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Does the timing of implant placement and loading influence biological outcomes of implant-supported multiple-unit fixed dental prosthesis—A systematic review with meta-analyses

Louise Leite Aiquel1 | João Pitta2 | Georgios N. Antonoglou1 | Irene Mischak1 | Irena Sailer2 | Michael Payer1

1Department of Oral Surgery and Orthodontics, University Clinic of Dental Medicine and Oral Health, Medical University of Graz, Graz, Austria
2Division of Fixed Prosthodontics and Biomaterials, University Clinics for Dental Medicine, University of Geneva, Geneva, Switzerland

Correspondence
Georgios N. Antonoglou, Department of Oral Surgery and Orthodontics, University Clinic of Dental Medicine and Oral Health, Billrothgasse 4, 8010 Graz, Austria. Email: antonoglou.georgios@gmail.com

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Abstract
Objective: To investigate the impact of timing of implant placement and loading on implant survival and biological outcomes of multiple-unit implant-supported fixed dental prosthesis (FDPs).

Material and Methods: A literature search was performed by three independent reviewers for studies reporting on ≥10 patients with FPDs supported by ≥two implants over ≥3 years of follow-up. Data were analyzed on implant survival and biological complications as primary outcomes and biological events, including changes in peri-implant marginal bone level (MBL), probing depth, soft-tissue level, and health condition as secondary outcomes.

Results: 7002 titles were identified, 360 full-texts were screened, and 14 studies were included. These comprised 6 randomized controlled studies (RCTs), 5 cohort studies, and 3 case series with identifiable implant placement and loading protocols in five of 09 possible combinations. All groups but one (IPIL) showed implant survival rates >90%. A meta-analysis based on 3 RCTs found no differences in survival rate between DPIL and DPDL (p = .227).

Conclusions: High survival rates for all studied implant placement and loading combinations were shown for FPDs over ≥3 years of follow-up. When a delayed implant placement protocol is applied, immediate or delayed loading demonstrated similar survival rates. The heterogeneity of the data did not allow to draw any further conclusions on the occurrence of biological complications related to timing of implant placement/loading.

KEYWORDS
biological outcomes, bone level change, dental implant, implant loading protocols, implant placement protocols, success rates, survival rate

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Fixed dental prostheses supported by implants have become a well-documented and reliable treatment option. Excellent survival rates of both the multiple-unit prostheses and their supporting implants have been reported notably for conventional metal-ceramic restorations (Saíler et al., 2018). Advances on the prosthetic materials, along with the development of different implant surfaces, digital planning tools and surgical techniques have contributed to the current success rates of implant-supported restorations (Buser et al., 2017).

All the contemporary treatment and fabrication concepts have aimed to minimize treatment durations and patient visits while maintaining optimal clinical and patient-related outcomes (Scheyer et al., 2017). This quest for greater efficiency also has resulted in a diversification of implant placement and loading protocols. Contemporary options include immediate, early, or placement, as well as immediate, early, or conventional loading (Gallucci et al., 2018). It is reasonable to assume that these expedited procedures and fewer patient visits involved in immediate or early placement or loading will reduce the cost of treatment, and possibly increase efficiency (Scheyer et al., 2017).

Numerous reviews have been published to classify these protocols and define their indications (Gallucci et al., 2009, 2014, 2018; Schrott et al., 2014). While both immediate/early placement and immediate/early loading can yield excellent results, they are subject to biological limitations and a need for careful patient selection and site assessment (Gallucci et al., 2018). Immediate or early placement requires a fair amount of residual bone for good primary stability of the implant (Benic et al., 2014; Gallucci et al., 2018).

Good primary stability is also crucial for immediate loading of implants. While surface modifications and advanced designs have improved the outcomes of all placement and loading protocols (Benic et al., 2014; Chu et al., 2020; Gallucci et al., 2018), immediate placement right after tooth extraction has repeatedly been shown not to prevent physiological remodeling of the alveolar bone (Sanz et al., 2017; Vignoletti et al., 2009). Thus, special care should be taken by clinicians in order to prevent biological and esthetic complications due to the natural ridge resorption and bone remodeling that will occur independently of implant placement (Araújo et al., 2005; Buser et al., 2009; Buser et al., 2013). These processes are accompanied by volume changes of the peri-implant soft tissue, with loss of mucosa seen more often after immediate than early placement (Lee et al., 2020). Nonetheless, mucogingival tissue findings are contradictory. While they demonstrate that biotype (in addition to residual bone volume) is another major modifier of biological outcomes after immediate/early placement or loading (Lee et al., 2020; Prati et al., 2020; Sanz-Martín et al., 2019), some authors have found significant mucosal recession around immediately placed and loaded implants (Blanco et al., 2019; Kolerman et al., 2016) whereas others have not (Chan et al., 2019; Östman et al., 2020; Parvini et al., 2020; Pohl et al., 2020; Yan et al., 2016).

Thus, it cannot be excluded that immediately inserted implants may be at higher risk of developing biological complications such as peri-implant disease (Parvini et al., 2020). The influence of soft-tissue biotypes on the incidence of peri-implant inflammation has been demonstrated in animal and clinical studies, suggesting the need for grafting procedures simultaneously to immediate implant placement (Chappuis et al., 2017; Perussolo et al., 2018).

Reversible inflammation affecting the soft tissue around the implant (mucositis) is a highly frequent condition that can progress to progressive bone loss (peri-implantitis) and eventually implant loss (Lee et al., 2017). Local and systemic conditions, such as poor oral hygiene, smoking, and diabetes, are already known risk factors for peri-implant diseases, and the influence of recently developed implant materials and surfaces has been studied (De Bruyn et al., 2017; Dreyer et al., 2018; Peixoto & Almas, 2016). However, the role of recently developed surgical techniques including placement and loading shorter time protocols and their combinations in the index of these biological complications and implant survival is little known.

Further discussed are flapless approaches, a particularly efficient method often utilized for immediate procedures, offer advantages but are limited by local anatomy, ongoing infections and surgical skills (Barone et al., 2016).

With efficiency (shorter treatment durations, fewer patient visits, better affordability) being more desirable than ever in times of a pandemic crisis and global financial constraints, there is a need for evidence-based insights into the biological indications and limitations of immediate/early placement and loading of implants, enabling clinicians to make appropriately efficient treatment decisions in carefully selected patients.

In this context, the present systematic review investigated the question of whether different timing protocols of implant placement and implant loading affect the biological outcomes and implant survival related to implant-supported fixed partial dentures (FPDs) in partially edentulous patients.

2 | MATERIAL AND METHODS

Ethics approval was not required for this systematic review and was registered in PROSPERO (IRD42020179528) and conducted in accordance with PRISMA (Liberati et al., 2009), PRISMA extension for abstracts (Beller et al., 2013), IOM (Institute of Medicine) standards (Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice, 2011), and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2017).

2.1 | Focusing the question for review

The PICO(S) (population, intervention, comparison, outcome, and studies) principle was applied to focus the question posed for this review. As population, the focus was on partially edentulous patients...
treated by implant-supported fixed partial dentures (FPDs). As intervention, the focus was on immediate or early placement or loading as compared to delayed placement or delayed loading. Outcome parameters included, as primary measures, implant survival and biological complications (e.g., peri-implantitis, peri-implant mucositis, and apical peri-implantitis) and as secondary measures, the radiographic parameter of marginal bone levels (MBL) and the clinical parameters of soft-tissue recession, bleeding on probing (BOP), probing depths (PD), preservation or loss of width of keratinized tissue (KT), and plaque index (PI) were analyzed (Vetter & Mascha, 2017). The study designs that were eligible for inclusion were prospective and retrospective comparative and non-comparative clinical trials.

The focused question was as follows: Does immediate or early implant placement and loading influence the biological complication rate and implant survival in partially edentulous patients when compared with conventional protocols?

