonetheless, even though some studies recommend delayed loading of dental implants, there are many benefits to immediate loading, as the treatment period is significantly shortened (De Bruyn et al., 2014; Strub et al., 2012). In fact, there is ongoing research into the immediate and early implant loading protocols for dental implants.

Specifically, there are many high- and good-quality randomized controlled trials (RCTs) that have explored various implant surface modifications and clinical techniques for immediate loading of dental implants (Barewal, Stanford, and Weesner, 2012; Danza et al., 2010; Merli et al., 2020; Romanos, Aydin, Locher, and Nentwig, 2016). These trials have found that there are high survival rates and reduced incidence of implant failure through immediate loading (Barewal et al., 2012; Danza et al., 2010; Merli et al., 2020; Romanos et al., 2016). Unfortunately, when considering existing systematic reviews and even meta-analyses, the evidence supporting immediate loading is not as clear (Engelhardt et al., 2015; Kern et al., 2016). There is ongoing

disagreement in the dental community regarding the evidence that has been found from RCTs, specifically in probing depth, implant stability, and marginal bone level changes associated with the various types of loading for dental implants. Therefore, in this systematic review of existing RCTs, the focus is on exploring the differences between clinical outcomes of immediate, early, and delayed loading.

Purpose

The quest to mimic the natural appearance of teeth is at the heart of aesthetic dentistry. Achieving this involves replicating the shape, color, translucency, and alignment of natural teeth. Materials like porcelain and composite resin have been instrumental due to their ability to mimic enamel's light- reflecting properties. Porcelain veneers, for instance, offer a lifelike appearance and stain resistance, making them a popular choice for smile makeovers (Pincus, 1938).

Aim

The aim of this study is to revising existing RCTs, comparing their findings on the use of immediate, early, and delayed loading techniques for dental implants.

Background to Thesis and Review of the literature

There are three accepted protocols for implant load timing: a) immediate loading implants within one week of implant placement; b) early loading implants between four to eight weeks after implant placement; and c) conventional loading implants 12 weeks or more after implant placement (Esposito et al., 2013). Additionally, the different loading modalities are identified through two classifications: a) Occlusal loading or non-occlusal loading, and b) Direct loading or Progressive loading (Esposito et al, 2013; Tettamanti et al., 2017). Based on existing systematic reviews, researchers have not found credible evidence in support of one implant load timing protocol over another, particularly in terms of significant differences in bone loss, implant failure, or prosthesis failure (Esposito et al, 2013).

Figure 1: Implant loading Protocol. (Gallucci et al., 2018)

Immediate Loading

In practicing implant dentistry, there are various loading techniques that dentists can use. For example, in immediate loading, a restoration is placed within two days of an implant being placed (Tettamanti et al., 2017). In other words, during the immediate loading of the implants, the implants are loaded by the provisional prosthetic within 48 hours after the placement of the implant (Gallucci et al., 2018). This is known as Immediate Function, or Immediate Provisionalization, which is when either a single tooth or multiple units are being restored (Tettamanti et al., 2017). Hence, Immediate Function involves both single crowns and multiple unit bridges (Tettamanti et al., 2017).

Within immediate occlusal loading (Classification A), dental implants are connected to a prosthesis in occlusion, with the opposing arch within one week after implant placement (Gallucci et al., 2018). Additionally, with immediate non-occlusal loading (Classification B), dental implants are connected to a prosthesis held out of occlusion (Gallucci et al., 2018).

The technique was first created in order to accommodate patients' requests for faster treatments, with the first loaded implants being placed in the mandible's anterior (Tettamanti et al., 2017). Eventually, partial protheses were able to be fixed to immediately loaded implants (Tettamanti et al., 2017). Research examining follow-up of the use of the immediate loading technique have demonstrated high cumulative survival rates of anywhere between 97% to 100% (Degidi et al. 2012; Mura, 2012; Polizzi et al., 2015).

There are many benefits for patients who receive immediate placement and loading, including decreased treatment time (Hof et al., 2014). Instead of patients having to wait for extended periods of time for their smile to be aesthetically corrected – not to mention to achieve a fully functional dentition – the immediate loading offers them the possibility to have their implant and prosthetic treatment performed in the same day at the office (Hof et al., 2014). Hence, patient satisfaction with the care they receive can be increased using this technique (Hof et al., 2014).

Additionally, older (seminal) studies have determined that there is good predictability associated with immediate implant placement and provisionalization (Degidi et al., 2003; Touati et al., 2002). Both complex bone grafting procedures and other surgical interventions are notably decreased through implementing immediate implant placement, as there is no need to restore resorbed ridges (Degidi et al., 2003; Touati et al., 2002). Hence, there is a much less complicated surgical workflow using immediate implant placement and loading, as there is only one stage required. This has significant benefits to patients, as they only have to undergo one surgery instead of two (or even more). Furthermore, in single-tooth rehabilitation, where flapless strategies are employed, studies have reported patients increased satisfaction with post-surgical experiences (Mankoo, 2004). However, there have also been positive findings from multiple implant placements using the immediate loading protocol (Meng et al., 2021; Wöhrle, 2014).

Early Loading

According to Dichter (2018), early loading lies between conventional loading and immediate loading, temporally speaking. It is viewed as prosthetic loading or implant utilization between immediate and conventional loading (Dichter, 2018; Gallucci et al., 2018). For early loading, dental implants are loaded by the prosthesis within four to eight weeks after the placement of the implant (Gallucci et al., 2018; Körmöczi et al., 2021). The loading refers to when the prosthetic comes on the implant, which is the topic of this thesis (Gallucci et al., 2018; Körmöczi et al., 2021).

Research has supported the use of early loading, with many dentists subscribing to the belief that by waiting for this time frame, patients could heal better (Körmöczi et al., 2021). In fact, the time enabled patient-specific variables to be compensated for, especially during a time when surgical and prosthetic protocols were not yet optimized (Gallucci et al., 2018). Nowadays, early loading is considered a viable and effective treatment modality for dental implants (Gallucci et al., 2018; Körmöczi et al., 2021).

Conventional Loading

Finally, the conventional loading protocol is the one that has historically been used in dental implants (Körmöczi et al., 2021). This is when the implants are loaded by prosthetic ,12 weeks after implant placement (Gallucci et al., 2018; Körmöczi et al., 2021).

As Dichter (2018) explains, conventional loading can be defined as the prosthetic restoration and functional loading of an osseointegrated implant following three to six months of healing. It was created initially for implants

with machined surfaces (Dichter, 2018). Delayed loading occurs within conventional loading, with implants first placed, after which the dentist closes the surgical site (Dichter, 2018). Hence, a second surgery is usually required to uncover the implant, as the implant is left submerged for the period of healing (Dichter, 2018).

Therefore, in conventional loading, implants are left submerged during the healing period (Mitsias et al., 2018). If the dental implant is going to be in the mandible, the implants heal for three to four months, while if they are in the maxillae, it usually takes six to eight months to completely heal (Mitsias et al., 2018). One reason for this delay is that it decreases the risk of soft-tissue encapsulation by keeping implants load free, as soft-tissue scar tissue can sometimes encapsulate the implant, especially when there is movement (Mitsias et al., 2018). Subsequently, this can cause failure, as osseointegrated dental implants must be directly anchored to the bone to be successful (Mitsias et al., 2018).

Consensus Statements

According to the International Team for Implantology (ITI), treatments for dental implants can utilize immediate, early, and delayed protocols, depending upon each patient's unique case (Gallucci et al., 2018). Both loading combinations and the implant placement timing must be taken into consideration when choosing a specific treatment (Gallucci et al., 2018; Körmöczi et al., 2021). Two clinically documented protocols involve immediate placement with immediate loading, which has a 98% survival rate, and immediate placement with early loading, which also has a 98% survival rate (Gallucci et al., 2018; Körmöczi et al., 2021). Additionally, a clinically valid protocol involves immediate placement with conventional loading, although this has a slightly lower survival rate of only 96% (Gallucci et al., 2018; Körmöczi et al., 2021).

There is not sufficient documentation to support the use of early placement with either early or immediate loading (Gallucci et al., 2018). On the other hand, another clinically valid protocol involves early placement with conventional loading, with a 96% survival rate (Gallucci et al., 2018). Additionally, another clinically documented protocol is late placement with immediate loading, which has a 98% survival rate (Gallucci et al., 2018). Furthermore, both late placement with early loading as well as late placement with conventional loading are clinically valid protocols that have a 98% survival rate (Gallucci et al., 2018).

Many different variables in placement and loading protocols can impact the intended treatment outcomes, such as patients requiring bone augmentation, insufficient primary stability, and other risk factors specifically associated with the patients themselves (Gallucci et al., 2018).

Clinical Recommendations

The ITI also presents clinical recommendations on dental implants and loading. For example, the first recommendation is that both implant placement and loading protocols must be planned before extracting the tooth (or teeth) (Gallucci et al., 2018). Additionally, predictable outcomes should be employed to help determine which protocol to implement, such as patient goals for functionality and aesthetics (Gallucci et al., 2018). Some other outcomes to keep in mind include decreasing the risk of complications as well as long-term tissue stability (for both hard and soft tissues) (Gallucci et al., 2018).

The second recommendation is that as part of the planning process, patients should be aware of all alternative treatment modalities that exist (Gallucci et al., 2018). This is especially true in case it is not possible to meet specific intra-operative procedural criteria (Gallucci et al., 2018). There are various levels of treatment risk and clinical difficulty associated with each of these

implant placement and restoration / loading protocols (Gallucci et al., 2018). Hence, whichever protocol is chosen must be one that is within the skills of the surgeon (Gallucci et al., 2018).

The third recommendation is that there must be careful consideration of the benefits that implant placement and loading protocols have on patients, while considering any risks (Gallucci et al., 2018). The fourth recommendation is that immediate placement and immediate restoration/loading not be used unless there are significant benefits to the patient, as it is a more complicated procedure (Gallucci et al., 2018). In fact, there are certain clinical conditions that must be met before proceeding with this procedure, not the least of which involves patient compliance (Gallucci et al., 2018). The other conditions include an insertion torque of between 25 and 40 Ncm and/or ISQ value greater than 70, primary stability (via bone availability both lingual/palatal and apical to the socket), occlusal scheme (to protect provisional restoration), absence of acute infection, thick soft tissue, facial bone wall (1mm thick or greater), and intact socket walls (Gallucci et al., 2018).

The fifth recommendation is that in early implant placement, conventional loading should be seriously considered (Gallucci et al., 2018). Many clinical situations can be treated with early implant placement, including at sites with defects and thin facial walls (Gallucci et al., 2018). However, as bone augmentation procedures are usually needed at the same time, conventional loading is the recommended protocol to go along with early implant placement (Gallucci et al., 2018). Overall, there is not enough evidence to support the use of either early or immediate loading protocols in combination with early implant placement (Gallucci et al., 2018).

The sixth recommendation is that because of alveolar ridge resorption risk, the option that is least desirable involves late implant placement (Gallucci et al., 2018). This placement also has been associated with prolonged treatment time and bone volume reduction (Gallucci et al., 2018). Finally, the seventh recommendation is that in late implant placement, both early and conventional loading are considered desirable protocols (Gallucci et al., 2018).

Hypothesis

Both the null and alternative hypotheses are presented as follows:

H0 = there are no statistically significant differences in the three types of loading for dental implants: immediate, early, and delayed (conventional).

HA = there are statistically significant differences in the three types of loading for dental implants: immediate, early, and delayed (conventional).

Research Question

Which loading protocol for dental implants results in the least marginal bone loss and highest survival rate in patients who require at least one implant: Immediate loading (with restoration within one week following insertion), Early loading (with restoration between four to eight weeks), or Conventional / Delayed loading (with restoration after 12 weeks)?

