J Periodontal Implant Sci. 2022 Dec;52(6):479-495
https://doi.org/10.5051/jpis.2200900045
pISSN 2093-2278·eISSN 2093-2286

JPIS
Journal of Periodontal & Implant Science

Research Article
Implant Science

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Rodent peri-implantitis models: a systematic review and meta-analysis of morphological changes

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OPEN ACCESS

Received: Feb 7, 2022
Revised: Mar 29, 2022
Accepted: May 17, 2022
Published online: Jun 20, 2022

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Trial Registration
PROSPERO Identifier: CRD42020209776

Funding
This study was self-funded by the authors and their respective institutions.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: Rodent models have emerged as an alternative to established larger animal models for peri-implantitis research. However, the construct validity of rodent models is controversial due to a lack of consensus regarding their histological, morphological, and biochemical characteristics. This systematic review sought to validate rodent models by characterizing their morphological changes, particularly marginal bone loss (MBL), a hallmark of peri-implantitis.
Methods: This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A literature search was performed electronically using MEDLINE (PubMed), and Embase, identifying pre-clinical studies reporting MBL after experimental peri-implantitis induction in rodents. Each study's risk of bias was assessed using the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) risk of bias tool. A meta-analysis was performed for the difference in MBL, comparing healthy implants to those with experimental peri-implantitis.
Results: Of the 1,014 unique records retrieved, 23 studies that met the eligibility criteria were included. Peri-implantitis was induced using 4 methods: ligatures, lipopolysaccharide, microbial infection, and titanium particles. Studies presented high to unclear risks of bias. During the osseointegration phase, 11.6% and 6.4%-11.3% of implants inserted in mice and rats, respectively, had failed to osseointegrate. Twelve studies were included in the meta-analysis of the linear MBL measured using micro-computed tomography. Following experimental peri-implantitis, the MBL was estimated to be 0.25 mm (95% confidence interval [CI], 0.14–0.36 mm) in mice and 0.26 mm (95% CI, 0.19–0.34 mm) in rats. The resulting peri-implant MBL was circumferential, consisting of supra- and infrabony components.
Conclusions: Experimental peri-implantitis in rodent models results in circumferential MBL, with morphology consistent with the clinical presentation of peri-implantitis. While rodent models are promising, there is still a need to further characterize their healing potentials, standardize experiment protocols, and improve the reporting of results and methodology.

Trial Registration: PROSPERO Identifier: CRD42020209776

Keywords: Dental implants; Peri-implantitis; Rodentia; Systematic review

Author Contributions

Conceptualization: Jacob Ren Jie Chew; Formal analysis: Jacob Ren Jie Chew, Jacinta Xiaotong Lu, Sim Yu Fan; Investigation: Jacob Ren Jie Chew; Methodology: Jacob Ren Jie Chew, Jacinta Xiaotong Lu; Project administration: Jacob Ren Jie Chew; Writing - original draft: Jacob Ren Jie Chew, Jacinta Xiaotong Lu, Sim Yu Fan, Alvin Boon Keng Yeo; Writing - review & editing: Jacob Ren Jie Chew, Jacinta Xiaotong Lu, Sim Yu Fan, Alvin Boon Keng Yeo.

INTRODUCTION

Peri-implantitis is the leading cause of implant failure, affecting 22% of patients worldwide [1]. It is defined as a biofilm-induced, pathological condition of the peri-implant tissues, characterized by inflammation within the supra-crestal connective tissue and progressive marginal bone loss [2]. Traditionally, its etiology and pathogenesis were thought to resemble periodontitis. As such, periodontal treatment protocols have been adapted to manage peri-implantitis [3]. However, these protocols are often deemed either ineffective or unable to predictably resolve peri-implantitis, regenerate lost tissues, and achieve re-osseointegration [4]. The observed inefficacy may be attributed to discrepancies in disease characteristics between peri-implantitis and periodontitis [5], especially microbiological and anatomical differences arising from the implant's surface properties and its unique hard and soft tissue interface [6]. Clinically, peri-implantitis is further complicated by several risk factors at the patient, implant, and site levels that may influence disease initiation and progression [2]. This results in a complex disease that remains poorly understood and impossible to fully unravel with just clinical studies alone.