2.2 | Protocols of implant placement and loading

Timing possibilities for implant placement and loading were defined as proposed by Gallucci et al., (2018; Siebers et al., 2010):

- IPIL: immediate placement + immediate restoration/loading
- IPEL: immediate placement + early loading
- IPDL: immediate placement + delayed loading
- EPI: early placement + immediate restoration/loading
- EPEL: early placement + early loading
- EPDL: early placement + delayed loading
- DPL: delayed placement + immediate restoration/loading
- DPEL: delayed placement + early loading
- DPDL: delayed placement + delayed loading

Previous reports (Chen & Buser, 2009; Chen et al., 2004; Gallucci et al., 2018; Hämmerle et al., 2004; Siebers et al., 2010) provided the blueprint for the definition of protocols to be reviewed.

- Immediate implant placement (IP): The implant is placed at the same day of tooth extraction.
- Early implant placement (EP): The implant is placed between 1 and 4 months after tooth extraction.
- Delayed implant placement (DP): Implant is placed >6 months after tooth extraction.
- Immediate loading (IL): The prosthesis is connected to the implant within 1 week following implant placement.
- Early loading (EL): Loading is performed between 1 week and 2 months after implant placement.
- Delayed loading (DL): Prosthesis is connected to the implant later than 2 months after implant placement.

Definition of periodontal and peri-implant diseases, conditions, health and complications were based on the proposed classification by the 2017 World Workshop, co-sponsored by the American Academy of Periodontology and the European Federation of Periodontology (Araujo & Lindhe, 2018; Caton et al., 2018; Heitz-Mayfield & Salvi, 2018; Schwarz et al., 2018).

2.3 | Search strategy

The search strategy was developed in close collaboration with a research methodologist (University of Malmö, Sweden) and a “reference and education services librarian” (Medical University of Graz, Austria). The databases which were searched included PubMed/ Medline, Embase, and Cochrane CENTER (Central Register of Controlled Trials) databases. Publications in English language were thus identified up to April 29, 2020. Whenever possible, controlled MeSH terms were included in the keyword combinations used for these database searches. The electronic search was complemented by an additional hand search that included the reference lists of all included publications and, in addition, systematic reviews on related topics.

For a detailed overview of search terms used in Embase and Cochrane, the reader is referred to Appendix S1. The basic terms used in PubMed, Embase, and Cochrane were as follows:

- (dental implant) AND (immediate OR early OR late OR delayed OR conventional OR post-extraction OR post-extractive)
- Filters: English, humans, year from 2000 up to April 29, 2020.

A reference management tool (EndNote X9.3.3; Clarivate Analytics, London, UK) was used for first entry of all references and elimination of double entries. Screening at the title, abstract, and full-text levels was accomplished using a web-based application for systematic reviews (rayyan.qcri.org) (Ouzzani et al., 2016).

2.4 | Inclusion and exclusion criteria

Any multiple publications on the same populations were handled by considering only the results of the latest study (the one reporting the longest follow-up) without making recourse to any of the preceding studies unless to retrieve truly additional information.

Studies meeting the criteria below were included:

- Randomized and non-randomized controlled trials
- Cohort and case-control studies
- Prospective or retrospective case series
- FPDs supported by ≥2 implants in partially edentulous patients
- Root-form or cylindrical implants supporting the FPDs
- ≥ 10 patients in each study arm and ≥3 years of follow-up
- Adequate reporting of implant placement protocols with timing
- Adequate reporting of implant loading protocols with timing
- Endosteal diameter of implant shoulder: 3–6 mm
- Reporting of one or more biological outcomes
Studies meeting the criteria below were excluded:

- Preclinical in vitro, experimental, or animal studies
- Full-arch dentures or removable superstructures
- Implants placed in previously irradiated bone or in alveolar clefts
- Medication compromising bone metabolism
- Studies not based on clinical examinations (e.g., questionnaire surveys)
- Studies published in languages other than English
- Restorations other than permanently screw-retained or cemented FPDs
- Studies with non-eligible designs
- Inability to distinguish between placement/loading protocols
- Inability to rule out single-unit or full-arch restorations

2.5 | Screening and contacting

The retrieved reference publications were independently screened by three reviewers (LLA, JP, and GNA), including a first screening at the title/abstract level (LLA and JP) followed by a second run of full-text screening conducted in duplicate (LLA, JP, and GNA). Any disagreements were settled either by discussion between the three reviewers or by obtaining a fourth and fifth opinion (IS and MP). The default approach was to include or exclude studies based on these full-text screens, although this decision was deferred for studies regarded as potentially relevant. In these cases, the authors were emailed and asked to provide additional data. Likewise, authors of potentially relevant and already included studies were emailed as needed to resolve issues and fill in missing bits of information for the ensuing data extraction (see below). All this extra information was analyzed, and the data integrated for the final datasets.

2.6 | Data extraction

As per the Cochrane recommendations, standardized pre-piloted forms were designed for data extraction from all included papers. Three reviewers (LLA, JP, and GNA) extracted in duplicate a defined set of study characteristics (design, setting, funding, country, patient number, and mean age) and additional data pertinent to the PICO question.

**Primary outcome measures**

- Implant survival rate (%)
- Biological complication rate (peri-implant mucositis and peri-implantitis) (number of events)

**Secondary outcome measures**

- Marginal bone levels (MBL) (in mm)
- Bleeding on probing (BOP); modified Bleeding Index; Gingival Index; Sulcus Bleeding Index; Bleeding Index
- Soft-tissue recession (in mm)
- Width of keratinized tissue (KT) (in mm)
- Plaque index (PI)
- Probing depths (PD) (in mm)

**Miscellaneous information**

- Systemic condition of patients
- Prescription of antibiotics
- Time of implant placement after tooth loss or removal
- Time of implant loading (functional or nonfunctional)
- Mean follow-up period
- Implant numbers and locations
- Implant diameters, lengths, surface characteristics
- Implant materials, types and brands
- Use and design of surgical access flaps
- Use of bone grafting (material, technique)
- Healing protocol (submerged, transmucosal)
- Type and occlusal design of interim prosthesis
- Design of the definitive FPD
- Implant survival rate(s)
- Prosthetic complications

2.7 | Bias assessments and synthesis

Risk-of-bias assessments were conducted to rate the risk of bias in each individual study, using appropriate tools for each study designs. The Cochrane RoB 2.0 tool was applied to RCTs [Sterne et al., 2019], the Newcastle-Ottawa scale to cohort studies (Wells et al., 2000), and the Joanna Briggs Institute’s Critical Appraisal Checklist to case series (The Joanna Briggs Institute, 2017). It was planned to assess reporting biases by applying Egger’s and Begg’s tests to the main outcomes, to interpret tests for funnel plot asymmetry with visual inspection, and to perform post hoc sensitivity analyses by excluding studies one by one from the global estimation. To judge the strength of clinical recommendations derived from studies, their overall qualities of evidence were assessed based on the GRADE approach (Guyatt et al., 2011).

2.8 | Statistical analysis

Cohen's kappa was used to determine inter-rater (i.e., between the three reviewers) agreement and descriptive statistics to elucidate survival and biological complication rates and clinical outcomes. For each protocol, a mean cumulative survival rate was planned to be calculated and weighted by follow-up durations and implant numbers. Thus, a weighted mean survival rate for each protocol was obtained by applying this formula:

\[ x = \frac{X_1 t_1 n_1 + X_2 t_2 n_2 + \cdots + X_k t_k n_k}{t_1 n_1 + t_2 n_2 + \cdots + t_k n_k} \times 100 \]
where $X$ is the reported survival rate, $t$ the follow-up period, and $n$ the number of implants reported in each study (study 1 to study $k$).

As the implant placement is bound to be affected by patient and treatment-related characteristics, a random-effects model was a priori deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning (Papageorgiou 2014), and an inverse variance estimator with the DerSimonian-Laird estimator for $\tau^2$ was chosen (Langan et al., 2019).