Material and Methods

Objective of the Study

The main objective of the study was to identify, review, and critically appraise the existing literature regarding immediate vs early and conventional (delayed) loading of dental implants. Clinical outcomes of RCTs examining these various loading protocols were explored in an effort to determine which may have the most evidence in support of its use.

Study Question/PICO Strategy

The study question asks which loading protocol for dental implants results in the least marginal bone loss and highest survival rate in patients who require at least one implant: Immediate loading (with restoration within one week following insertion), Early loading (with restoration between four to eight weeks), or Conventional / Delayed loading (with restoration after 12 weeks)? The Population involves patients who need at least one implant, while the Intervention is immediate loading. It is compared to both early and conventional loading, while the outcomes of interest include marginal bone loss (primary) and survival rate (secondary).

Eligibility Criteria

There are certain eligibility criteria for which studies were chosen for inclusion in the systematic literature review. Inclusion criteria specified that all studies must be randomized controlled trials (RCTs). These studies may include split mouth studies, studies on human subjects, studies on dental implants, as well as studies with single crowns or fixed partial prosthesis. All clinical studies had to have enrolled at least 10 participants / patients. Additionally, they all had to explore quantitative outcomes, specifically marginal bone loss and survival rate. Any studies published between 2002 and 2022 that met these criteria were included. Additionally, all studies were written in English and were peer reviewed.

There were also exclusion criteria, with certain studies not being included in the systematic literature review. These included animal studies along with studies focusing on removable prosthetic, full arch prosthetic, palatal implants, and/or zygomatic implants. Additionally, both case reports and case series were excluded, as well as any studies that used a qualitative or mixed method (qualitative plus quantitative) research design.

Search Strategy

A Medline (PubMed) search was performed on 4 November 2022 for studies published in dental journals within the last 20 years, or from November 2002 to November 2022. The search was limited to English language publications (Table x). The search terms and key words used were Dent*, Impl*, Immediate, Loading, Early, and Conventional. The following search terms were grouped to the subjects (Filters: humans, RCT) and linked with the Boolean operator “AND”:

• dent* AND impl* AND failure AND early loading AND fixed (n=22)

• dent* AND Impl* AND immediate AND loading AND conventional (n=89)

• dent* AND Impl* AND immediate AND loading AND early (n=88)

• dent* AND Impl* AND immediate loading (n=388)

This electronic search was complemented by manual searching of the bibliographies and/or references of the most recent systematic reviews and of all included publications.

Study Selection and Data Selection Process

All obtained titles and abstracts were checked for inclusion by one independent reviewer. For all included publications, a full text article was acquired and selected for independent assessment by the reviewer. In case the information in the title and abstract was insufficient for inclusion or exclusion, the full-text articles were also obtained.

Types of Outcome Measures

The primary outcome was marginal bone loss, while the secondary outcome was survival rate. A data extraction sheet (Excel Table) was used to extract the relevant data from the included publications (see Master Table). The following criteria were recorded:

- Author
- Year of Publication
- Title of Study
- Title of Journal
- Type of Study Design
- Presence of Control / Comparison Group
- Follow-up Time (in months)
- Mean Age of Participants
- Total Number of Participants
- Total Number of Implants
- Implant System
- Implant Diameter
- Implant Length
- IL Total Number of Implants
- IL Number of Participants
- CL Total Number of Implants
- CL Number of Participants
- EL Total Number of Implants
- EL Number of Participants
- Number of Implants Posterior
- Number of Implants Anterior
- Number of Implants Maxilla
- Number of Implants Mandible
- Flap / Flapless
- Presence of Augmentation
- Number of Prosthetics
- Type of Prosthetics
- Number of Failures
- MBL IL (mm)
- MBL EL (mm)
- MBL CL (mm)
- Survival Rate IL
- Survival Rate EL
- Survival Rate CL
- Type of Assessment

Quality and Risk of Bias Assessment in individual Studies

The Critical Appraisal Skills Programme (CASP) checklist for RCTs was used to evaluate the quality of the individual studies. It includes four sections: a) basic study design valid for a RCT, b) methodologically sound study, c) results, and d) results applicable locally (CASP, 2020). There are 11 questions in total. First, under the section evaluating the design of the study (A), the checklist asked the following three questions: a) Did it address a clearly focused research question, b) was participant assignment randomised to the interventions, and c) did all participants enrolled in the study stay until its completion (CASP, 2020).

For the second section that determines the methodological soundness of the study (B), the checklist asked if the participants were blind to the intervention, if the researchers were blind to what they were giving participants, and if those evaluating the outcomes were also blinded (CASP, 2020). This section also asked if the study groups were similar at the beginning of the RCT as well as if each study group received the same care level (besides the experimental intervention) (CASP, 2020).

For the third section exploring the results of the study(C),

three questions were asked: a) were the intervention effects comprehensively reported, b) was the precision of the estimate of the intervention effect reported, and c) do the benefits of the intervention outweigh any costs / harms (CASP, 2020). Finally, for the fourth section, the checklist asks if the results can be applied to the local population (CASP, 2020).

Data Analysis/Statistical Methods

Marginal bone loss was the primary outcome evaluated, while survival rate of the implant was the secondary outcome. A descriptive analysis was performed on the studies, specifically the data extracted (See Master Table).

Authors name (Year)	Year of Publication	Title	Journal	Study Design	Control group (Yes/No)	Follow up (months)	Mean age	Total no. Patients	Total no. Implants	Implant system	Implant Diameter	Implant length
Meloni et al	2018	Immediate non-occlusal vs delayed loading of mandibular first molars.	Eur J Oral implantol.	RCT Split-mouth	Yes	60	48	20	40	Nobel Replaced Tapered Groovy (Nobel Bio care)	4.3 5.0	8.0 10.0
Romanos et al	2015	Immediate Vs. Delayed loading in the posterior mandible	Clin Oral Impl Res.	RCT Split mouth	Yes	180	50.75±7.95	10	60	Ankylos	3,5 4,5	9.5 11
Kokovic et al	2012	Immediate Vs. Early loading of SLA implants in posterior mandible	Clin Oral Impl Res.	RCT Split-mouth	Yes	60	49	12	72	Straumann SLA surface	4,10	8 10
Fadi Daher et al	2019	Immediate Vs. Conventional loading of variable tapered implants supporting 3-4 unit FPD in the posterior maxilla	Int. J Oral implantol.	RCT Split-mouth	Yes	36	49.2±9.7	24	160	Nobel biocare	3.5 4.3 5.0	10 11.5 13 15
Cannizzaro et al	2012	Immediate Vs. Early loading of 6.6 mm flapless implants	Eur J Oral implantol.	RCT Split-mouth	Yes	48	35	30	60	NanoTite External hex Biomet 3i	4.0 5.0 6.0	06:50
Baris Guncu et al	2008	In-patient comparision of Immediate and conventional loaded implants in mandibular molar sites	Clin Oral Impl Res.	RCT Split-mouth	Yes	12	41,09±8,46	12	24	Nobel Biocare	4	11,5
Van de Velde et al	2010	The clinical and radiographic outcome of the implantsplaced in the posterior maxilla with a guided flapless approach and immediately restored with a provisional rehabilitation	Clin Oral Impl Res.	RCT Split-mouth	Yes	18	55,7	13	70	Straumann SLA TE	4,1 4,8	8 10 12
Zembic et al	2010	Immediate Vs Early loading of dental implants	Clin Oral Impl Res.	RCT Split-mouth	Yes	36	54,8	11	51	Nobel Biocare	4	7 8,5 10 11,5 13 15

Table 1 Master Table Part A

IL Total no. Implants	IL No. of patients	CL Total no. Implants	CL No. of patients	EL Total no. Implants	EL No. of patients	No. Implants posterior	No. Implants anterior	No. Implants in Maxilla	No. Implants in Mandible	Flap/Flapless	Augmentation (Yes/No)	No. of prosthetics	Type of prosthetics	No. of failures
20	20	20	20	0	0	40	0	0	40	Flap	No	40	Single crown	0
30	10	30	10	0	0	60	0	0	60	Flap	No	NR	Fixed bridge on 3 implants	0
36	12	0	0	36	12	72	0	0	72	Flap	No	72	Fixed	0
80	24	80	24	0	0	160	0	160	0	Flap	No	NR	Fixed bridge	7
29	NR	0	0	31	NR	53	7	33	NR	Flapless (13 flaps had to be raised)	for immediately placed implants (9 implants) bio-oss	60	Single crown	2
12	12	12	12	0	0	24	0	0	24	Flap	No	24	Metal-Ceramic Crowns	1
36	NR	0	0	34	13	70	0	70	0	36 Flapless 34 Flap	17 in IL 17 in EL	24	3-4 unit FPD	1
22	11	0	0	22	11	51	0	0	51	Flap	In 31 implants	NR	Fixed Bridge	3

Table 2 Master Table Part B

MBL IL mm	SD MBL IL mm	MBL EL mm	SD MBL EL mm	MBL CL mm	SD MBL CL mm	Survival rate IL	Survival rate EL	Survival rate CL	Type of assessment (Radiographic, Histologic etc.)
0.62	0.45	NA		0,69	0,33	100%		100%	Radiographic (Parallel technique)
3,12		NA		3,78		100%		100%	Radiographic (Panoramic) Clinical : PI,PPD,SBI,KG,Rec,PV
0.4	0.24	0.8	00:19	NA		100%	100%		Radiographic mBI (Modified bleeding index) , mPI (Modified plaque index) RFA (Implant stability)
0,42	0,45	NA		00:46	0,30				Radiographic
0.37	0.35	00:31	0,36	NA		93.3%	93.3%		Radiographic Binomial test (assessing patients preference)
0.45	0,35	NA		0,68	0,3	91,70%	NA	100%	Rdiographic (Long cone Parallel tec.) RFA (Resonance frequency analysis) PI (plaque index) GI (Gingival Index) PD (probing Depth GBTI (Gingival bleeding time Index)
1.0	0.58	0,77	00:39			97,30%	100%	NA	Radiographic (Long cone parallel tec.) Plaue score Bleeding score Probing Debth
1.51	0.79	0,89	0,07	NA		85%	100%		Radiographic ISQ

Table 3 Master Table Part C

Results

Study Selection

The search strategy yielded in a total of 587 articles by four different keyword searches conducted on PubMed. The search included all articles published between 2002-2022 and written in the English language. There were no articles identified through other sources.

The title and abstracts of all the articles identified by the search, were screened by the reviewer. There were 109 related articles identified, 55 of which were duplicates. This left 54 full text articles that were screened, with 40 of them excluded. Hence, 14 full-text articles were assessed for eligibility, with six excluded for reasons. Specifically, only RCTs and SPLIT MOUTH studies were chosen to be included in the systematic literature review. Therefore, there was a total of eight articles chosen for inclusion and integrated into the master table. See Figure 1 for PRISMA diagram.