To address these issues, there is a need for mechanistic studies to shed light on the pathologic processes of peri-implantitis and the biological pathways through which risk factors exert their influence. For this purpose, *in vivo* research using animal models is indispensable. In the last decade, there have been increasing efforts to develop rodent intraoral experimental peri-implantitis models. Rodent models would enable researchers to conduct mechanistic studies more efficiently with reduced costs and a shorter healing time [7]. Furthermore, rodents possess several advantages, including the availability of many established protocols for reproducing systemic diseases, knockout and transgenic rodents, and the wide array of antibodies against rodent antigens for immunohistochemical analyses. These advantages provide a means to probe into the roles played by systemic disease, specific genes, and pathways in the disease process of peri-implantitis.

While rodents have been employed extensively for periodontal research, they are not well established for experimental peri-implantitis. In addition, there is a lack of consensus regarding these models, since existing systematic and narrative reviews were published before the development of these models and were focused on larger animals, particularly dogs and non-human primates [8]. The poor understanding of the histological, morphological, and biochemical characteristics of these models has thus limited their acceptance and utility. Therefore, this review sought to assess the construct validity of rodent peri-implantitis models by characterizing the morphological changes of rodent experimental peri-implantitis, in particular marginal bone loss (MBL), the key hallmark that distinguishes it from peri-implant mucositis.

MATERIALS AND METHODS

Protocol and registration

The study protocol was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The protocol for this systematic review was registered in the PROSPERO database (CRD42020209776).

https://doi.org/10.5051/jpis.2200900045

Table 1. Search strategy and terms used for the respective electronic databases

Databases	Search strategy
PubMed	
Component 1: Animal	((Rodent) OR (Rodentia[MeSH Terms]) OR (Murine) OR (Murinae[MeSH Terms]) OR (Mouse) OR (Mice[MeSH Terms]) OR (Rat) OR (Rats[MeSH Terms]))
Component 2: Peri-implantitis	((Dental Implants [Mesh] OR Peri-Implant OR Periimplant OR Peri-Implant Disease OR Periimplant Disease OR Peri-Implant Diseases OR Periimplant Diseases OR Peri-Implant Mucositis OR Periimplant Mucositis OR Peri-Implantitis [Mesh] OR Periimplantitis))
Embase	
Component 1: Animal	('rodent'/exp OR 'rodentia'/exp OR 'murine'/exp OR 'murinae'/exp OR 'mice'/exp OR 'mouse'/exp OR 'rat'/exp OR 'rats'/exp)
Component 2: Peri-implantitis	('dental implant'/exp OR 'peri-implant' OR 'periimplant' OR 'peri-implant disease' OR 'periimplant disease' OR 'peri-implant diseases' OR 'periimplant diseases' OR 'peri-implant mucositis' OR 'periimplant mucositis' OR 'peri-implantitis'/exp OR 'periimplantitis'/exp)

Focused question

This systematic review was conducted to answer the following focused question: "In rodent pre-clinical studies, what are the morphological changes and expected MBL resulting from experimental peri-implantitis, compared to healthy controls?"

Information sources and search

An electronic systematic search of MEDLINE (PubMed) and Embase was conducted for articles published from 1/1/2011 through 1/9/2021. The results were imported into Endnote reference management software (Endnote version X9.3.1; Clarivate Analytics, Philadelphia, PA, USA). The reference lists of the included studies were then screened to identify any additional eligible studies. The Open Grey and WorldWideScience databases were searched to identify unpublished, yet inclusion-worthy research; however, no relevant studies were identified. The detailed search strategy is summarized in **Table 1**.