Absolute and relative between-trial heterogeneity was assessed using the $t^2$ and $I^2$ indices, respectively. The latter ($I^2$) index was defined as percentage variation in the global estimate due to heterogeneity, with $I^2$ scores of 25%, 50%, or 75% indicating low, moderate, or high heterogeneity, respectively. Forest plots were created to illustrate the effects in a meta-analysis. SPSS Statistics (v. 26, IBM, Armonk, NY, USA) and R (v. 1.3; R Project for Statistical Computing, Vienna, Austria) software was used for all statistical operations. Differences were considered significant at $p \leq .05$.

The potential of publication bias of this review was assessed by the funnel plot and an additional statistical test; the Egger’s test was performed (Figure 3).

## RESULTS

### 3.1 Selected studies and their characteristics

The applied search strategy, returned a total of 7002 titles, after the identification and exclusion of 1593 duplicated hits (Figure 1). Screening at the title/abstract level left 360 articles for full-text screening to assess their eligibility. Inter-rater agreement (kappa score) was 0.63 for the title/abstract and 0.96 for the full-text screens. A total of 153 studies were categorized as potentially relevant, eight of which could be included upon contacting their authors (Daher et al., 2019; Göthberg et al., 2018; Oxby et al., 2015; Payer et al., 2010; Si et al., 2016; Siebers et al., 2010; Simons et al., 2015; Vogl et al., 2019). Fourteen studies were finally included: Six RCTs, five cohort (four observational cohort and one case–control) studies, and three case series (two prospective and one retrospective).

Each of these 14 studies was carefully selected based on parameters reported. In each assessment for eligibility, care was taken to identify well-defined information on the placement and loading protocols used.

Table 1 gives an overview of excluded studies and reasons for their exclusion. For additional information on the reasons for exclusion during
| Main reason for exclusion                                      | N  | Studies                                                                 |
|---------------------------------------------------------------|----|------------------------------------------------------------------------|
| Insufficient data for screening assessment                    | 67 | Agliardi et al. (2014)                                                 |
|                                                               |    | Ali Amri et al. (2017)                                                 |
|                                                               |    | Alasqah et al. (2018)                                                  |
|                                                               |    | Arlin et al. (2007)                                                    |
|                                                               |    | Bilhan et al. (2010)                                                   |
|                                                               |    | Bornstein et al. (2007)                                                |
|                                                               |    | Bornstein et al. (2005)                                                |
|                                                               |    | Bruschi et al. (2017)                                                  |
|                                                               |    | Cassetta et al. (2016)                                                 |
|                                                               |    | Cesaretti et al. (2015)                                                |
|                                                               |    | Cochran et al. (2009)                                                  |
|                                                               |    | Crespi et al. (2010)                                                   |
|                                                               |    | Degidi et al. (2009a)                                                  |
|                                                               |    | Degidi et al. (2009b)                                                  |
|                                                               |    | Ferrini et al. (2018)                                                  |
|                                                               |    | Glauser et al. (2013)                                                  |
|                                                               |    | Gilbert et al. (2016)                                                  |
|                                                               |    | Gomez-Roman et al. (2001)                                              |
|                                                               |    | Han et al. (2017)                                                      |
|                                                               |    | Harel et al. (2013)                                                    |
|                                                               |    | Jungner et al. (2014)                                                  |
|                                                               |    | Jungner et al. (2012)                                                  |
|                                                               |    | Kim et al. (2017)                                                      |
|                                                               |    | Kokovic et al. (2014)                                                  |
|                                                               |    | Maddalone et al. (2018)                                                |
|                                                               |    | Malchiodi et al. (2011)                                                |
|                                                               |    | Montero et al. (2012)                                                  |
|                                                               |    | Muelas-Jiménez et al. (2015)                                           |
|                                                               |    | Mura (2018)                                                            |
|                                                               |    | Nicolau et al. (2019)                                                  |
|                                                               |    | Nicolau et al. (2013)                                                  |
|                                                               |    | Peñarrocha-Diago et al. (2012)                                         |
|                                                               |    | Pettersson and Sennerbry (2013)                                        |
|                                                               |    | Polizzi et al. (2000)                                                  |
|                                                               |    | Polizzi et al. (2013)                                                  |
|                                                               |    | Pozzi et al. (2012)                                                    |
|                                                               |    | Pozzi et al. (2015)                                                    |
|                                                               |    | Rammelsberg et al. (2016)                                              |
|                                                               |    | Rocci et al. (2012)                                                    |
|                                                               |    | Roccuzzo et al. (2018)                                                 |
|                                                               |    | Rocha et al. (2016)                                                    |
|                                                               |    | Rossi et al. (2017)                                                    |
|                                                               |    | Sato et al. (2014)                                                     |
|                                                               |    | Schlepke et al. (2012)                                                 |
|                                                               |    | Šener-Yamaner et al. (2017)                                            |
|                                                               |    | Sullivan et al. (2005)                                                 |
|                                                               |    | Sullivan et al. (2001)                                                 |
|                                                               |    | Tallarico and Meloni (2017)                                            |
|                                                               |    | Testori et al. (2017)                                                  |
|                                                               |    | Valerón and Valerón (2007)                                            |
|                                                               |    | Villa (2018)                                                           |
|                                                               |    | Wagenberg and Froum (2014)                                             |
|                                                               |    | Zembić et al. (2010)                                                  |
|                                                               |    | Madani et al. (2018)                                                   |
|                                                               |    | Jung et al. (2016)                                                     |
|                                                               |    | Cochran et al. (2011a)                                                 |
|                                                               |    |                                                                  |
| Mean follow-up less than 3 years                              |  3 | Schwartz-Arad et al. (2007)                                            |
|                                                               |    | Cordero et al. (2010)                                                  |
|                                                               |    | Degidi et al. (2008)                                                   |
|                                                               |    |                                                                  |
| Less than 10 patients at 3 years                              |  1 | Ding and Wang (2017)                                                  |
|                                                               |    |                                                                  |
| Absence of FPDs supported by ≥2 implants                      |  7 | Prati et al. (2016)                                                    |
|                                                               |    | Kolinsky et al. (2013)                                                 |
|                                                               |    | Merli et al. (2020)                                                    |
|                                                               |    | Romeo et al. (2012)                                                   |
|                                                               |    | Salina et al. (2019)                                                   |
|                                                               |    | Crespi et al. (2016)                                                   |
|                                                               |    | Bruschi et al. (2014)                                                  |
|                                                               |    |                                                                      |
| Insufficient data do separate different placement protocols   |  4 | Ferrini et al. (2018)                                                  |
|                                                               |    | Glauser et al. (2016)                                                  |
|                                                               |    | Glauser et al. (2006)                                                  |
|                                                               |    | Degidi et al. (2018)                                                   |
|                                                               |    |                                                                  |
| Insufficient data to separate single/full mouth from multiple units | 44 | Pozzi et al. (2014)                                                    |
|                                                               |    | Anitua et al. (2016)                                                   |
|                                                               |    | Botticelli et al. (2018)                                               |
|                                                               |    | Crespi et al. (2017)                                                   |
|                                                               |    | Crespi et al. (2016)                                                   |
|                                                               |    | Crespi et al. (2010a)                                                  |
|                                                               |    | Crespi et al. (2010b)                                                  |
|                                                               |    | Crespi et al. (2014)                                                   |
|                                                               |    | Degidi et al. (2012)                                                   |
|                                                               |    | Degidi et al. (2003)                                                   |
|                                                               |    | Galindo-Moreno et al. (2014)                                           |
|                                                               |    | Liu et al. (2019)                                                      |
|                                                               |    | Malchiodi et al. (2010)                                                |
|                                                               |    | Maló et al. (2011)                                                     |
|                                                               |    | Maló et al. (2015)                                                     |
|                                                               |    | Maló et al. (2000)                                                     |
|                                                               |    | Maló et al. (2007)                                                     |
|                                                               |    | Maló et al. (2016)                                                     |
|                                                               |    | Maló et al. (2014)                                                     |
|                                                               |    | Martinez-Rodriguez et al. (2018)                                       |
|                                                               |    | Mengel et al. (2005)                                                   |
|                                                               |    | Merli et al. (2020)                                                    |
|                                                               |    | Mura et al. (2012)                                                     |

(Continues)
full-text screening, the reader is referred to Appendix S2. Table 2 lists the 14 included studies and their 21 cohort groups enabling us to analyze combined protocols of implant placement and loading.