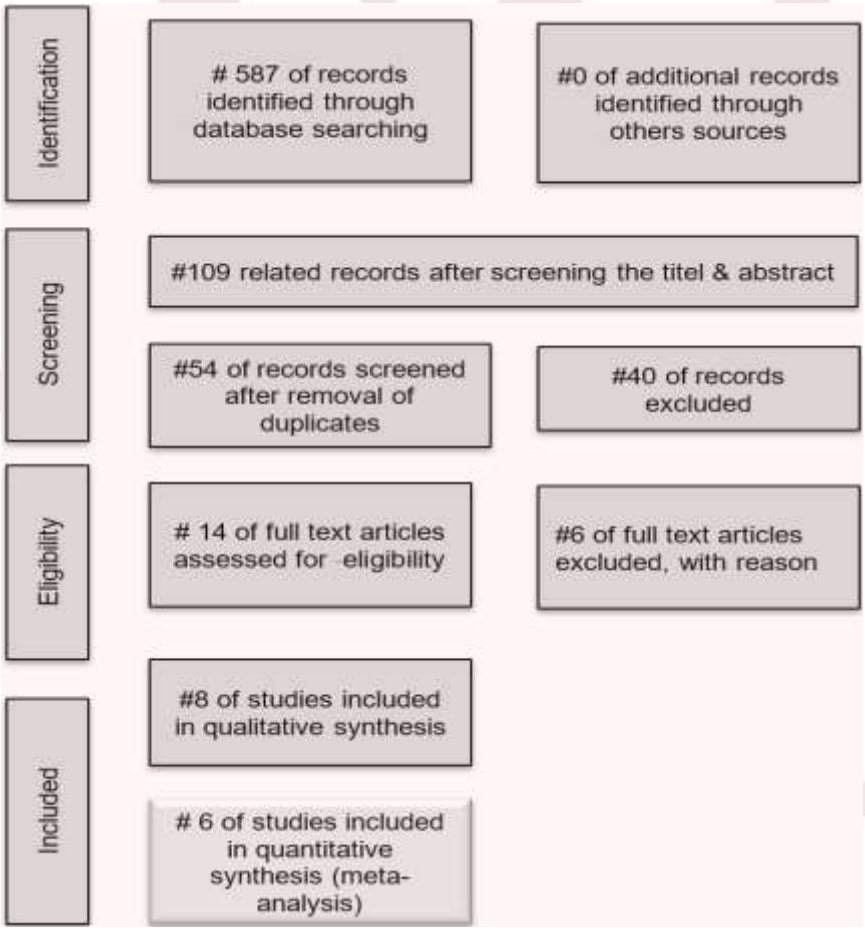

Figure 2. Flow Chart Diagram

Study Range and Characteristics

In the eight chosen peer-reviewed articles (Table), all of them were RCTs with a Split Mouth design, meaning that they all included a control group. The articles were published between 2008 and 2019. Additionally, there was a total of 132 patients (known as participants), with the average or mean age of the participants being 47.69 years. Out of these eight articles, there was 537 total implants, four of which used the Nobel Biocare or the Nobel Replaced Tapered Groovy. The other half of the articles used other implant systems, with two studies employing the Straumann SLA surface. One article used the NanoTite External hex Biomet 3i implant system, while the last article used the Ankylos® implant system.

As for immediate loading (IL), there was a total of 102 participants who received this loading protocol, accounting for 265 implants. There was a 95.3% survival rate for IL, with an average marginal bone loss (MBL) of 0.98 mm. For conventional loading (CL), there was a total of 66 participants who received this loading protocol, with 142 total implants and a 100% survival rate. Additionally, the average MBL was 1.4 mm. There was a total of 36 participants who received the early loading (EL) protocol. This comprised of 123 implants, while the EL protocol had a 98.3% survival rate with an average MBL of 0.69 mm.

Finally, as for where the implants were located, there was a total of 530 posterior implants and seven anterior implants. There were also 263 implants in the maxilla, while 247 implants were placed in the mandible. Overall, there were only 14 failures.

Meloni et al (2018)

In the article by Meloni et al. (2018), 20 participants received 40 implants, with one molar restored using immediate loading and the contralateral molar restored using conventional / delayed loading. For the immediate loading group, after implanting the molar, a non-occlusal temporary crown was placed within 24 hours, as opposed to the delayed loading group, which received a definitive crown four to five months later (Meloni et al., 2018). Outcome measures that were focused on included implant failure, complications, radiographic marginal bone level changes, probing pocket depths (PPDs), and bleeding on probing (BOP), with clinical data gathered at four different time intervals: a) implant placement, b) six month follow up, c) 12 month follow up, and d) 60 month follow up (Meloni et al., 2018).

The results showed there to be no implant failures, while there were only six minor complications, including two provisional acrylic crown fractures in the immediate loading group and four ceramic chipping in the conventional loading group (Meloni et al., 2018). Additionally, two patients experienced BOP along with bilateral peri- implant mucosal inflammation at the six-month follow-up (Meloni et al., 2018). However, the groups did not show statistically significant differences (OR = 0.500; 95% CI: 0.045 to 3.489; P = 0.6831) (Meloni et al., 2018).

The immediate loading group had an average marginal bone level of 0.83 ± 0.16 mm (95% CI: 0.75 to 0.91) at one-year follow-up, while the conventional loading group was 0.86 ± 0.16 mm (95% CI: 0.78 to 0.94) (Meloni et al., 2018). Again, these differences between the two groups are not statistically significant (difference = 0.03 ± 0.15 mm; 95% CI: -0.07 to 0.07; P = 0.53) (Meloni et al., 2018). As for the five-year follow-up, the immediate loading group's average marginal bone level was 1.06 ± 0.38 mm (95% CI: 0.97 to 1.15), while it was 1.07 ± 0.32 mm (95% CI: 0.95 to 1.16) for the conventional loading group (Meloni et al., 2018). These differences were not statistically significant (difference = 0.01 ± 0.22 mm; 95% CI: -0.10 to 0.10; P = 0.96) (Meloni et al., 2018).

Additionally, at this five-year follow-up, the average

marginal bone loss (MBL) was 0.62 ± 0.45 mm for the immediate loading group, while the conventional loading group was 0.69 ± 0.33 mm, which is not statistically significant (difference = 0.07 ± 0.32 mm; 95% CI: -0.10 to 0.18; P = 0.567) (Meloni et al., 2018). At this time period, the average PPD for the immediate loading group was 2.82 ± 0.65 mm, while it was 2.85 ± 0.53 mm for the conventional loading group (difference = 0.03 ± 0.15 mm; 95% CI: -0.15 to 0.21; P = 0.990) (Meloni et al., 2018). The immediate loading group's average BOP was 1.17 ± 0.92 compared to 1.17 ± 0.86 in the conventional loading group (difference = 0.01 ± 0.07; 95% CI: -0.06 to 0.08; P = 1.000) (Meloni et al., 2018). Again, both PPD and BOP values were not different to a statistically significant degree between these two groups (Meloni et al., 2018).

Romanos et al. (2016)

In the second article by Romanos et al. (2016), the researchers also compared immediate vs. delayed (or conventional) loading protocols in a split-mouth study. Each participant had one side of their jaw randomly chosen as the control group, which received three implants through platform switching (Romanos et al., 2016). Three months later, resin-splinted crows were occlusally loaded, being replaced six weeks later with final prostheses (Romanos et al., 2016). In the experimental group, three additional implants were placed on the contralateral side in symmetrical locations for each participant (Romanos et al., 2016). However, these implants were immediately loaded (Romanos et al., 2016). Outcome measures included both bone loss and periodontal indexes (Romanos et al., 2016).

The findings of this study showed that there were no statistically significant differences (P > 0.05) between immediate loading and conventional (delayed) loading (Romanos et al., 2016). The follow-up was an average of 12 years (Romanos et al., 2016). Specifically, the immediate loading group had an average crestal bone loss of 0.70 ±1.09 mm compared to the conventional loading group's 1.17 ±1.27 mm (Romanos et al., 2016). Additionally, the average distal bone loss for the immediate loading group was 0.43 ±1.02 mm, while it was 1.06 ±1.33 mm in the conventional loading group (Romanos et al., 2016). These findings are statistically insignificant between the test and control groups (P > 0.05) (Romanos et al., 2016). Overall, the immediate loading group's maximum crestal bone loss was 3.12 mm compared to 3.78 mm for the conventional / delayed loading group (Romanos et al., 2016). In fact, this means that the immediate loading group and delayed loading group showed no significant difference in bone loss. However, the immediate loaded implants showed significantly higher implant stability ($p<0.05$) (Romanos et al.,2016)

Daher et al. (2019)

In the article by Daher et al. (2019), the researchers compared the three-year outcomes between posterior maxilla implants that were loaded with immediate loading protocols compared to conventional loaded protocols. There were 26 participants enrolled in the study, all of which received three or four implants (Daher et al., 2019). One on side of the mouth, implants were immediately loaded, while implants on the contralateral side were restored three to three-and-a-half months later (Daher et al., 2019). The outcomes measured included both prosthesis and implant failure rates along with complications and peri-implant bone level changes (Daher et al., 2019).

The findings from this study were based on 24 participants, as two dropped out (Daher et al., 2019). In one participant, four implants that were immediately loaded failed at three-months follow-up, while the same participant also had three of their contralateral implants – which were loaded conventionally – fail 14 months later (Daher et al., 2019). Nonetheless, for the other 23 participants, the differences between the immediate

loading and conventional loading groups were not statistically significant in terms of failure (difference = 0%; 95% CI 0.0% to 14.2%; P = 0.999) (Daher et al., 2019).

There were complications noted in both groups as well at the three-year follow-up. For example, one participant was diagnosed with peri-implantitis at two adjacent implants that were conventionally loaded (Daher et al., 2019). Additionally, there were four minor complications with prosthetics in the immediate loading protocol group, while there was also one minor ceramic failure in each of the two groups (Daher et al., 2019). Hence, there were no statistically significant differences in terms of complication rates between the immediate and conventional groups (difference = 13%; 95% CI 3.4% to 27.7%; P = 0.453) (Daher et al., 2019).

In 23 participants, implants were examined for peri-implant marginal bone level changes, including 77 in the immediate loading protocol group and 76 in the conventional loading protocol group (Daher et al., 2019). In the immediate loading group, the average MBL was 0.79 ± 0.62 mm compared to 0.91 ± 0.82 mm in the conventional loading group (Daher et al., 2019). These differences were again not statistically significant (difference = 0.12 mm; 95% CI -0.31 to 0.55 mm; P = 0.590) (Daher et al., 2019).

Güncü et al. (2008)

In the article by Güncü et al. (2008), the clinical outcomes associated with immediate loading and conventional loading for mandibular molar implants were compared. Enrolling 12 participants, 24 dental implants were placed, with one side being immediately loaded while the contralateral side was conventionally loaded (Güncü et al., 2008). The researchers followed up with participants over a period of one year, evaluating outcomes such as implant stability and marginal bone levels (Güncü et al., 2008).

The results of the study showed that there was only one implant lost, which occurred in the immediate loading group (Güncü et al., 2008). At the time or surgery, the immediate loading group's implant stability quotient values were 74.18 +/- 5.72 as compared to the conventional loading group's 75.18 +/- 3.51 (Güncü et al., 2008). Additionally, at one-year follow-up, the values were 75.36 +/- 5.88 for the immediate group and 75.64 +/- 4.84 for the conventional group (Güncü et al., 2008). These differences between the two groups were not statistically significant (P>0.05) (Güncü et al., 2008). Finally, implants in both groups had 1 mm or less of marginal bone resorption at this follow-up one year later (Güncü et al., 2008).

Van de Velde et al. (2010)

In the article by Van de Velde et al. (2010), the researchers compared dental implant outcomes using both immediate loading and early loading protocols. There were 14 participants enrolled in the study, with implants on one side of the mouth placed using the immediate loading protocol (experimental group), while implants on the contralateral side were placed according to the early loading protocol (control group). six weeks later (Van de Velde et al., 2010). There were several time periods were clinical outcomes such as survival rate and marginal bone levels were measured: a) surgery time, b) one-week follow-up, c) six-week follow-up, d) three-months follow- up, e) six-months follow-up, f) 12-months follow-up, and g) 18-months follow-up (Van de Velde et al., 2010).

The results showed that out of the 70 implants placed – 36 in the immediate loading group and 34 in the early loading group – only one implant was lost (Van de Velde et al., 2010). Hence, the survival rate was 97.3% in the immediate group, while it was 100% in the early group, which is not statistically significant (Van de Velde et al., 2010). Additionally, at follow-up, there were no statistically significant differences in marginal bone levels

between the two groups (Van de Velde et al., 2010). However, it should be noted that baseline marginal bone level changes were much higher during baseline ($P < 0.05$) (Van de Velde et al., 2010). In the immediate loading group, the average bone level was 1.95 mm ± 0.70 compared to 1.93 mm ± 0.42 in the early loading group at 18-months follow-up, which was also not statistically significant (Van de Velde et al., 2010).