Study selection

Two calibrated reviewers (J.R.J.C. and J.X.L.) performed the title and abstract screening independently. To minimize the exclusion of potential candidates, studies without abstracts or with unclear abstracts were included for the full-text analysis. Any disagreement was resolved by discussion among the reviewers. The Cohen kappa coefficient was used to assess the agreement between the reviewers for the title and abstract screening. The remaining full-text manuscripts were analyzed independently, and those fulfilling the eligibility criteria were included. The following eligibility criteria were employed:

Inclusion criteria

- Studies involving experimental peri-implantitis in rodents
- Reported outcomes including MBL

Exclusion criteria

- Studies utilizing other animals
- Studies reporting implants placed extra-orally
- Studies without a clear protocol for experimental peri-implantitis
- Studies with simultaneous implant placement and peri-implantitis induction
- Studies published before 1/1/2011
- Studies published in languages other than English
- Conference abstracts, reviews, clinical trials, and in vitro studies

https://doi.org/10.5051/jpis.2200900045

Data extraction process

Data extraction from the included studies was performed by 2 independent reviewers (J.R.J.C. and J.X.L.) using predefined, standardized, and pre-tested electronic data collection forms. The variables of interest included information pertaining to the study (author[s], and year of publication, type of peri-implantitis research), rodents (number, breed, and age), implants (material, surface, and length and diameter), surgical procedures (implant site, placement protocol, and the time for osseointegration), experimental peri-implantitis protocols (methods and duration), and outcomes (MBL and implant loss during the osseointegration phase). In the event of missing data, attempts were made to contact the corresponding author to seek clarification.

Quality assessment of included studies

The risk of bias in the included studies was assessed by 2 independent reviewers (J.R.J.C. and J.X.L.) using the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) Risk of Bias (RoB) tool [9]. This tool consists of 10 criteria corresponding to the sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and/or investigators, random outcome assessment, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Each criterion was graded as either high, unclear, or low, and the percentage of studies with high, unclear, or low risk of bias was reported. Any disagreements were resolved by consensus following discussions between the 2 reviewers.

Quantitative analysis (meta-analysis)

The quantitative measurements of MBL were recorded for each included study. If the standard deviation (SD) was not reported directly in the included studies, it was estimated from the standard error (SE). A validated software (WebPlotDigitizer; Automeris LLC, Pacifica, CA, USA) was used to extract the data when MBL measurements were only reported graphically in figures [10]. For paired-design studies (i.e., with pre- and post-comparisons), all measurements were analyzed as if the studies had a parallel-group design, which is more conservative. Meta-analysis was carried out to estimate the weighted mean difference with 95% confidence interval (CI) in bone loss between controls and after the induction of experimental peri-implantitis. A random-effects model was used in the meta-analysis with evidence of statistical heterogeneity.

Statistical heterogeneity across the studies was assessed using both the I^2 statistic and the χ^2 test. A threshold P-value <0.1 for the χ^2 test indicated evidence of heterogeneity, while an I^2 statistic of 50% or greater was considered as showing substantial heterogeneity. Meta-regression was employed to investigate potential sources of variability between studies. The between-study characteristics examined through the random-effect meta-regression model included species (mice and rats) and the protocol used to induce peri-implantitis (ligature, oral infection, and titanium particles). All analyses were performed using meta and meta for package in R software (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

https://doi.org/10.5051/jpis.2200900045

RESULTS

Study selection

Figure 1 illustrates the study selection process. An electronic search of MEDLINE (PubMed) and Embase yielded 1,014 unique titles and abstracts that were subsequently screened, identifying 48 full-text articles for eligibility assessment (inter-examiner agreement: κ=0.89). Hand searching did not identify any additional articles. The full-text was not available for 1 study, and 24 studies did not meet the eligibility criteria (**Figure 1**). The remaining 23 studies were included in this review, with 12 studies included for the meta-analysis of MBL.

Study characteristics

Table 2 summarizes the characteristics of the included studies. They were published between 2015 and 2021, involving a total of 256 rats and 678 mice. The inserted implants were either customized screws or mini-implants, made of titanium or Ti6Al4V alloy. Their length ranged from 1 mm to 4.5 mm, while their diameter ranged from 0.2 mm to 2 mm. While the machined surface implants were the most common (n=13), surface modifications were also employed (sandblasted and acid-etched surfaces [11-13], acid-etched surfaces [14], and hydroxyapatite-coated surfaces [15]). The implant surface properties were not reported in 6 studies [16-21].