All 14 studies included information on implant survival and on one or more biological outcomes, but the biological outcomes reported across studies did differ. Since we would only consider MBL changes from prosthetic loading to follow-up whereas some studies only reported MBL values measured at the time of implant placement, these latter values were not evaluable. Details on peri-implant inflammation were reported based on clinical indices (Gingival Index, Sulcus Bleeding Index, Bleeding on Probing (BOP), modified Bleeding Index, Bleeding Index) so heterogeneous as to preclude a comparison across cohort groups. Group-specific mean Plaque Index (PI) scores and Probing Depths (PD) were reported in few of the 14 studies, while mean soft-tissue recession and mean width of keratinized tissue (KT) dimensions were reported in only one of them [Romanos et al., 2016].

Some studies indicated that implant placement had taken place >3 months (Göthberg et al., 2018; Oxby et al., 2015; Van Nimwegen et al., 2015). >4 months (Fung et al., 2011), or >3 to 6 months (Spies et al., 2015) after tooth extraction. Others were categorized as delayed placement based on statements that the implants had been inserted in healed (An et al., 2019; Degidi et al., 2011; Simons et al., 2015; Vogl et al., 2019) or edentulous (Romanos et al., 2016) ridge areas. As most placement and loading protocols were covered by few or no studies, only one direct comparison was performed (DPIL versus DPDL).

3.2 | Within-study risks of bias

Tables 3-5 summarizes the risk-of-bias assessments based on the Cochrane RoB 2.0 tool, Newcastle-Ottawa scale, and Joanna Briggs Institute’s Critical Appraisal Checklist.

All cohort and case series were rated with low risk of bias. Regarding RCT studies, 3 of them (Daher et al., 2019; Fung et al., 2011; Van Nimwegen et al., 2015) were evaluated as having some concerns in terms of risk bias. Two were rated with high risk of bias (Romanos et al., 2016; Vogl et al., 2019), and only one was rated with low risk of bias (Göthberg et al., 2018).

3.3 | Within-study results

Table 6 lists the data extracted from the included studies. None of these reported on IPDL, EPIL, EPDL, or EPDL combinations of placement and loading. Given the unspecific wording by which many authors refer to the timing of implant placement, any studies reporting on implants placed >3 months after tooth extraction without giving a time range (e.g., between 3 and 6 months) were considered delayed placement. Thus, eleven cohort groups were available for DPIL (delayed placement + immediate restoration/loading), seven for DPDL (delayed placement + delayed loading), one for DPEL (delayed placement + early loading), one for IPIL (immediate placement + immediate restoration/loading), and one for type IPEL (immediate placement + early loading).

3.3.1 | IPIL (immediate placement + immediate restoration/loading)

Only one prospective cohort study was available on this combination of protocols [Siebers et al., 2010]. It gave a mean follow-up of 47.64 ± 6.48 months, two of these 20. Implants failed (implant survival rate: 90%). Even though immediate placement and immediate restoration/loading tended to produce a lower survival in this specific study, the MBL changes appeared favorable compared to delayed placement protocols.

3.3.2 | IPEL (immediate placement + early loading)

One prospective cohort study was available (Oxby et al., 2015). Based on a mean follow-up of 55 months, none of the 67 implants in this category failed (survival rate: 100%) and merely one biological complication (soft-tissue recession) was reported.
### 3.3.3 DPIL (delayed placement + immediate loading)

Data on this combination of protocols were available from five randomized controlled trials, three prospective cohort studies, and two prospective case series, including 11 cohort groups with data on implant outcomes. Overall, 14 of 502 implants in this category failed. Based on a mean follow-up of 60.1 ± 37.8 months, a weighted cumulative survival of 97.2% was obtained. Data for 378 implants revealed a mean MBL change of 0.71 ± 0.66 mm and data for 361 implants a 2.6% rate of biological complications. Probing depths were reported in four studies (An et al., 2019; Fung et al., 2011; Göthberg et al., 2018; Romanos et al., 2016) resulting in a calculated mean of 2.83 ± 0.92 mm. A sub-analysis on the type of loading revealed an approximately similar MBL change for functional (0.65 mm) versus nonfunctional (0.62 mm) loading.

| Study                          | Study design          | Setting/Country      | Total number of patients | Drop-outs | Presence of smokers Yes/no (n) | Patients with history of periodontitis included (n) |
|-------------------------------|-----------------------|----------------------|--------------------------|-----------|-------------------------------|--------------------------------------------------|
| An et al. (2019)              | Case series (prospective) | University/South Korea | 33                       | 0         | NR                            | NR                                               |
| Daher et al. (2019)           | RCT (split-mouth)    | University/Lebanon   | 24                       | 2         | Yes (13)                      | Yes (NR)                                         |
| Degidi et al. (2011)          | Observational cohort (prospective) | Private practice/Italy | 24                       | 3         | NR                            | NR                                               |
| Fung et al. (2011)            | RCT (split-mouth)    | University/USA       | 10                       | 0         | Yes (2)                       | NR                                               |
| Göthberg et al. (2018)        | RCT                   | University/Sweden    | 50                       | 0         | NR                            | Yes (NR)                                         |
| Oxby et al. (2015)            | Observational Cohort (prospective) | Private practice/Sweden | 39                       | 4         | NR                            | NR                                               |
| Payer et al. (2010)           | Case Series (prospective) | University/Austria    | 24                       | 0         | NR                            | NR                                               |
| Romanos et al. (2016)         | RCT (split-mouth)    | University/Germany   | 24                       | 4         | NR                            | NR                                               |
| Si et al. (2016)              | Case Series (retrospective) | University/China     | 10                       | 0         | Yes (24)                      | Yes (41)                                         |
| Siebers et al. (2010)         | Observational cohort (prospective) | Private practice/Germany | 45                       | NR        | Yes (15)                      | Yes (45)                                         |
| Spies et al. (2015)           | Observational cohort (prospective) | University/Germany   | 13                       | 0         | NR                            |                                                  |
| Simons et al. (2015)          | Case–control (retrospective) | University/Belgium    | 70                       | NR        | Yes (29)                      | Yes (267)                                        |
| Van Nimwegen et al. (2015)    | RCT                   | University/Netherlands | 40                       | 5         | NR                            | NR                                               |
| Vogl et al. (2019)            | RCT                   | University/Austria   | 20                       | 0         | NR                            | NR                                               |

Abbreviation: NR, not reported.
### 3.3.4 | DPEL—(delayed placement + early loading)

There was only one prospective cohort study [Oxby et al., 2015]. Based on a mean follow-up of 55 months, none of the 107 implants in this category failed (survival rate: 100%) and merely one biological complication (soft-tissue recession) was reported.