Kokovic et al. (2014)

In the article by Kokovic et al. (2014), the researchers compared the clinical outcomes between immediate loading and early loading protocols used for posterior mandible implants. A total of 12 participants were recruited for this study, with each side of their mouth randomly assigned to either the immediate loading protocol (experimental group) or the early loading protocol (control group) (Kokovic et al., 2014). Immediate loading implants were placed on the surgery day, while early loading implants were placed six weeks after (Kokovic et al., 2014). Several clinical outcomes were measured, including bleeding index, modified plaque, bone resorption, and implant stability (Kokovic et al., 2014). Implant stability was evaluated on the day or surgery (i.e., baseline) along with six-weeks, 12-weeks, and one-year later, while the other outcomes were measured at one- and five-years follow-up (Kokovic et al., 2014).

The results of this study indicated a 100% survival rate for both immediate and early loading groups, with an average implant stability value of 76.92 ± 0.79 implant stability quotient (ISQ) (Kokovic et al., 2014). In the immediate loading protocol group, ISQ values showed a statistically significant increase during the first six weeks, going from 77.92 ± 1.16 at the surgery day to 79.61 ± 0.90 (Kokovic et al., 2014). Similarly, the increase in ISQ in the early loading protocol group was also statistically significant, rising from 7.92 ± 1.05 to 77.55 ± 0.99 (Kokovic et al., 2014). However, these findings do not indicate statistical significance in regard to the differences between the two loading groups ($P > 0.05$) (Kokovic et al., 2014).

Similarly, there were no statistically significant differences after five years in terms of the other clinical outcomes (Kokovic et al., 2014). Specifically, the immediate loading group had an average crestal bone loss of 0.4 ± 0.24 compared to the early loading group's 0.8 ± 0.15 mm, while the average bleeding index was 0.22 ± 0.11 in the immediate group in comparison to 0.25 ± 0.11 for the early group (Kokovic et al., 2014). Finally, the average plaque index was 0.17 ± 0.15 for the immediate group, while it was 0.19 ± 0.20 for the early group (Kokovic et al., 2014).

Cannizzaro et al. (2018)

In the article by Cannizzaro et al. (2018), 30 participants were enrolled to receive two single implants, with each side of the mouth randomly assigned to either the immediate loading protocol or the early loading protocol. Follow-up occurred for a period of nine years, with clinical outcomes such as implant failures, complications, and peri-implant marginal bone level changes measured (Cannizzaro et al., 2018). Overall, there were 29 implants loaded using the immediate protocol, while 31 were loaded early (Cannizzaro et al., 2018).

The results showed that after two months following loading, each group had one implant failure (Cannizzaro et al., 2018). Additionally, each group also had six participants who demonstrated complications (difference of proportions = 0.00; 95% CI -0.20 to 0.20, $P = 1.000$), so there were no statistically significant differences between the groups in terms of this clinical outcome (Cannizzaro et al., 2018).

Similarly, in the immediate loading protocol group, the average peri-implant bone loss was 0.60 mm as compared

to the early loading protocol group, which experienced a bone loss of 0.46 mm on average (Cannizzaro et al., 2018). Again, these findings were not statistically significant (mean difference = 0.14 mm, 95% CI -0.13 to 0.41, P = 0.283) (Cannizzaro et al., 2018).

Zembić et al. (2010)

Finally, Zembić et al. (2010) compared survival rates of implants between an immediate loading protocol group and an early loading protocol group. There was a total of 11 participants recruited for the study, with those in the immediate protocol (experimental) group receiving provisional implants on surgery day, while those in the early protocol (control) group received implants six weeks later (Zembić et al., 2010). Clinical outcomes that were measured included ISQ, plaque, and prosthesis stability at both one- and three-years follow-up (Zembić et al., 2010).

The findings of this study showed that there was a much lower survival rate of implants in the immediate loading group, as three implants were lost in two participants, leading to an 85% survival rate (Zembić et al., 2010). In comparison, the early loading group did not lose any implants, indicating a 100% survival rate (Zembić et al., 2010). These differences are statistically significant. Additionally, in the immediate loading group, the average marginal bone level at baseline was 0.36 +/-0.5 mm, which is much higher compared to the 1.08 +/- 0.37 mm average level in the early loading group (Zembić et al., 2010).

Similarly, between the surgery date (i.e., baseline) and three-years follow-up, both groups had reduced average bone levels, with the immediate loading group measured at 1.51 +/- 0.79 mm compared to the early loading group's 0.89 +/- 0.94 mm (Zembić et al., 2010). There was a significant difference regarding the bone level at the baseline between the test and control group. The value for the test implants was higher (P=0.0017). The study did not show a significant difference in bone loss between the two groups in three years, even though the immediate loaded implants showed significantly high marginal bone resorption from the baseline to one and three years, due to deeper insertion depth of the implants.

As for ISQ, however, the differences between the groups were not significant, with the immediate loading group having a 63.59 +/- 4.62 mm ISQ at baseline compared to 65.35 +/- 7.43 mm in the early loading group (Zembić et al., 2010). At three years, the ISQ for the immediate group was 66.47 +/- 7.47 mm in comparison to the early group, which had an ISQ of 68.80 +/- 8.75 mm (Zembić et al., 2010).

Data Extraction: Qualitative Synthesis

A qualitative synthesis was conducted, using the CASP checklist for the RCTs, to critically appraise the quality of the including studies.

Results of CASP checklist assessment are reported as following:

Article no. 1 (Meloni et al. 2018)

Section A:

Meloni et al. 2018 Question 1:

This question is asking if the PICO strategy is clear in this study. This study was designed to assess the outcomes of immediate non-occlusal loading protocol on the dental implants. The population is the patients who are missing bilaterally first molar. The intervention is immediate loading of the dental implant. The comparison (comparator) is delayed (conventional) loading of the implants. The outcome measures were implant survival rate, complications, peri-implant marginal bone level

changes, PPD and BOP.

The answer to question 1. in the checklist can confidently be checked as YES.

Meloni et al. 2018 Question 2:

This question is about the randomization of the participants. In this study the assignment of the participants to the interventions was completely randomized by computer software and the codes were packed in opaque envelopes by independent operators. The envelopes containing the randomization codes to assign the delayed or immediate site were only opened at the time of surgery by a blinded independent doctor. This made randomization very sufficient to eliminate the systematic bias.

The answer to question 2. Is YES.

Meloni et al. 2018 Question 3:

Is about whether all the participants continued to take part in the study in the assigned groups until the end. There were no dropouts and all the 20 participants continued follow-ups to 5 years, which was the intended follow-up period for this study.

The answer to this question is YES.

Section B:

Meloni et al. 2018 Question 4:

a) Since the patients could see that the implants of one side are loaded and the implants on the other side are not, it was not possible to 'blind' the patients blind to the intervention they were given.

The answer to this part is NO.

b) Since the prosthetic and surgical procedures were done by the same oral surgeon, but it is not mentioned is the surgeon has been blinded to the intervention. The answer to this part is NO. c) All the results were assessed by blinded independent operators.

The answer is checked as YES.

Meloni et al. 2018 Question 5:

a) Since this was a split-mouth study, and the number of the implant in each group was the same in all the patients, there was no difference between the baseline characteristics of the two study groups.

The answer to this part is NO.

b) Since all the implants were in region first mandibular molar, and the test and control were in the same patient, there was no differences that could change the outcomes.

The answer to this part is NO.

Meloni et al. 2018 Question 6:

All the participants were given the same clinical, surgical, and prosthetic procedure and were treated by the same oral surgeon. The follow-ups were done for all the patients on 6,12, and 60 months.

The answer to this question is YES.

Section C:

Meloni et al. 2018 Question 7:

This question is about the level of comprehension of the effects of intervention. According to the article, a power calculation was not performed to determine a minimal sample size, since this study was meant preliminary to be a large clinical trial (Meloni et al.,2018). Nevertheless, all the outcomes were measured and clearly specified. The only binary outcome was the survival rate which was 100% for the both study groups. The results were precisely described, but only for the first and the last follow-ups (6 and 60 months). The main limitation of the study is that no power calculation was performed, despite of the small sample size, which can be the resulted in some differences between groups has been hidden. Paired t test and McNamar's test with odds ratio (OR) were performed to detect any differences. Statistical significance was reported at 0.05 probability level.

The answer to this question in summarize is YES.

Meloni et al. 2018 Question 8:

All the measurements were reported with the confidence interval of 95%.

The answer to this question is YES.

Meloni et al. 2018 Question 9:

Since the study did not result in a significant difference in outcomes of the two study groups, the size of the intervention effect was not big. There was no cost-effectiveness analysis performed. However, the intervention (immediate loading of the implants) can be beneficial to the population in many ways and could minimize the number of the surgeries and subsequently the costs for the cost of the treatment for the patients. The answer to this question is YES.

Section D:

Meloni et al. 2018 Question 10:

All in all, the results of this study can be implemented and used in every practice and in every country.

The answer is YES.

Meloni et al. 2018 Question 11:

The immediate loading of the implants could be beneficial in several different aspects both for the patients and the clinicians.

The answer is YES.

To summarize, the current study is assessed as a high ranked study, as it is positive regarding all the standards of the CASP checklist of RCTs.

Article no. 2 (Romanos et al. 2015)

Section A:

Romanos et al. 2015 Question 1:

This split-mouth prospective study was designed to assess the clinical and radiographic outcomes of the immediately loaded implants. The population was consisting of patients who were bilaterally edentulous in the mandible, distally to canine region. The intervention was the immediate loading of the implants, and the comparator was the conventional (delayed) loading of the implants. The outcome measures were clinical (survival rate and periodontal parameters) and radiological outcomes (marginal bone level changes).

The answer is YES.

Romanos et al. 2015 Question 2:

There is no report of randomization methods or sufficiency of them in this study.

The answer is NO.

Romanos et al. 2015 Question 3:

There were 12 patients initially enrolled in the study. After two years there were two dropouts. Therefore, the Final evaluations and analysis is done on the 10 patients. The study was able to be continued for the follow-ups to 15 years as it was planned.

The answer to this question is YES.

Section B:

Romanos et al. 2015 Question 4:

As the study before, the patients could not have been blinded to the intervention, and it is not reported if the surgeon was blinded to the intervention. But all the analysis was performed by blinded operators, unaware of which group the patient belonged to.

Therefor the answers to these parts are consequently NO, NO, YES.

Romanos et al. 2015 Question 5:

The split-mouth design of the study minimizes the risk of biological and other baseline differences between the two study groups.

The answer to this question is YES.

Romanos et al. 2015 Question 6:

The study protocol was clearly defined and reported in the article, and both study groups received the same level of treatment. The follow-up intervals were identical for both study groups. The answer to this question is YES.

Section C:

Romanos et al. 2015 Question 7:

There is not mentioned in the article if a power calculation was performed prior to the study. The outcome measures were only reported for the last follow-up. The data related to mean marginal bone level changes and standard deviation was not reported at all, which leaves an important part of data missing. There is only report of mesial, distal, and maximal marginal bone loss and only in the last follow-up. Since the final data analysis and evaluations are only done on the 10 patients, the dropouts could not affect the results. However, the anatomical limitations in the posterior mandible can be a reason for limiting the possibility of use of longer implants with higher diameter. Moreover, the higher occlusal loads in the posterior mandible can result in higher risk of failure. The R-Pack- age nparLD software (http://www.jstatsoft. org/v50/i12/) was used for this statistical evaluation. The significance level was set as $P<0.05$. In the end there are some missing important data in the result report, which makes it difficult to decide if the results have been reported comprehensively.

Romanos et al. 2015 Question 8:

The confidence interval is not reported for any of the measurements.

The answer is NO.