The implants were all inserted into the maxilla, either at the diastema between incisors and molars [11,12] or at the alveolar ridge of the molars (21 studies). The former was

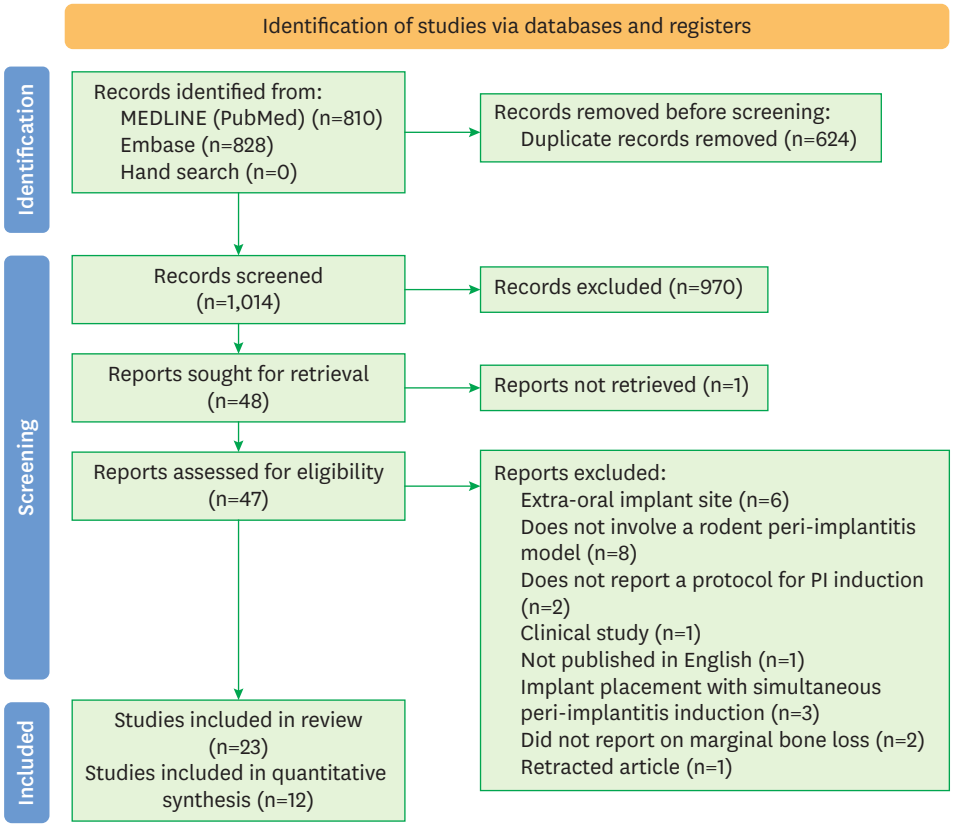

Figure 1. PRISMA flow chart illustrating the selection process of the included studies.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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Table 2. Characteristics of the included studies