### 3.3.5 | DPDL—(delayed placement + delayed loading)

Data on this combination of protocols were available from three randomized controlled trials, one prospective cohort study, one retrospective cohort study, and one retrospective case series.

| Reported timing of implant placement | Reported timing of restoration/loading | Type of implant placement and loading protocol | Number of implants | Implant material | Implant brand/Manufacturer |
|-------------------------------------|---------------------------------------|-----------------------------------------------|--------------------|----------------|--------------------------|
| NR                                 | Day of implant placement              | DPIL                                          | 68                 | Titanium       | NR                       |
| >9 months                          | Immediately after implant placement   | DPIL                                          | 80                 | Titanium       | NobelActive/Nobel Biocare |
| >9 months                          | 3.5 months after implant placement    | DPDL                                          | 80                 | Titanium       |                          |
| NR                                 | Immediately after implant placement   | DPIL                                          | 48                 | Titanium       | ANKYLLOS/Dentsply         |
| ≥4 months                          | Within 24 h after implant placement   | DPIL                                          | 42                 | Titanium       | Brånemark System Mk IV    |
| >3 months post-extraction          | Within 48 h after implant placement   | DPIL                                          | 78                 | Titanium       | TIUnite/Nobel Biocare     |
| >3 months post-extraction          | 3–4 months after implant placement    | DPDL                                          | 72                 | Titanium       |                          |
| ≥3 months post-extraction          | Within 60 days after implant placement| DPEL                                          | 107                | Titanium       | Astra Tech/Dentsply       |
| Immediately post-extraction        | Within 60 days after implant placement| IPEL                                          | 67                 | Titanium       |                          |
| 6 months post-extraction           | Immediately/within 1 week after implant placement | DPIL | 40 | Titanium | Xive/Dentsply |
| NR                                 | Within 24 h after implant placement   | DPIL                                          | 36                 | Titanium       | ANKYLLOS/Dentsply         |
| NR                                 | 3 months after healing                 | DPDL                                          | 36                 | Titanium       |                          |
| >3 months after tooth extraction   | 3–4 months after healing               | DPDL                                          | 21                 | Titanium       | Straumann AG              |
| Immediately after tooth extraction | Within 48 h after implant placement   | IPIL                                          | 20                 | Titanium       | Camlog; 3i; Lifecore      |
| Healed sites                       | Within 48 h after implant placement   | DPIL                                          | 33                 | Titanium       |                          |
| Healed sites                       | 6 months after implant placement      | DPDL                                          | 46                 | Titanium       |                          |
| >3 months after tooth extraction   | Immediately after implant placement   | DPIL                                          | 26                 | Zirconia       | Metoxit/Ziraldent         |
| Healed sites                       | 3–6 months after implant placement    | DPDL                                          | 151                | Titanium       | Branemark MK III/Nobel Biocare |
| ≥3 months post-extraction          | ≥3 months after implant placement     | DPDL                                          | 70                 | Titanium       | Nobel Perfect Groovy/ Nobel Biocare |
| Healed sites                       | Immediately after implant placement   | DPIL                                          | 19                 | Titanium       | Xive/Dentsply             |
| Healed sites                       | Immediately after implant placement   | DPIL                                          | 32                 | Titanium       |                          |
### TABLE 3  Risk of bias assessments of RCTs based on the Cochrane RoB 2.0 tool

| Study                              | Outcome                          | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|------------------------------------|----------------------------------|-----------------------|----------------------------------------|----------------------|---------------------------|----------------------------------|---------|
| Fung, et al., 2011                 | Radiographic bone level          | ?                     | +                                      | +                    | +                         | ?                                | ![Low risk] |
| Van Nimwegen, et al., 2015         | Radiographic bone level          | ![Some concerns]     | ![High risk]                           | ![High risk]        | ![High risk]               | ![High risk]                     | ![High risk] |
| Vogl, et al., 2019                 | Marginal bone defect             | ![High risk]          | ![High risk]                           | ![High risk]        | ![High risk]               | ![High risk]                     | ![High risk] |
| Gothenberg, et al., 2018           | Radiographic bone level          | ![High risk]          | ![High risk]                           | ![High risk]        | ![High risk]               | ![High risk]                     | ![High risk] |
| Daher, et al., 2019                | Radiographic bone level          | ![High risk]          | ![High risk]                           | ![High risk]        | ![High risk]               | ![High risk]                     | ![High risk] |
| Romanos, et al., 2016              | Radiographic bone loss           | ![High risk]          | ![High risk]                           | ![High risk]        | ![High risk]               | ![High risk]                     | ![High risk] |

### TABLE 4  Risk of bias assessments of Cohort studies based on New Castle - Ottawa Quality Assessment Scale

| Study                              | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Outcome not present at the start of the study |
|------------------------------------|------------------------------------------|------------------------------------|---------------------------|-----------------------------------------------|
| Degidi et al. (2011), Oxby et al. (2015) | *                                        | *                                  | *                         | *                                             |
| Oxby et al. (2015)                 | *                                        | *                                  | *                         | *                                             |
| Siebers et al. (2010)              | *                                        | *                                  | *                         | *                                             |
| Simons et al. (2015)               | *                                        | *                                  | *                         | *                                             |
| Spies et al. (2015)                | *                                        | *                                  | *                         | *                                             |

**Note:** Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

- **Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

### TABLE 5  Risk of bias assessments of Case Series based on Joanna Briggs Institute's Critical Appraisal Checklist

| Study                              | Were there clear criteria for inclusion in the case series? | Was the condition measured in a standard, reliable way for all participants included in the case series? | Were valid methods used for identification of the condition for all participants included in the case series? | Did the case series have consecutive inclusion of participants? | Did the case series have complete inclusion of participants? |
|------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------|
| An et al. (2019)                   | Yes                                                      | Yes                                                                                                | Yes                                                                                                    | Unclear                                                      | Yes                                                         |
| Payer et al. (2010)                | Yes                                                      | Yes                                                                                                | Unclear                                                                                               |                                                               | Yes                                                         |
| Si et al. (2016)                   | Yes                                                      | Yes                                                                                                | Yes                                                                                                    | Yes*                                                         | Unclear                                                     |
Overall, 14 of 476 implants in this category failed. Based on a mean follow-up of 74.2 ± 43.4 months, the weighted cumulative survival was 98.1%. Data for 217 implants yielded a mean MBL change of 1.68 ± 0.97 mm and data for 242 implants a 3.7% cumulative rate of biological complications. From 3 studies, in a mean probing depth of 3.12 ± 1.08 mm was calculated (Göthberg et al., 2018; Romanos et al., 2016; Van Nimwegen et al., 2015).

3.4 | Results of meta-analysis

The reported results of analysis were based on data extracted directly from included studies but also on additional raw data provided by some of the authors (Daher et al., 2019; Göthberg et al., 2018; Oxby et al., 2015; Payer et al., 2010; Siebers et al., 2010; Simons et al., 2015; Vogl et al., 2019). Due to heterogeneity, mostly related to study designs and variable radiographic and clinical measures, only three RCTs comparing the same types of implant placement and implant loading protocols (DPIL vs. DPDL) were available for a quantitative synthesis (Daher et al., 2019; Göthberg et al., 2018; Romanos et al., 2016). The meta-analysis revealed an overall effect size of 1.57 [95% CI: 0.19; 13.1], so that no significant difference in terms of survival rate (p = .227) emerged between the type DPIL (74 patients/188 implants) and DPDL (182 implants/72 patients) combinations of placement and loading (Figure 2). Between-trial heterogeneity was minimal in absolute ($t^2$: 0.0022) and relative ($t^2$: 0) terms ($p = .77$).

Regarding the publication bias assessment, Egger’s test does not indicate the presence of funnel plot asymmetry (Figure 3). However, since the meta-analysis contains three studies ($k = 3$) the Egger’s test may lack the statistical power to detect bias (i.e., $k < 10$).