Romanos et al. 2015 Question 9:

The size of the intervention effect was only significant in the case of clinical implant stability, which was much higher in the implants treated with the immediate loading protocol. There was no cost-effectiveness analysis reported in this study. The answer to this question is YES.

Section D:

Romanos et al. 2015 Question 10:

The results of this study show better clinical implant stability by applying the immediate loading protocol, and since the benefits of the immediate loading protocol can be to any patient regardless of their location in the world, it is possible to generalize and implement it in the practice of implantology in any global region.

The answer is YES.

Romanos et al. 2015 Question 11:

Performing the immediate loading of the implants in practicing implantology can improve the quality of life for the patients and result in much higher level of patient satisfaction in every practice.

The answer is YES.

To summarize, according to the CASP checklist for the RCTs this study does not attain the positive check regarding some sections. There is no data and report about the randomization in this study. There are missing data (not reported) for each follow- up and the mean marginal bone level and SD is not reported for none of the follow- ups, which leaves an unclear point for performing Meta-analysis in a literature review. Moreover, there is no confidence interval (CI) reported related to any of the measurements, which again leaves a question mark about the precision of the estimate of the intervention in the reported follow-up periods.

However, the result of this study is highly useful in the practice of implantology and is applicable in the daily implant dentistry practice.

Article no 3. (Daher et al., 2019)

Daher et al., 2019 Question 1:

This study was designed to assess the outcomes of the Immediately loaded implants. The population is the patients who were bilaterally edentulous in the posterior maxilla. The intervention was immediate loading. The comparator was conventional (delayed) loading. Then outcome measures were survival rate, complications, marginal bone level changes up to 3 years after the definitive prosthetic.

The answer could confidently be checked as YES.

Daher et al., 2019 Question 2:

The study is designed as a randomized study. A randomization list was programmed by one of the authors for the total of 20 patients prior to the clinical procedures, later there was generated a second list for the last six enrolled participants.

Randomization was to assignment to the left or right side of the maxilla. The free online randomizer (www.randomizer.org), was used to generate a random set of digits between one and twenty, and they were allocated to the first block of participants. The patients who were assigned to digits 1-10 were treated by the intervention order of immediate loading on the left side and delayed loading on the right side. The remaining participants who received digits between 11-20 received the intervention in a reversed order. The second block of 6 patients were allocated to a similar randomization.

But the 1:1 allocation ratio did not associated with the equal number of the Immediate and Conventionally loaded implants in every patient and among the patients, which can maximize the risk of bias resulted by the biological factors created by the lifestyle and sex.It is not mentioned in the article that whether the allocation

sequence were concealed from the investigators or the participants.

The answer to this question is YES.

Daher et al., 2019 Question 3:

Twenty-six patients were initially enrolled in the study, but there were two dropouts before the definitive prosthetic phase. Therefore, all the results were computed based on 24 patients (26 randomized patients minus the two dropouts). The analysis in this study is performed on a per-protocol and not an intention -to-treat basis. The participants continued the participation in the study for 3 years. The answer to this part is NO.

Section B:

Daher et al., 2019 Question 4:

The participants could not be blinded about the intervention given, but the surgeon was blinded to the intervention. A blinded assessor who did not participated in the surgical or prosthetic procedure served as the rater.

The answer to this part is NO, YES, YES.

Daher et al., 2019 Question 5:

There were no differences between the two groups in baseline, except for the implant length. The answer is YES.

Daher et al., 2019 Question 6:

The study protocol is explained in the article. There was no difference between the level of care between the two study groups, and the follow-up interval for both Immediate loading and the conventional loading group was the same. The answer to this part is YES.

Daher et al., 2019 Question 7:

A power calculation was done prior to the study to determine the sample size. The outcome measures were implant and prosthetic failure rate, complications, and marginal bone level changes. This study is reported according to consolidated Standards of Reporting Trials (Consort 2010). All the outcome measures are reported on 1- and 3-years follow-ups. Both study groups had the same intervals for the follow-ups. There were two patients who dropped out, prior to the definitive restoration. These two patients were excluded from the result of the study. Since this was a split-mouth study, the exclusion of the dropouts cannot affect the result of the study. 7 implants were lost In one patient. This patient was excluded from the 1 and 3 years analysis of the marginal bone level changes. In 3 years, analysis for the implant and prosthetic failure and the marginal bone level changes, there was one patient excluded because of sudden death.

Chi-square test was used for the power analysis, Mc Namar's test was used to compare the dichotomous (Binary) outcomes. For comparing the contentious outcome (MBL), paired t test was used. The distal MBL was not measurable in two implants in two patients. The mesial MBL was accounted in these two patients. All the P-values were reported precisely for the related measurements.

The answer to this question will be YES.

Daher et al., 2019 Question 8:

The confidence interval (CI) of 95% was reported for all the measurements.

Ther answer to this question is YES.

Daher et al., 2019 Question 9:

The result of this study outweighs the harms. It helps the dentists/surgeons to decide about which implant loading protocol they chose for their patients in order to have the best long-term treatment prognosis. The answer is YES.

Section D:

Daher et al., 2019 Question 10:

The result of this study could be generalized to the daily practice in any locations in the world. The answer is YES.

Daher et al., 2019 Question 11:

Since the result of this study shows the comparable outcomes between immediate loaded and conventional loaded implants, it introduces the use of immediate loading protocol in implant dentistry, which can result in the shorter treatment period and higher patient satisfaction.

The answer is YES.

In summarize this study have been keeping the standards of a highly evidenced RCT, with minimized risk of the bias and high confidence in the reported data. Therefor it is assumed that this study can be used to change the intervention of loading of the dental implants in practicing dentistry / implantology.

Article no 4. (Güncü et al., 2008)

Section A:

Güncü et al., 2008 Question 1:

In this study population is described as the patients who have lost mandibular first molars bilaterally. The intervention is immediate loading of the dental implants and the comparator is delayed (conventional) loading. The implant stability, MBL changes and the peri-implant parameters.

The answer is YES.

Güncü et al., 2008 Question 2:

The randomization of the IL and CL side was performed by coin toss. The risk of systematic bias is minimized because of the split-mouth design. The randomization of the IL and CL side was performed after the placement of the implants.

The answer is YES.

Güncü et al., 2008 Question 3:

There was no dropouts and all the participants continued to participate in the study for the indented period (12 months).

The answer is YES.

Section B:

Güncü et al., 2008 Question 4:

It is not mentioned if the participants were blind to the treatment they were taking, but again since the study was split-mouth, the participants could see which side was immediately loaded and which side not. The surgeon was blind to the intervention and the randomization was performed first after placement of the implants. It is not mentioned in the article whether the operators who analyzed the outcomes were blinded to the intervention.

The answer is NO, YES, can’t tell

Güncü et al., 2008 Question 5:

The split-mouth design of the study and the inclusion criteria allowed the similar baseline characteristics in both groups.

Answer is YES.

Güncü et al., 2008 Question 6:

The study protocol was clear and explained in detail to the patients before the operation. All the participants got the same level of treatment and were examined by the same type of tests. The follow up intervals were the same for both study groups.

The answer is YES.

Section C:

Güncü et al., 2008 Question 7:

There is not mentioned if a power analysis was performed. All the mentioned outcomes were measured. The implant stability and the peri-implant parameters were measured in the months 1, 3, 6, 9, 12 months, while the radiographic assessment for the MBL was done in months 6, 12. The outcome measures were reported for the follow-ups 6 and 12 months. The P-values were reported and the significance level was reported at $P<0.05$.

The answer is YES.

Güncü et al., 2008 Question 8:

The confidence intervals for the measurements were not reported. The answer is NO.

Güncü et al., 2008 Question 9:

The benefits of this study outweigh the harms and there is no significant cost needed for implementing the intervention.

The answer is YES.

Section D:

Güncü et al., 2008 Question 10:

The results of this study are applicable to the population of the world, regardless of the location. The answer is YES.

Güncü et al., 2008 Question 11:

The setting and the intervention in this study is generalizable to the routine clinical practice of implantology and can benefit the patients and the clinicians.

The answer is YES.

To summarize, although the present study didn't check a few boxes (power calculation, CI) in the checklist, but it is considered as a study of a good level of evidence.

Article no 5. (Van de Valde et al., 2010)

Section A:

Van de Valde et al., 2010 Question 1:

This study introduces the population as patients with bilaterally maxillary posterior edentulous areas. The intervention is immediate loading of the implants and

flapless placement of the implants. The comparator is early loading of the implants together with conventional implant placement protocol. The outcomes are marginal bone level changes and clinical peri-implant tissue changes and implant/prosthetic survival rate.

The answer is YES.

Van de Valde et al., 2010 Question 2:

The randomization of the test side (flapless and immediate loading) and control side (conventional and early loading) was done by use of the website Randomization.com, by an external investigator and just before the surgery.

The answer is YES.

Van de Valde et al., 2010 Question 3:

Out of 14 patients who were selected for the study, one female was excluded for the reason of needing bone augmentation during the surgery and one male was dead for a reason not related to the study. These two patients were not included in the statistical analysis and the rest of 12 participants continued the follow-ups till 18 months.

The answer is YES.

Section B:

Van de Valde et al., 2010 Question 4:

It is not mentioned if the participants were blind to the interventions, but the surgeon was blind to the intervention, since the randomization of the sides were done right before the surgery and after the surgeon had done the digital planning of the surgeries. It is not mentioned if the analysts of the results were blinded. The answer is Can't tell, YES, can't tell.

Van de Valde et al., 2010 Question 5:

It cannot be told from this study that the baseline characteristics have been completely similar in the two study groups, since the number of the implants are different in two groups and we cannot tell how many implants from every study group was placed in female or male participants. The patient did not receive the equal number of implants on each side. These factors can affect the results.

The answer is Can't tell.

Van de Valde et al., 2010 Question 6:

The study protocol is described in details in the article. All the participants were treated with the same protocols and the follow-ups were the same for the two groups.

The answer is YES.

Section C:

Van de Valde et al., 2010 Question 7:

A power calculation with power of 80% and significance level of 0.05 was done. All the outcomes were reported in 6 weeks, 3, 6, 12, and 18 months, and the p values were reported. Wilcoxon signed rank test was used. The patient who died was excluded from the study because of the missing data. However, the differences in the number and the sex and age of participants could be a possible source of bias.

The answer is YES.

Van de Valde et al., 2010 Question 8:

The confidence interval (CI) was not reported for any of the measurements.

Answer is NO.

Van de Valde et al., 2010Question 9:

The benefits of this study can outweigh the harms and the costs.

The answer is YES.

Section D:

Van de Valde et al., 2010 Question 10:

The results of the study can be applied in the population everywhere in the world regardless of the location. The answer is YES.

Van de Valde et al., 2010 Question 11:

This study provides greater value to the patients and the clinicians in the field of implantology.

The answer is YES.

In summary this study provides good level of evidence in the present subject, in order to be included in the systematic literature review

Article no 6. (Kokovic et al., 2014)

Section A:

Kokovic et al., 2014 Question 1:

The population in this study is described as patients with bilateral edentulous posterior mandible. The intervention is immediate loading of the implants, while the comparison is early loading. The outcome measures are MBL, peri-implant tissue changes, implant stability and survival rate.

The answer is YES.

Kokovic et al., 2014 Question 2:

The randomization was done by using a lot after the surgery for implant placement. The level of randomization was high and allocation sequence was concealed from investigators and participants.

The answer is YES.

Kokovic et al., 2014 Question 3:

There was no losses or dropouts, and all the participants continued the study for the intended period (5 years).

The answer is YES.

Section B:

Kokovic et al., 2014 Question 4:

The participants were blind to the intervention until after the surgery, which they could see on which side they have received the prosthetic. The surgeon was blinded to the intervention; however, it is not mentioned in the article if the results were measured by blinded operators.

The answer is NO, YES, can’t tell.