Author	Type of research	Animals		Implants			
		Species (No. of rodents)	Age (wk)[a]	Material, surface	Diameter×length (mm)	Site	Time for osseointegration
Pirih et al. [28]	PI model development	Mice – C57BL/6J (18)	12 wk	Ti_6Al_4V, machined	0.5 mm×1 mm	Maxillary molars (delayed)	4 wk
Pirih et al. [29]	PI model development	Mice – C57BL/6J (26)	12 wk	Ti_6Al_4V, machined	0.5 mm×1 mm (threaded surface)	Maxillary molars (delayed)	4 wk
Koutouzis et al. [25]	PI model development	Rats – Wistar (12)	9 wk	Titanium, machined	1.5 mm×2 mm	Maxillary 1st molar (delayed)	8 wk
Nguyen Vo et al. [22]	Pathogenesis & PI model development	Mice – C57BL/6NCrSlc (60)	12 wk	Titanium, machined	0.8 mm×1.5 mm	Maxillary 1st molar (delayed)	4 wk
Takamori et al. [19]	Pathogenesis	Rats – Lewis (25)	5 wk	Ti_6Al_4V, NR	2 mm×4.5 mm	Maxillary 1st molar (immediate)	4 wk
Tzach-Nahman et al. [14]	PI model development	Mice – BALB/c (32)	8–9 wk	Ti_6Al_4V, acid-etched	0.7–0.2 mm×1.7 mm (tapered geometry)	Maxillary 1st molar (immediate)	4 wk
Wong et al. [20]	Wound healing	Mice – C57BL/6J (35)	12 wk	Ti_6Al_4V, NR	0.5 mm×1 mm (threaded surface)	Maxillary molars (delayed)	4 wk
Hiyari et al. [30]	Pathogenesis	Mice – C57BL/6J (85)	12 wk	Ti_6Al_4V, machined	0.5 mm×1 mm (threaded surface)	Maxillary molars (delayed)	4 wk
Hiyari et al. [23]	Pathogenesis	Mice – C57BL/6J (22), C3H/HeJ (22) and A/J (21)	12 wk	Ti_6Al_4V, machined	0.5 mm×1 mm (threaded surface)	Maxillary molars (delayed)	4 wk
Wong et al. [26]	Wound healing	Mice – C57BL/6J (31)	12 wk	Titanium, machined	0.5 mm×1 mm	Maxillary molars (delayed)	4 wk
Ding et al. [15]	Treatment	Mice – C57BL/6NCrSlc (20)	12 wk	Titanium, hydroxyapatite coating±doxycycline	0.8 mm×1.5 mm	Maxillary 1st molar (delayed)	4 wk
Li et al. [33]	Treatment	Mice – C57BL/6J wildtype (60)	12 wk	Titanium, machined	0.5 mm×1 mm (threaded surface)	Maxillary molars (delayed)	4 wk
Varon-Shahar et al. [13]	Pathogenesis	Mice – BALB/c (90)	5–6 wk	Titanium, machined and SLA	0.5 mm×1.5 mm	Maxillary 1st molar (immediate)	21 and 42 d
Wang et al. [24]	Pathogenesis	Rats – Sprague Dawley (16)	12 wk	Titanium, machined	1.2 mm×2 mm	Maxillary 1st molar (delayed)	4 wk
Deng et al. [32]	Pathogenesis	Mice – C57/BL6: wild type (12) & Tlr4-KO (12)	10 wk	Titanium, machined	0.5 mm×1 mm	Maxillary molars (delayed)	4 wk
Ozawa et al. [16]	Treatment	Rats – Sprague Dawley (32)	5 wk	Titanium, NR	2 mm×4 mm	Maxillary 1st molar (immediate)	7 d
Pan et al. [34]	Treatment	Mice – C57/BL6, wild type (48) & Tlr2/4-KO (48)	10 wk	Titanium, machined	0.5 mm×1 mm	Maxillary molars (delayed)	4 wk
Sun et al. [11]	PI model development	Rats – Sprague Dawley (35)	NR	Titanium, SLA	1.3 mm×4 mm	Maxillary Diastema	21 d
Yamazaki et al. [21]	Systemic interaction	Rats – Wistar (36)	8 wk	Titanium, NR	1.8 mm×2 mm	Maxillary 1st molar (delayed)	4 wk
He et al. [17]	Systemic interaction	Rats – Sprague Dawley (32)	8–9 wk	Titanium, NR	1.5–1.4 mm×2 mm	Maxillary 1st molar (delayed)	4 wk
Hori et al. [18]	Systemic interaction	Rats – Wistar (20)	8 wk	Titanium, NR	1.8 mm×2 mm	Maxillary 1st molar (delayed)	4 wk
Li et al. [27]	Systemic interaction	Mice – C57BL/6, wild type (6) & leptin receptor-deficient (30)	10 wk	Titanium, machined	0.5 mm×1 mm	Maxillary molars (delayed)	4 wk
Wu et al. [12]	Treatment	Rats – Wistar (48)	8 wk	Titanium alloy, SLA	1.1 mm×3 mm	Maxillary Diastema	28 d

PI: peri-implantitis, Ti6Al4V: alpha-beta titanium alloy, SLA: sandblasted and acid-etched, NR: not reported, TLR-2 KO: Toll-like receptor 2 knockout, TLR-4 KO: Toll-like receptor 4 knockout, TLR-2/4 KO: Toll-like receptor 2 and 4 knockout.