3.5 | Certainties of evidence

Table 7 illustrates the overall quality of meta-evidence. The following outcome was assessed across the various combinations of implant placement and loading protocols: BOP, pocket depths, MBL changes, peri-implantitis, peri-implant mucositis, and implant survival rates. A GRADE summary-of-evidence compilation is provided (Table 7) for each of the four comparisons that could be made between any two of the evaluable placement-plus-loading combinations (DPIL vs. DPDL, IPIL vs. DPDL, DPEL vs. DPDL, and IPEL vs. DPDL). Both direct and indirect study comparisons and all (available) biological outcomes have been entered. A low certainty was identified for one comparison (DPIL vs. DPDL) and one outcome (BOP) based on one RCT exhibiting a high risk of bias (Romanos et al., 2016). Other than that, the certainty of evidence was rated as very low in all comparisons for all outcome parameters. In relation to the reference combination of protocols (type DPDL), all

| Comparability of cases and controls | Assessment of outcome | Sufficient follow-up time for outcomes to occur | Adequacy of follow-up of cohorts | Total |
|------------------------------------|-----------------------|-----------------------------------------------|---------------------------------|-------|
| *                                  | *                     | *                                             | *                               | 8     |
| *                                  | *                     | *                                             | *                               | 8     |
| *                                  | *                     | *                                             | *                               | 7     |
| *                                  | *                     | *                                             | *                               | 7     |
| *                                  | *                     | *                                             | *                               | 8     |

| Was there clear reporting of the demographics of the participants in the study? | Was there clear reporting of clinical information of the participants? | Were the outcomes of follow-up results of cases clearly reported? | Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | Was statistical analysis appropriate? | Overall appraisal |
|-----------------------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------|------------------|
| Yes                                                                         | Yes                                                                   | Yes                                                              | Yes*                                                                                       | Yes                              | Included         |
| Yes                                                                         | Yes                                                                   | Yes                                                              | Yes                                                                                       | Yes                              | Included         |
| Yes                                                                         | Yes                                                                   | Yes                                                              | Yes                                                                                       | Yes                              | Included         |
| Study              | Placement and loading protocol | Type of loading | Mean ± SD follow-up (months) | No. implants placed | No. implants available at follow-up | Implant survival rate | Mean ± SD MBL changes at follow-up (mm) | Mean ± SD on peri-implant inflammation (different indexes) |
|-------------------|--------------------------------|-----------------|-----------------------------|---------------------|-------------------------------------|----------------------|----------------------------------------|---------------------------------------------------------------|
| An et al. (2019)  | DPIL                           | Non-functional  | 36                          | 68                  | 68                                  | 100%                 | 0.42 ± 0.39                            | 0.65 ± 0.81 (Gingival Index)                                  |
| Daher et al. (2019) | DPIL                            | Functional      | 36                          | 80                  | 69                                  | 95.5%                | 0.78 ± 0.72                            | NR                                                            |
| Degidi et al. (2011) | DPIL                         | Non-functional  | 36                          | 48                  | 48                                  | 100%                 | 0.57 ± 0.52                            | NR                                                            |
| Fung et al. (2011) | DPIL                           | Functional      | 36                          | 42                  | 40                                  | 95.2%                | 0.26 ± 0.44                            | 0.25 ± 0.30 (Sulcus Bleeding Index)                           |
| Göthberg et al. (2018) | DPIL                        | Functional      | 60                          | 78                  | 62                                  | 94.9%                | NR                                     | NR                                                            |
| Oxbry et al. (2015) | DPEL                           | NA              | 55                          | 107                 | 107                                 | 100%                 | 0.28 ± 0.88                            | NR                                                            |
| Siebers et al. (2010) | DPIL                        | Both            | 45.1 ± 7.2                  | 33                  | 32                                  | 97%                  | 2.15 ± 0.81                            | 1.59 ± 1.39 (from 0 to 6)                                    |
| Romanos et al. (2016) | DPIL                        | Functional      | 145.7 ± 10.7                | 36                  | 30                                  | 100%                 | 0.57 ± 1.06                            | 0.07 ± 0.25 (Sulcus Bleeding Index)                           |
| Si et al. (2016)   | DPDL                           | NA              | 66                          | 21                  | 19                                  | 90.5%                | 0.5 ± 0.68                             | NR                                                            |
| Spies et al. (2015) | DPIL                           | Non-functional  | 60                          | 26                  | 26                                  | 100%                 | 1.14 ± NR                              | 1.1 ± NA (modified Bleeding Index)                            |
| Van Nimwegen et al. (2015) | DPDL          | NA              | 60                          | 70                  | 58                                  | 97.1%                | 40 ± NR                                | Bleeding Index                                                  |
| Vogl et al. (2019) | DPIL                           | Functional      | 36                          | 19                  | 17                                  | 100%                 | 0.37 ± 0.46                            | NR                                                            |
|                  | DPIL                           | Non-functional  | 36                          | 32                  | 30                                  | 97%                  | 0.39 ± 0.47                            | NR                                                            |

**FIGURE 2** Forest plot with individual effects and heterogeneity measures
alternative combinations seem to improve biological outcomes and survival rates.

4 | DISCUSSION

It has been suggested as a fundamental principle in implant dentistry that the implant-restoration complex should be considered as a single variable in assessing clinical outcomes (Garber & Belser, 1995) and consequently success of treatment. In the present review, this

| Mean ± SD soft-tissue recession at follow-up (mm) | Mean ± SD width KT at follow-up (mm) | Mean ± SD PI at follow-up (mm) | Mean (SD) PD at follow-up (mm) | No. of reported biological complications | Rate of biological complications (%) (except implant failure) |
|-------------------------------------------------|-------------------------------------|--------------------------------|--------------------------------|-----------------------------------------|-------------------------------------------------------------|
| NR                                              | NR                                  | 0.35 ± 0.64                   | 2.68 (1.00)                    | 0                                       | 0%                                                          |
| NR                                              | NR                                  | NR                             | NR                             | 2 implants with peri-implantitis        | 2.8%                                                        |
| NR                                              | NR                                  | NR                             | NR                             | 0                                       | 0%                                                          |
| NR                                              | NR                                  | 2.82 (0.75)                    | 0                              | 0%                                      |                                                             |
| NR                                              | NR                                  | NR                             | 3.15 (0.87)                    | 3 implants with peri-implantitis       | 4.8%                                                        |
| NR                                              | NR                                  | NR                             | 3.18 (0.94)                    | 2 implants with peri-implantitis       | 6.3%                                                        |
| NR                                              | NR                                  | NR                             | NR                             | 1 implant with soft-tissue recession    | 0.9%                                                        |
| NR                                              | NR                                  | NR                             | NR                             | 1 implant with soft-tissue recession    | 1.5%                                                        |
| NR                                              | NR                                  | 3.33 (1.73)                    | 2 implants with peri-implantitis | 3.4%                                    |
| NR                                              | NR                                  | 1.6 ± 0.7                      | NR                             | 0                                       | 0%                                                          |
| NR                                              | NR                                  | 1.6 ± 0.7                      | NR                             | 0                                       | 0%                                                          |

**FIGURE 3** Funnel plot describing the publication bias assessment
### TABLE 7 GRADE I-IV summary-of-evidence compilation for each of the four comparisons that could be made between any two placement and loading combinations (DPIL vs. DPDL, IPIL vs. DPDL, DPEL vs. DPDL, IPEL vs. DPDL)

#### Summary of findings: GRADE I

Delayed placement and immediate loading (DPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

**Patient or population:** Implant treatment in partially edentulous individuals (analysis at implant level)

**Setting:** University/private clinic

**Intervention:** delayed placement and immediate loading (DPIL)

**Comparison:** delayed placement and delayed loading (DPDL)

| Outcomes                                      | Anticipated absolute effects | Weighted effect with delayed placement and immediate loading (DPIL) |
|-----------------------------------------------|------------------------------|---------------------------------------------------------------------|
| Rx bone loss around the implant platform      | The mean rx bone loss around the implant platform was 1.68 mm ± 0.97 | The mean rx bone loss around the implant platform was 0.71 mm ± 0.66 |
| Bleeding on probing assessed with: Sulcus     | The mean SBI was 0.066 (±0.253) | The mean SBI was 0.00 (±0.00)                                      |
| Peri-implant probing depth                    | The mean peri-implant pocket depth was 3.12 mm ± 1.08                | The mean peri-implant pocket depth was 2.83 mm ± 0.92               |
| Peri-implantitis prevalence assessed with:    | The mean percentage of implants with peri-implantitis was 3.5%     | The mean percentage of implants with peri-implantitis was 0.9%    |
| Radiographic and clinical examination^d       |                                                                           |                                                                     |
| Mucositis                                     | No mucositis was reported in all studies with data on peri-implantitis |