Kokovic et al., 2014 Question 5:

The baseline characteristics for the study groups were totally similar. The same number of implants was placed on each side of every patient. And even the different size of implants was being compared with the similar sizes.

The answer is YES.

Kokovic et al., 2014 Question 6:

The study protocol was well defined and described in the article, and both study groups received the same level of treatment, and the follow-up intervals were the same for the study groups.

The answer to this part is YES.

Section C:

Kokovic et al., 2014 Question 7:

The sample size was calculated by the statistical analysis. The MBL was measured in 1- and 5-years follow-ups, while the ISQ and the peri-implant parameters were measured in 6-, 12- and 52-weeks follow-ups. Wilcoxon signed rank test was used for the statistical analysis and the risk of bias was absolutely minimized. All the p values were reported.

The answer to this part is YES.

Kokovic et al., 2014 Question 8:

The confidence interval (CI) was not reported in this article.

The answer is NO.

Kokovic et al., 2014 Question 9:

The benefits of the study outweigh the harms and costs.

The answer is YES.

Section D:

Kokovic et al., 2014 Question 10:

The result of this study can be applied in the population everywhere globally.

The answer is YES.

Kokovic et al., 2014 Question 11:

This study can provide higher values to the patient and the clinicians in the field of implantology.

The answer is YES.

To summarize, this study is a highly ranked study according to the evaluation by the CASP checklist.

Article no 7. (Cannizzaro et al., 2012)

Cannizzaro et al., 2012 Question 1:

The population of this study was partially edentulous patients who required at least 2 single implants. The intervention was immediate loading, and the comparison was early loading.

The outcome measures were marginal bone loss, complications, survival rate and patient preference.

The answer is YES.

Cannizzaro et al., 2012 Question 2:

Randomization was done by codes 1 or 2 in the closed envelope. The sealed and opaque envelopes first were opened after the placement of both implants.

The answer is YES.

Cannizzaro et al., 2012 Question 3:

There were no dropouts and the data of all the patient was included in the statistical analysis. An ITT (intention-to-treat) analysis was done in case that the implants allocated to the immediate loading groups could not be loaded immediately. The answer to this part is confidently YES.

Section B:

Cannizzaro et al., 2012 Question 4:

The surgeon and the investigator were blinded to the intervention. Although it is not mentioned if the data were collected by the blinded analysts. The answer is YES. Cannizzaro et al., 2012 Question 5: The study groups were identical regarding the baseline characteristic.

The answer is YES.

Cannizzaro et al., 2012 Question 6:

The study protocol and setting were well defined and described. Both study groups were given the same level of treatment, and the follow-up intervals were similar for the two groups.

The answer is YES.

Section C:

Cannizzaro et al., 2012 Question 7:

A power calculation was conducted by two group continuity corrected chi-square test. The power of significance was 80%. The outcome measures were clearly reported.

The binary outcomes (dichotomous outcomes) were measured by Mc Namar's chi- square test. The paired sample t test was used to measure MBL at 6 months and 4 years. The p values were reported.

The answer is confidently YES.

Cannizzaro et al., 2012 Question 8:

All the measurements were reported at the confidence interval of 95%.

The answer is YES.

Cannizzaro et al., 2012 Question 9:

The benefits of the experiment outweigh the harm and costs.

The answer is YES.

Section D:

Cannizzaro et al., 2012 Question 10:

The result of this experiment can be applied to the global population regardless of the location. The answer is YES.

Cannizzaro et al., 2012 Question 11:

The result of this study has added a higher value to both

patients and the practitioners in the field of implantology.

The answer is YES.

In summarized, this study ranks as a very high level of RCTs according the CASP checklist, by checking all the questions positively.

Article no 8. (Zembic et al., 2010)

Zembic et al., 2010 Question 1:

The population of this study consisted of patients with bilaterally free end mandibles. The Intervention was immediate loading, and the comparison was early loading of the dental implants. The outcome was ISQ, MBL changes, peri-implant parameters, and survival rate.

The answer is YES.

Zembic et al., 2010 Question 2:

The randomization of the immediate and the early loaded sides was done using a lot, just before the implant placement surgery.

The answer is YES.

Zembic et al., 2010 Question 3:

Eleven patients enrolled in the study and 10 of them were available for the 3 years follow-up. It is not mentioned if a intention-to-treat analysis was performed.

The answer is NO.

Section B:

Zembic et al., 2010 Question 4:

Neither the participants or the surgeon were blinded to the intervention, but the descriptive statistics were performed by a masked biostatistician.

The answer is NO, NO, YES.

Zembic et al., 2010 Question 5:

There was significant difference between the two study groups regarding the bone level at the base line, which can be a reason for the higher MBL changes in the immediate loading group. There was also differences in the bone quality and length of the implants between the two groups.

The answer is NO.

Zembic et al., 2010 Question 6:

The study protocol was well defined and described, and the participants and study groups received the same level of treatment and care. The answer is YES.

Section C:

Zembic et al., 2010 Question 7:

No power calculation was performed, and the sample size was too small, which can be a source of bias. Also, the fact that randomization of the immediate and early loading sides was done before the implant placement, can be the reason for the deeper position of the implants with the immediate loading protocol. This situation has also been noticed in the similar studies, where the randomization was done prior to the implant placement. There was missing data regarding some patients with the failed implants, and the missing data was not included in the statistical analysis. For the statistical analysis

student's paired t test and Wilcoxon's signed-rank test was used. The p value was only reported for the MBL. The answer to this part is Can't tell.

Zembic et al., 2010 Question 8:

The confidence interval was not reported for any of the measurements.

The answer is NO.

Zembic et al., 2010 Question 9:

The benefit of this study outweighs the harms and costs.

The answer is YES.

Section D:

Zembic et al., 2010 Question 10:

The result of this study can be generalized to the population regardless of the location.

The answer is YES.

Zembic et al., 2010 Question 11:

This intervention can benefit the patients and the practitioners in the filed of oral implantology.

The answer is YES.

To summarize the result of this study, there are good and useful data provided in this article. However, due to the small sample size and the other limitations shall be interpreted with caution. This study offers average level of evidence.

After the critically appraisal of these eight articles by CASP checklist, it is apparent that these studies were all meticulously and methodically conducted. Hence, the evidence extracted from these articles can be considered to be of high quality.

	Was their a clear statement of the aims of the research?	Is the qualitative methodology appropriate?	Was the research design appropiate to adresse the question?	Was the recruitment stragegy appropiate to the aim of the research?	Were the data collected on a way that adresse the aim?	Have ethical issues been taken into considerations?	Was the data analysis sufficiently regorous?	Is their a clear statement of findings?	Is the research valuable?
Meloni et al - 2018									
Romanos et al - 2015									
Kokovic et al - 2012									
Fadi Daher et al - 2019									
Cannizzaro et al - 2012									
Baris Guncu et al - 2008									
Van de Velde et al - 2010									
Zembic et al - 2010									

Table 4: Overview of CASP result

Data Extraction: quantitative Synthesis

Biocompatible Materials

A quantitative synthesis of the eight articles identified during the systematic literature review was also undertaken, with data presented statistically. Data from these eight studies were first extracted and then evaluated, drawing conclusions about the outcomes, effects, limitations, and practical applications of the findings. All eight studies used a split mouth research design, meaning that the same patient received both of the treatments / loading protocols: one on each side of the mouth.

Specifically, these eight primary studies indicated that there were comparable clinical outcomes found in immediate, conventional (or delayed), and early loading protocols. Basically, both immediate and conventional (or delayed) loading protocols yield similar clinical outcomes. Four of the eight articles identified in the systematic literature review focused on comparing these two protocols. For example, Meloni et al.'s (2018) study found that the clinical outcomes are comparable for both immediate and delayed loading of implants in mandibular fist molar sites. Romanos et al. (2016) determined that immediate loading is actually linked with minimal bone loss, improving the stability of implants in the posterior mandible. Additionally, this loading protocol did not have adverse effects on long-term prognosis of these dental implants (Romanos et al., 2016).

Corroborating these findings, Daher et al. (2019) concluded that immediate loading of posterior maxilla implants is able to attain similar clinical outcomes as conventional loading of these implants. Güncü et al.'s (2008) findings showed that both immediate and conventional loading of single-tooth implants had similar clinical outcomes, including both marginal bone levels and implant stability.

As for immediate vs. early loading protocols, the other four articles identified during the systematic literature review compared these two protocols. In the article by Kokovic et al. (2014), adequate primary stability was shown for both the immediate and early loading protocols and there was no significant difference between the two groups regarding the marginal bone loss. Similarly, Cannizzaro et al. (2018), both immediate and early loading protocols demonstrated comparable clinical outcomes, while showing continued success at nine-years follow-up. The study by Zembić et al. (2010) concluded that immediate loading actually led to a reduced implant survival rate compared to early loading. However, at three-years follow-up, there were no differences between the two groups in terms of marginal bone levels (Zembić et al., 2010). Finally, Van de Velde et al. (2010) determined that both immediate loading and early loading protocols are successful in posterior maxilla implants, with similar clinical outcomes associated with each protocol.

Immediate vs. Conventional Loading

For the immediate loading protocol vs. the conventional (or delayed) loading protocol, there were four primary research articles that compared these loading protocols: Meloni et al. (2018), Romanos et al. (2016), Daher et al. (2019), and Güncü et al. (2008).

Immediate vs. Early Loading

There were four articles that compared the immediate loading protocol to the early loading protocol: Kokovic et al. (2014), Cannizzaro et al. (2018), and Zembić et al. (2010), and Van de Velde et al. (2010).

Meta-Analysis

Sufficient quantitative data was available to conduct

meta-analysis. The data from the primary studies was analysed using statistical methods, with the odds ratios from each outcome measure combined. Analysis of statistical significance, with a 95% confidence interval (CI), was employed. This enabled both the magnitude of effect and heterogeneity between the primary studies to be estimated, after which the effect sizes were ranked and plotted into forest plots.

There was available data on marginal bone loss of IL vs CL and IL vs EL in 1 year after loading of the implants. Two meta-analyses were able to be performed, both of which used marginal bone loss (MBL) as the chosen outcome measure. The first meta-analysis examined immediate loading (IL) vs early loading (EL) after one year. There were three studies involved in this meta-analysis (Kokovic et al.,2012 and Zembic et al.,2010, Van De Valde et al.,2010. See table 1)

Study	N1	Mean1	Sd1	N2	Mean2	Sd2	subgroup
Kokovic et al., 2012	36	0.1	0.18	36	0.08	0.31	subgroup1
Zembic et al.,2010	22	1.23	0.89	22	0.44	0.66	subgroup1
Van de Valde et al., 2010	36	01:10	00:39	34	0,88	0,37	subgroup1

Table 5: Included articles and MBL data used in Meta-analysis 1 year IL vs EL

The second meta-analysis examined immediate loading (IL) vs Conventional loading (CL) after one year and in this meta-analysis, 3 studies were involved. (Meloni et al.,2018, Fadi et al.,2019, Guncu et al.,2008. See table 2).

Study	N1	Mean1	Sd1	N2	Mean2	Sd2	subgroup
Meloni et al., 2018	20	0.39	0.24	20	0.48	0.19	subgroup1
Fadi et al., 2019	80	0.42	0.45	80	0.46	0.30	subgroup1
Guncu et al., 2008	12	0.45	0.35	12	0.68	0.30	subgroup1

Table 6: Included articles and MBL data in Meta-analysis 1 year IL vs CL

When analysing MBL in patients after one year – specifically comparing IL vs EL – the meta-analysis showed that there were no significant differences between the IL group and the EL group (p=0.06). The fixed standard mean difference in MBL was 0.46 [0.17; 0.76] at 95% CI (See Figure 2), while the random standard mean difference in MBL was 0.51 [-0.60; 1.63] (See Figure 3). The p-value for both was 0.06, which is statistically insignificant.

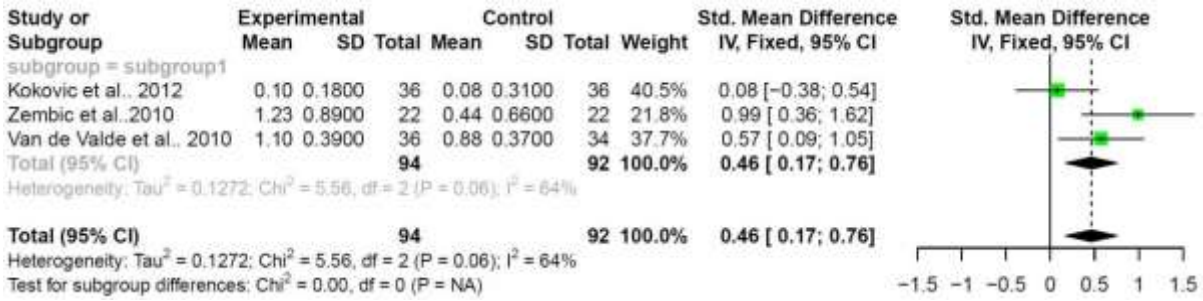

Figure 2 Forest Plot (Fix Effect) IL vs EL

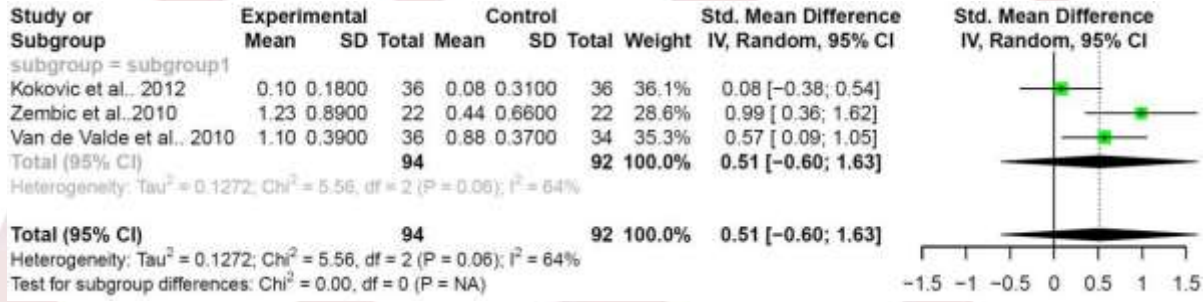

Figure 3: Forest Plot (Random Effect) IL vs EL

The second meta-analysis was performed on MBL in patients after one year, comparing IL to CL this time. Again, the results demonstrated that the difference in MBL was not statistically significant between the IL group and the CL group (p=0.35). The fixed standard mean difference in MBL was -0.22 [-0.48; 0.05] at 95% CI (See Figure 4), while the random standard mean difference in MBL was -0.25 [-0.89; 0.39] (See Figure 5). The results were statistically insignificant, with the p-value again at 0.35.

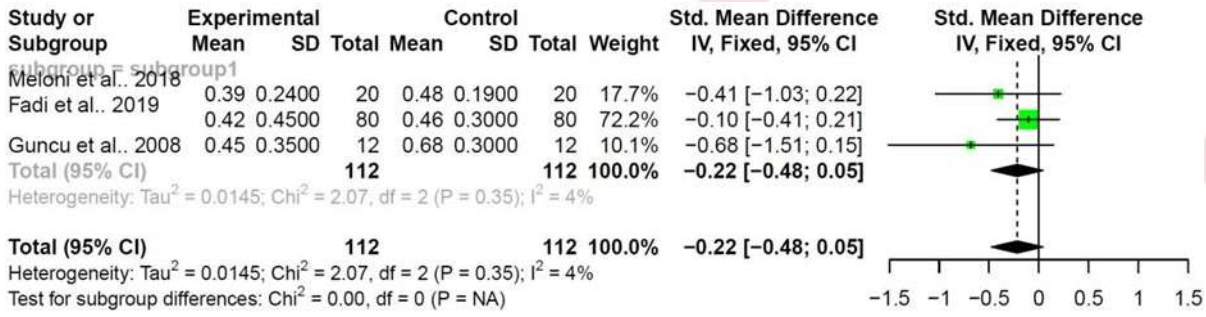

Figure 4: Forest Plot (Fix Effect) IL vs CL

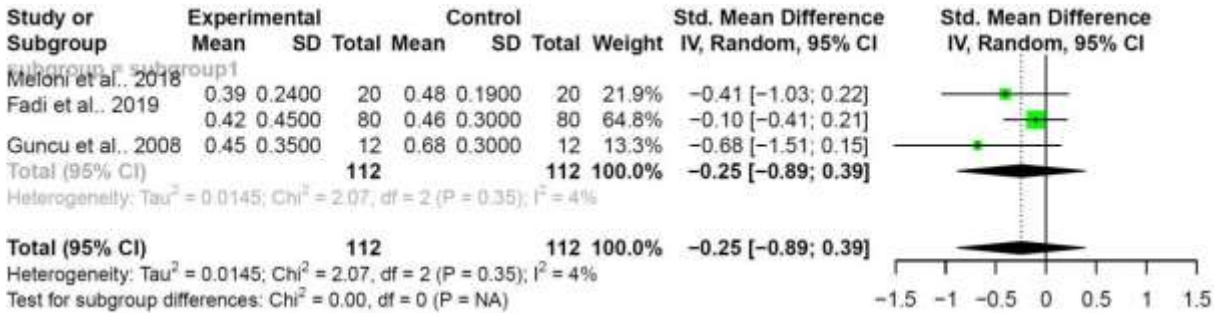

Figure 5: Forest Plot (Random Effect) IL vs CL

In summary, the meta-analyses showed that the MBL in immediate loaded implants were comparable to both early loaded implants, and conventionally loaded implants.

Discussion and Conclusion

Discussion

Summary of Major Findings

The findings from this systematic literature review of quantitative original studies identified and reviewed eight randomized controlled trials (RCTs) exploring clinical outcomes associated with various dental implant protocols. Because the articles all had comparable clinical outcomes between immediate, early, and conventional or delayed loading protocols, both average marginal bone loss and survival rates of dental implants were able to be examined and compared. Overall, the findings of these studies showed similar clinical outcomes for patients, no matter which loading protocol was employed.

For immediate and conventional/delayed loading protocols, four of the eight articles compared these protocols in terms of measured clinical outcomes (Daher et al., 2019; Güncü et al., 2008; Meloni et al., 2018; Romanos et al., 2016). While immediate loading was associated with reduced marginal bone loss in patients in one study (Romanos et al., 2016), most of the RCTs concurred that participants' clinical outcomes in general for immediate loading were neither superior nor inferior to conventional/delayed loading (Daher et al., 2019; Güncü et al., 2008; Meloni et al., 2018).

For immediate and early loading protocols, the remaining four articles compared these protocols, again looking specifically at certain clinical outcomes like marginal bone loss (Cannizzaro et al., 2018; Kokovic et al., 2014; Zembić et al., 2010; Van de Velde et al., 2010). Three of these articles found that immediate and early protocols led to similar clinical outcomes in patients (Cannizzaro et al., 2018; Kokovic et al., 2014; Van de Velde et al., 2010). In addition, the last article actually determined that the survival rate of implants suffered with immediate occlusal loading protocols, meaning that patients had better survival rates when they received an early loading protocol (Zembić et al., 2010). Nonetheless, marginal bone loss levels did not differ significantly over time between these two protocols (Zembić et al., 2010).

After completing the systematic literature review, two meta-analyses were then conducted. The findings from these meta-analyses also indicated no statistically significant differences in terms of marginal bone loss, comparing IL with CL, nor IL with EL. Hence, there is evidence in support of slightly higher survival rates for the conventional or early loading protocols, as immediate

loading protocols is clearly more associated with higher implant failure.

Limitations

The are some limitations to this systematic review, such as the small sample size in some of the included studies, due to lacking the power analysis prior to the studies. Additionally, the fact that there was no ITT analysis performed in some of the articles, and some of the failures, dropouts and missing data were excluded from the statistical analysis, could create bias in the result of the final analyses. Also missing report of data in some follow-up intervals in some studies, can affect the precision of the analysis. Another limitation could be the methods of randomization in the included studies; in some of the studies the randomization to allocate the IL and the CL or the EL, was performed before the implant placement surgery, therefor the surgeon has not been blinded to the intervention (loading protocol) at the time that they placed the implants. The result of these studies and the similar studies from the other literature reviews shows that the surgeon has placed the implants, which were allocated to be loaded immediately, deeper. This can result in higher marginal bone level of the immediate loaded implants at the baseline, which again can be an important source of bias.

Strengths and Weaknesses

Only articles published in the English language were included in the systematic literature review. Hence, studies written in other languages were not integrated into the review, which meant that many reliable and peer-reviewed sources of evidence were not included in the literature review. This represents a definite weakness of the review methods used in this dissertation. Additionally, some of the articles included in the systematic review may be considered outdated, as they were published years ago (with the earliest article published in 2008).

There were also strengths in the systematic literature review. For instance, a detailed and effective search strategy was created, the research question and the PICO strategy was clearly defined. Specific inclusion and exclusion criteria were also well described, with all articles meticulously reviewed and critically appraised using the CASP tool for RCTs. Furthermore, a master table was developed, outlining the specific data that would be extracted from each of the eight chosen articles. This data extraction included marginal bone loss and survival rate of dental implants, as these were the two clinical outcome measures compared among the three different loading protocols. Another very important point of strength in this review is that all the included articles had to be Split-Mouth designed. This minimises the risk of bias resulting by the exclusion of the selected patients, and also provides the highest possibility of the identical baseline characteristics for the study groups in each study.

Comparison with Other Systematic Literature Reviews

As only original RCTs were included in the chosen articles from the systematic literature review, it was important to compare the findings from this dissertation to what is accepted in the current literature. For example, in the systematic review and meta-analysis of RCTs by Chen et al. (2019), immediate loading was compared to early or conventional loading. Besides Medline, the researchers also searched Central and Embase databases, evaluating outcomes such as marginal bone level changes, probing depth, survival rate, and implant stability (Chen et al., 2019).

The results showed that within the immediate loading protocol, the survival rate of the dental implant was significantly reduced compared to the rate within the conventional loading protocol (Chen et al., 2019). While there were no other statistically significant differences in clinical outcomes, the results still provide clear evidence that immediate loading represents an effective option that

may lead to similar marginal bone level changes and implant survival rates as in early loading (Chen et al., 2019). However, as it does result in a greater incidence of implant failure, immediate loading may not be ideal for all patients (Chen et al., 2019).

In an earlier systematic literature review and meta-analysis, Engelhardt et al. (2015) examined both yearly marginal bone level changes and failure rates for immediate loading of dental implants, comparing these outcomes to those associated with conventional loading. Out of 154 full-text articles, 10 RCTs were chosen to be evaluated and analysed (Engelhardt et al., 2015). The findings showed a 2.3% failure rate for patients undergoing the conventional protocol, which was better than the 3.4% failure rate for those choosing an immediate loading protocol (Engelhardt et al., 2015).

Additionally, the weighted mean difference (WMD) for marginal bone level changes between immediate and conventional loading at one year was 0.02 mm, rising slightly at two years to 0.08 mm, then at three years to - 0.10 mm, and finally at five years to - 0.3 mm, combining for a total WMD of 0.01 mm at patient follow-up (Engelhardt et al., 2015). Overall, the researchers concluded that there were no statistically significant differences in bone level changes or yearly failure rates between these two dental loading protocols, conventional and immediate (Engelhardt et al., 2015).