Survival rate assessed with: Radiographic and clinical examination^d

The mean survival rate was 98.1.2%  
The mean survival rate was 97.2% 

**GRADE Working Group grades of evidence:** High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.  
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

#### Summary of findings: GRADE II

Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

**Patient or population:** Implant treatment in partially edentulous individuals

**Setting:** University/private clinic

**Intervention:** immediate placement and immediate loading

**Comparison:** delayed placement and delayed loading

| Outcomes                                      | Weighted effect with delayed placement and delayed loading (DPDL) | Weighted effect with immediate placement and immediate loading (IPIL) |
|-----------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| Rx bone loss around the implant platform      | The mean rx bone loss around the implant platform was 1.68 mm ± 0.97 | The mean rx bone loss around the implant platform 1.57 mm ± 0.91 |
| Bleeding on probing assessed with: 0 to 6 scale (unknown reference) | Mean bleeding was 2.91 ± 2.11 | Mean bleeding was 1.76 ± 1.79 |

Evidence is scarce on mucositis. No cases were reported in the included studies.

Evidence is scarce on peri-implantitis and low rates were reported in the included studies. This could be in part due to poor reporting of the study of the clinical examination. Follow-up period varied from 3 years up to 15 years.

Immediate loading after delayed placement seems to reduce potential for peri-implantitis and bone loss after loading. Follow-up period varied from 3 years up to 15 years.

Immediate loading after delayed placement does not seem to affect the mean rx bone loss around the implant platform. Follow-up period varied from 3 years up to 15 years.

Implants placed with immediate implant placement and immediate loading may exhibit decreased bleeding on probing. Follow-up was 15 years.

Implants placed with immediate implant placement and immediate loading may exhibit comparable mean bone loss.
TABLE 7
GRADE I-IV summary of evidence compilation for each of the four comparisons that could be made between any two placement

| Outcomes | Comparison | Intervention | Patient or population | Setting | No. of implants (contributing arm/studies) | Certainty of the evidence (GRADE) | Comments |
|----------|------------|--------------|-----------------------|---------|------------------------------------------|---------------------------------|----------|
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals (analysis at implant level) | | 535 (4 RCTs, 4 observational studies) | ★★★★★ VERY LOW° | Evidence is scarce on peri-implantitis and low rates were reported in the included studies. This could be in part due to poor reporting of the study of the clinical examination. Follow-up period varied from 3 years up to 15 years |
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals | | 535 (4 RCTs, 4 observational studies) | ★★★★★ VERY LOW° | Evidence is scarce on mucositis. No cases were reported in the included studies but this could be in part due to poor reporting of the study of the clinical examination. Follow-up period varied from 3 years up to 15 years |
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals | | 879 implants (6 RCTs, 7 observational studies) | ★★★★★ VERY LOW° | Both delayed and immediate loading after delayed placement after delayed implant placement present high survival rates. Follow-up period varied from 3 years up to 15 years |
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals | | 676 implants (4 RCTs, 6 observational studies) | ★★★★★ VERY LOW° | Immediate loading after delayed placement seems to reduce potential bone loss after loading. Follow-up period varied from 3 years up to 15 years |
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals | | 60 implants (1 RCT) | ★★★★★ LOW° | Immediate loading after delayed placement does not seem to affect the Sulcus Bleeding Index. Follow-up was 15 years |
| Survival rate assessed with: Radiographic and clinical examination | Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals | University/private clinic | implant treatment in partially edentulous individuals | | 352 (4 RCTs, 1 observational studies) | ★★★★★ VERY LOW° | Peri-implant pocket depth does not exhibit substantial difference between immediate and delayed loading after delayed implant placement |

(Continues)
Summary of findings: GRADE II

Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

Patient or population: implant treatment in partially edentulous individuals
Setting: University/private clinic
Intervention: immediate placement and immediate loading
Comparison: delayed placement and delayed loading

| Outcomes                        | Anticipated absolute effects | Weighted effect with delayed placement and delayed loading (DPDL) | Weighted effect with immediate placement and immediate loading (IPIL) |
|--------------------------------|------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------|
| Peri-implant probing depth      | No comparison was possible    |                                                                |                                                                     |
| Peri-implantitis prevalence     | No comparison was possible    |                                                                |                                                                     |
| Mucositis                      | No comparison was possible    |                                                                |                                                                     |
| Survival rate assessed with:   |                              |                                                                |                                                                     |
| Radiographic and clinical       | Survival rate was 98.1%       | Survival rate was 75%                                           |                                                                     |
| examination                    |                              |                                                                |                                                                     |

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Summary of findings: GRADE III

Delayed placement and early loading (DPEL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

Patient or population: implant treatment in partially edentulous individuals
Setting: University/private clinic
Intervention: delayed placement and early loading
Comparison: delayed placement and delayed loading

| Outcomes                        | Anticipated absolute effects | Weighted effect with delayed placement and delayed loading (DPDL) | Weighted effect with delayed placement and early loading (DPEL) |
|--------------------------------|------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| Rx bone loss around the implant platform assessed with: Radiographic image | The mean rx bone loss around the implant platform was 1.68 mm ± 0.97| The mean rx bone loss around the implant platform was 0.28 ± 0.88 |
| Bleeding on probing             | No comparison was possible    |                                                                |                                                                     |
| Peri-implant probing depth      | No comparison was possible    |                                                                |                                                                     |
| Peri-implantitis prevalence     | No comparison was possible    |                                                                |                                                                     |
| Mucositis                      | No comparison was possible    |                                                                |                                                                     |
| Survival rate assessed with:   |                              |                                                                |                                                                     |
| Radiographic and clinical       | Survival rate was 98.1%       | Survival rate was 100%                                         |                                                                     |
| examination                    |                              |                                                                |                                                                     |

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
### Summary of findings: GRADE II
Immediate placement and immediate loading (IPIL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

| No. of implants (contributing arm/studies) | Certainty of the evidence (GRADE) | Comments |
|------------------------------------------|----------------------------------|----------|
| -                                        | -                                | -        |
| -                                        | -                                | -        |
| -                                        | -                                | -        |
| 318 (2 RCTs, 3 observational studies)    | 💫★★★★



### Summary of findings: GRADE III
Delayed placement and early loading (DPEL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals

| No. of participants (contributing arm/studies) | Certainty of the evidence (GRADE) | Comments |
|-----------------------------------------------|----------------------------------|----------|
| 298 + 107 (2 RCTs, 3 observational studies)  | 💫★★★★



| No. of participants (contributing arm/studies) | Certainty of the evidence (GRADE) | Comments |
|-----------------------------------------------|----------------------------------|----------|
| 439 + 107 (3 RCTs, 3 observational studies)   | 💫★★★★



*Implants placed using both delayed placement with delayed loading may present higher survival rates compared to immediate placement with immediate loading. Follow-up period varied from 3 years up to 15 years.*

*Implants placed with delayed implant placement and early loading may exhibit decreased mean bone loss after loading. Follow-up period varied from 3 years up to 15 years.*

*Implants placed using both delayed placement with delayed loading and delayed placement with early loading seem to present high survival rates. Follow-up period varied from 3 years up to 15 years.*
principle was adopted by evaluating all outcomes of placement and loading from the 14 studies in combination, as recently suggested (Gallucci et al., 2018). Five of the 9 categories are covered by the included studies: immediate placement combined with immediate or early loading (types IPIL and IPEL), and delayed placement combined with immediate, early, or delayed loading (types DPIL, DPEL, and DPDL). Three to 15 years after surgery, all groups showed implant survival rates >90%, except one observational study representing type IPIL (Siebers et al., 2010).