Finally, a systematic review and meta-analysis conducted in 2018 by Pigozzo et al., compared the immediate loading of a dental implant to early loading. Again, Medline, Embase, and the Cochrane Library were the databases searched, with the researchers including only RCTs, although there were no restrictions on when the studies had to be published (Pigozzo et al., 2018). They reviewed 5,710 articles, selecting five that met inclusion criteria and performing a meta-analysis on both mean differences and risk differences (Pigozzo et al., 2018). When considering both one- year and three-year follow-up, the survival rates and marginal bone loss associated with both the early loading protocol and immediate loading protocol were not different to a statistically significant degree (Pigozzo et al., 2018). In other words, the study determined there were no differences between these two loading protocols in terms of these two clinical outcomes (Pigozzo et al., 2018).

Conclusion

Overall, the findings from this systematic literature review suggest that the clinical outcomes of these three different loading protocols are comparable. Hence, one loading protocol is not superior or inferior to the others. However, there is some evidence that patients receiving immediate loading protocols are at a slightly higher risk of implant failure compared the conventional loading or early loading, but there are other factors that can correlate to this result and increase the risks, such as single standing implants, or immediate occlusal loading. On the other hand, assessing the patient opinion about speech, function, self-confidence, and aesthetic indicates significant differences in favour of the immediate loading protocol. (Van de Valde et al.,2010).

Future Outlook

The findings from this systematic literature review have several implications for current practice in dentistry / implantology. The comparable clinical outcome for the immediate loading protocol, provides more confidence for using this protocol in the routine implantology practice, this can favour specifically the patients in aspect of gaining functionality and aesthetic immediately after the placement of the implant, resulting in the higher self-confidence and positive psychological effects. Also reducing the smaller number of the surgeries and treatment sessions, the immediate loading protocol can be a factor helping to minimise the costs of the treatment for the patients.

Overall, however, as each of these three loading protocols for dental implants had similar clinical results, the combination of the different biological and mechanical factors with each of the three different protocols identifies the true final results, therefore, it is recommended that dentists and surgeons use their clinical judgement when making the decision on which protocol shall be used, and take all the existing factors in to the account at the level of treatment planning.

Finally, there are also implications for future research. While a more comprehensive systematic literature review may be warranted, it is recommended that more original studies like RCTs be performed. Additional quantitative information is needed, with more studies comparing these loading protocols in an objective manner. Even more, qualitative studies focusing on patients' perspectives and experiences with these different loading protocols are also needed. In fact, future qualitative studies may be needed to examine the opinions and viewpoints of dentists, exploring their thoughts and experiences with the various loading protocols. This way, these studies will provide even greater insight into this phenomenon, helping researchers to make more conclusive decisions regarding which protocol could be preferred under different circumstances.

References

1. Barewal, R. M., Stanford, C., and Weesner, T. C. (2012). A randomized controlled clinical trial comparing the effects of three loading protocols on dental implant stability. The International journal of oral & maxillofacial implants, 27(4), pp.945–956.
2. Cannizzaro, G., Felice, P., Leone, M., et al. (2012). Immediate versus early loading of 6.5 mm-long flapless-placed single implants: a 4-year after loading report of a split-mouth randomised controlled trial. European journal of oral implantology, 5(2), pp.111–121.
3. Chen, J., Cai, M., Yang, J., et al. (2019). Immediate versus early or conventional loading dental implants with fixed prostheses: A systematic review and meta- analysis of randomized controlled clinical trials. The Journal of prosthetic dentistry, 122(6), pp.516–536. Available at: https://doi.org/10.1016/j.prosdent. 2019.05.013
4. Critical Appraisal Skills Programme (2020). CASP Randomised Controlled Trial Checklist. [online] Available at: https://casp-uk.net/images/checklist/ documents/CASP-Randomised-Controlled-Trial-Checklist/CASP-RCT- Checklist-PDF-Fillable-Form.pdf
5. Daher, F. I., Abi-Aad, H. L., Dimassi, H. I., et al. (2019). Immediate versus conventional loading of variable-thread tapered implants supporting three- to four-unit fixed partial dentures in the posterior maxilla: 3-year results of a split- mouth randomised controlled trial. International journal of oral implantology, 12(4), pp.449–466.
6. Danza, M., Tortora, P., Quaranta, A., et al. (2010). Randomised study for the 1-year crestal bone maintenance around modified diameter implants with different loading protocols: a radiographic evaluation. Clinical oral investigations, 14(4), pp.417–426. Available at: https://doi.org/10.1007/s00784-009-0314-0
7. De Bruyn, H., Raes, S., Ostman, P. O., and Cosyn, J. (2014). Immediate loading in partially and completely edentulous jaws: a review of the literature with clinical guidelines. Periodontology 2000, 66(1), pp.153–187. Available at: https://doi.org/10.1111/prd.12040
8. Degidi, M., Nardi, D., and Piattelli, A. (2012). 10-year follow-up of immediately loaded implants with TiUnite porous anodized surface. Clinical implant dentistry and related research, 14(6), pp.828–838. Available at: https://doi.org/10.1111/j.1708-

8208.2012.00446.x

9. Degidi, M., and Piattelli, A. (2003). Immediate functional and non-functional loading of dental implants: a 2- to 60-month follow-up study of 646 titanium implants.
10. Journal of periodontology, 74(2), pp.225–241. Available at: https://doi.org/10.1902/jop.2003.74.2.225
11. Dichter, D. (2018). Loading Protocols for Dental Implants. SPEAR. Available at: https://www.spearеducation.com/spear-review/2016/04/loading-protocols-for- dental-implants-
12. Engelhardt, S., Papacosta, P., Rathe, F., et al. (2015). Annual failure rates and marginal bone-level changes of immediate compared to conventional loading of dental implants. A systematic review of the literature and meta-analysis.
13. Clinical oral implants research, 26(6), pp.671–687. Available at: https://doi.org/10.1111/clr.12363
14. Esposito, M., Grusovin, M. G., Maghaireh, H., and Worthington, H. V. (2013).
15. Interventions for replacing missing teeth: different times for loading dental implants. The Cochrane database of systematic reviews, 2013(3), pp.CD003878. Available at: https://doi.org/10.1002/14651858.CD003878.pub
16. Gallucci, G., Hamilton, A., Zhou, W., Buser, D., and Chen, S. T. (2018). Implant Placement and Loading Protocols. Prosthodontics and Implant Dentistry, ITI CC 2018. Available at: https://www.iti.org/academy/consensus-database/consensus-statement/-/consensus/implant-placement-and-loading-protocols/ 1802
17. Güncü, M. B., Aslan, Y., Tümer, C., et al. (2008). In-patient comparison of immediate and conventional loaded implants in mandibular molar sites within 12 months. Clinical oral implants research, 19(4), pp.335–341. Available at: https://doi.org/10.1111/j.1600-0501.2007.01471.x
18. Hof, M., Tepper, G., Semo, B., et al. (2014). Patients' perspectives on dental implant and bone graft surgery: questionnaire-based interview survey. Clinical oral implants research, 25(1), pp.42–45. Available at: https://doi.org/10.1111/clr.12061
19. Kern, J. S., Kern, T., Wolfart, S., and Heussen, N. (2016). A systematic review and meta-analysis of removable and fixed implant-supported prostheses in edentulous jaws: post-loading implant loss. Clinical oral implants research, 27(2), pp.174–195. Available at: https://doi.org/10.1111/clr.12531
20. Kokovic, V., Jung, R., Feloutzis, A., et al. (2014). Immediate vs. early loading of SLA implants in the posterior mandible: 5-year results of randomized controlled clinical trial. Clinical oral implants research, 25(2), pp.e114–e119. Available at: https://doi.org/10.1111/clr.12072
21. Körmöczi, K., Komlós, G., Papócsi, P. et al. (2021). The early loading of different surface-modified implants: a randomized clinical trial. BMC Oral Health, 21, pp.207. Available at: https://doi.org/10.1186/s12903-021-01498-z
22. Mankoo, T. (2004). Contemporary implant concepts in aesthetic dentistry--Part 2: Immediate single-tooth implants. Practical procedures & aesthetic dentistry : PPAD, 16(1), pp.61–70.
23. Meloni, S. M., Baldoni, E., Duvina, M., et al. (2018). Immediate non-occlusal versus delayed loading of mandibular first molars. Five-year results from a randomised controlled trial. European journal of oral implantology, 11(4), pp.409–418.
24. Meng, H. W., Chien, E. Y., and Chien, H. H. (2021). Immediate Implant Placement and

Provisionalization in the Esthetic Zone: A 6.5-Year Follow-Up and Literature Review. Case reports in dentistry, 2021, pp.4290193. Available at: https://doi.org/10.1155/2021/4290193

25. Merli, M., Merli, M., Mariotti, G., et al. (2020). Immediate versus early non-occlusal loading of dental implants placed flapless in partially edentulous patients: A 10-year randomized clinical trial. Journal of clinical periodontology, 47(5), pp.621–629. Available at: https://doi.org/10.1111/jcpe.13279
26. Mitsias, M., Siormpas, K., Pistilli, V., Trullenque-Eriksson, A., and Esposito, M. (2018). 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. European journal of oral implantology, 11(1), pp.63–75.
27. Mura, P. (2012). Immediate loading of tapered implants placed in postextraction sockets: retrospective analysis of the 5-year clinical outcome. Clinical implant dentistry and related research, 14(4), pp.565–574. Available at: https://doi.org/10.1111/j.1708-8208.2010.00297.x
28. Pigozzo, M.N., da Costa, T.R., Sesma, N., and Laganá, D.C. (2018). Immediate versus early loading of single dental implants: A systematic review and meta‐analysis. The Journal of Prosthetic Dentistry, 120, pp.25–34. Available at: https://doi.org/10.1016/j.prosdent.2017.12.006
29. Polizzi, G., and Cantoni, T. (2015). Five-year follow-up of immediate fixed restorations of maxillary implants inserted in both fresh extraction and healed sites using the NobelGuide™ system. Clinical implant dentistry and related research, 17(2), pp.221–233. Available at: https://doi.org/10.1111/cid.12102
30. Romanos, G. E., Aydin, E., Locher, K., and Nentwig, G. H. (2016). Immediate vs. delayed loading in the posterior mandible: a split-mouth study with up to 15 years of follow-up. Clinical oral implants research, 27(2), pp.e74–e79. Available at: https://doi.org/10.1111/clr.12542
31. Strub, J. R., Jurdzik, B. A., and Tuna, T. (2012). Prognosis of immediately loaded implants and their restorations: a systematic literature review. Journal of oral rehabilitation, 39(9), pp.704–717. Available at: https://doi.org/10.1111/j.1365-2842.2012.02315.x
32. Tettamanti, L., Andrisani, C., Bassi, M. A., et al. (2017). Immediate loading implants: review of the critical aspects. ORAL & implantology, 10(2), pp.129–139. Available at: https://doi.org/10.11138/orl/2017.10.2.129
33. Touati, B., and Guez, G. (2002). Immediate implantation with provisionalization: from literature to clinical implications. Practical procedures & aesthetic dentistry :PPAD, 14(9), pp.699–708.
34. Van de Velde, T., Sennerby, L., and De Bruyn, H. (2010). The clinical and radiographic outcome of implants placed in the posterior maxilla with a guided flapless approach and immediately restored with a provisional rehabilitation: a randomized clinical trial. Clinical oral implants research, 21(11), pp.1223– 1233. Available at: https://doi.org/10.1111/j.1600-0501.2010.01924.x
35. Wöhrle, P. S. (2014). Predictably replacing maxillary incisors with implants using 3-D planning and guided implant surgery. Compendium of continuing education in dentistry, 35(10), pp.758–768
36. Zembić, A., Glauser, R., Khraisat, A., and Hämmerle, C. H. (2010). Immediate vs. early loading of dental implants: 3-year results of a randomized controlled clinical trial. Clinical oral

implants research, 21(5), pp.481–489. Available at: https://doi.org/10.1111/j.1600-0501.2009.01898.x