Heterogeneity in study designs, inconsistencies in outcome reporting, and a lack of comparative studies, reflected by the low level of evidence in the GRADE table, allowed to include only three RCT's in one quantitative synthesis (Daher et al., 2019; Göthberg et al., 2010; Romanos et al., 2016). The meta-analysis revealed no significant difference in terms of survival rate ($p = .227$) emerged between the type DPIL (74 patients/188 implants) and DPDL (182 implants/72 patients) combinations of placement and loading.

The only biological outcome measure that could be extracted from pooled data was mean MBL. However, their heterogeneity and quality did not allow to draw any conclusions on the effect of different timing of placement and loading protocols on peri-implant marginal bone changes.

Biological complications were poorly reported in the studies here reviewed. Low rates of 2.6% or 3.7% emerged in two groups of delayed placement time combined with either immediate loading (type DPIL) or delayed loading (type DPDL). Our extraction of data on biological outcomes and complications was based on definitions of peri-implant disease (Heitz-Mayfield & Salvi, 2018; Schwarz et al., 2018) and health (Araujo & Lindhe, 2018) adopted by the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions, co-sponsored by the

| TABLE 7 (Continued) |
|----------------------|
| **Summary of findings: GRADE IV** |
| Immediate placement and early loading (IPEL) compared to delayed placement and delayed loading (DPDL) for implant treatment in partially edentulous individuals |
| **Patient or population:** implant treatment in partially edentulous individuals |
| **Setting:** University/private clinic |
| **Intervention:** immediate placement and early loading |
| **Comparison:** delayed placement and delayed loading |
| **Outcomes** | **Anticipated absolute effects $\pm$ (95% CI)** |
| Rx bone loss around the implant platform assessed with: Radiographic image $\dagger$ | The mean rx bone loss around the implant platform was $1.68 \text{ mm } \pm 0.97$ |
| Bleeding on probing | No comparison was possible |
| Peri-implant probing depth | No comparison was possible |
| Peri-implantitis prevalence | No comparison was possible |
| Mucositis | No comparison was possible |
| Survival rate assessed with: Radiographic and clinical examination $\dagger$ | Survival rate was 98.1% |

**GRADE Working Group grades of evidence:**

*High certainty:* We are very confident that the true effect lies close to that of the estimate of the effect.  
*Moderate certainty:* We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
*Low certainty:* Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
*Very low certainty:* We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

$\dagger$ All studies except for one RCT (Gothberg et al., 2018) showed from some concerns to high risk of bias; only 3 direct comparisons.  
$\ddagger$ The study Romanos et al. (2014) was rated with high risk of bias.  
$\ddagger\ddagger$ Based on withing study comparisons.  
$\ddagger\ddagger\ddagger$ Based on within and between study comparisons  
$\ddagger\ddagger\ddagger\ddagger$ All studies except for one RCT (Gothberg et al., 2017) showed from some concerns to high risk of bias.  
$\ddagger\ddagger\ddagger\ddagger\ddagger$ Based on between study comparisons.
American Academy of Periodontology and the European Federation of Periodontology (Caton et al., 2018). Unfortunately, many studies do not clearly define peri-implant diseases or do not consider clinical parameters in their definition, which can lead to inaccuracy and biased results. Thus, in this systematic review, only survival rates and mean bone level could be quantitatively assessed.

The results of this review are consistent with a previous finding of overall treatment outcomes being similar for immediately placed and loaded implants as in control groups of delayed placement and/or delayed loading (Parvini et al., 2020). In addition, a systematic review has reported survival rates >97% across all protocols of placement and loading (Gallucci et al., 2018), while another systematic review focusing on placement protocols did not find a significant difference between differently timed implant procedures (Bassir et al., 2018).

No solid conclusions arise on how smoking and histories of periodontitis relate to the biological outcomes of the various timing options. History of periodontitis has been postulated as a risk factor for peri-implantitis (Schwarz et al., 2017), and there is some consensus on this despite some conflicting reports (Canullo et al., 2016; Dvorak et al., 2011; Marrone et al., 2013; Rokn et al., 2017; Schwarz et al., 2017). The majority of studies in the present review had specifically excluded patients with such histories or merely indicated that all included patients had been periodontally stable.

The integrity of the facial extraction socket wall has been regarded as a critical factor in deciding upon an implant placement protocol (Tonetti et al., 2019), and certainly, the anatomy of the extraction socket is a useful consideration regarding implant success and biological outcomes (Parvini et al., 2020). Most of the 14 studies dealt with healed sockets and yielded little information on bone grafting, which usually was performed simultaneously with the implant surgery, either in immediate or in delayed placement protocols (Oxby et al., 2015; Siebers et al., 2010). This suggests the
presence of less-than-ideal socket anatomies even during immediate placement. Reference to post-extraction socket anatomy was made in only one study, to the effect that grafting was performed when the buccal plate was "questionable" and preference given to submerged healing in the presence of a bone defect >3 mm (Siebers et al., 2010).

One strength of this systematic review is its broad literature base of over 7000 unique (i.e., deduplicated) publications which were returned by the search terms and carefully screened by the reviewers. Its methodology based on the Cochrane textbook is also a significant strength as well. Limitations arise from its inclusion of study designs that might weaken conclusions, as non-RCT studies generally increase the risk of incurring biases in systematic reviews (Hoy et al., 2012). As shown in the GRADE listings (Table 7), certainty of evidence was very low for all outcomes across all combinations of protocols. One exception, with a low certainty of evidence based on one RCT (Romanos, et al.), was bleeding on probing compared between immediate and delayed loading in conjunction with delayed placement (type DPIL versus DPDL).

Another limiting factor was the small sample size (low number of included studies) the small number of implants included, and that only three studies were available for meta-analysis. Thus, large parts of the conclusions from this systematic review are based on pooled data, which needs to mentioned as a limiting factor.

Yet this scarcity does reflect the current level of evidence on how different protocols of implant placement and loading may affect the risk of biological complications related to implant-supported FPDs. Given this inadequate base of evidence to shed light on these issues, this systematic review cannot possibly yield any robust conclusions.

The need for well-designed and adequately powered RCTs specifically reporting and evaluating biological outcomes of different implant placement as well as loading protocols is warranted.

5 | CONCLUSION

Within its limitations, this review showed high rates of survival of all the studied implant placement and loading combinations for FPDs over ≥3 years of follow-up. The small number of studies (n = 14), allowing data synthesis from only 3 trials, revealed no differences in terms of survival rates of implants immediately or delayed loaded after delayed placement. In addition, the analysis of pooled data did not reveal differences in survival rates nor marginal bone levels when DPDL and DPIM were compared.

The heterogeneity and quality of the data did not allow to draw any further conclusions on the occurrence of biological complications related to timing of implant placement/loading. Most comparisons across studies were precluded by major inconsistencies in outcome reporting, such as lack of definition of the peri-implant diseases and scarcity of reported biological outcomes for each placement and loading combination. This suggests that the currently available evidence on the PICO question which was investigated is scarce and highlights the need for well-designed and adequately powered RCTs comparing biological outcomes of different implant placement and loading protocols in the long term.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Louise Leite Aiquel: Data curation (equal); formal analysis; methodology (equal); project administration (equal); software (lead); writing-original draft (equal); writing-review & editing. Joao Pitta: Data curation (equal); Formal analysis (equal); methodology (equal); software (equal); writing-original draft (equal); writing-review & editing (equal). Georgios N. Antonoglou: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing-original draft (equal); writing-review & editing (equal). Irene Mischak: Data curation (lead); validation (equal). Irena Sailer: Conceptualization (equal); supervision (equal); writing-original draft. Michael Payer: Conceptualization (equal); project administration (equal); supervision (equal); writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.
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