[a]Age at implant placement.

only performed in rats. For the latter, implants were inserted either immediately into the extraction socket or after the alveolar ridge had healed. Subsequently, an osseointegration phase was provided before initiating experimental peri-implantitis. This lasted at least 4 weeks in the majority of studies (n=21), with 3 studies having shorter durations of 7 days [16] and 21 days [11,13]. Implant failure during this phase was reported by 20 studies. For implants placed at the molar region, failure rates of 11.6% (60/517 implants) and 8.1% (17/210

https://doi.org/10.5051/jpis.2200900045

implants) were observed for mice and rats, respectively. In comparison, of the 47 implants placed at the maxillary diastema in rats, 3 (6.4%) failed to osseointegrate after 4 weeks [12]. When the osseointegration phase was shortened to 21 days, 11.3% (7/62 implants) failed to osseointegrate [11].

Experimental peri-implantitis was induced using 4 different protocols: ligature, lipopolysaccharide, microbial infection, and titanium particle injections. Details pertaining to the experimental protocols are summarized in **Tables 3-6**. Several histological features of peri-implantitis were reported, including the apical migration and formation of pocket epithelium [19,22], degradation of collagen fibers [20,23] with concomitant inflammatory cell infiltration of the connective tissue [19,24,25], increased osteoclastogenesis [20,22,23,26,27], and MBL [11,13,15,17-23,25,27-30]. Although histology was performed in 22 studies, histomorphometric measurements of the MBL and supracrestal soft tissue alterations were reported in only 5 and 2 studies, respectively. **Table 7** summarizes the histomorphometric measurements of peri-implant bone levels and supracrestal soft tissue alterations. A meta-analysis was not feasible due to heterogenicity and the limited number of studies.

In comparison, micro-computed tomography (CT) was most frequently used to quantify MBL, volumetrically (n=11) and linearly (n=15). **Table 8** summarizes the reported linear measurements of MBL. Although significantly greater MBL volume (n = 9) and significantly lower residual

Table 3. Methodology for PI induction and analysis: Ligature

Author	Groups	Ligature	Duration of PI
Pirih et al. [28]	Control group, Ligature group	6-0 silk	12 wk
Nguyen Vo et al. [22]	Day 0, 7, 14, 21, 28 groups	5-0 silk	7, 14, 21, 28 d
Wong et al. [20]	Control group, Ligature-retained group, Ligature-removed group	6-0 silk	4, 5, 6 wk
Hiyari et al. [30]	Control group, Ligature group	6-0 silk	1 wk, 1 mo, 3 mo
Hiyari et al. [23]	Control group, Ligature group	6-0 silk	1, 4 wk
Wong et al. [20]	Control group, Ligature-retained group, Ligature-removed group	6-0 silk	7, 12, 21 d
Ding et al. [15]	Hydroxyapatite group, Doxycycline group	5-0 silk	4 wk
Li et al. [33]	Control group, Vehicle-treated peri-implantitis group, Mangiferin-treated peri-implantitis group	6-0 silk	6 wk
Deng et al. [32]	Control and experimental groups for wild type and TLR-4KO	7-0 silk soaked in *P. gingivalis*	2 wk
Pan et al. [34]	Implant only, Implant + ligation, Implant + ligation + anti-RANKL antibody, Implant + ligation + anti-RANKL antibody + miR-146a, for both wild type and TLR-2/4KO	7-0 silk	2 wk
Yamazaki et al. [21]	Control group, Hyperglycemia group, Hyperglycemia + insulin group	4-0 silk	4 wk
Hori et al. [18]	Control with ligature, Control without ligature, Xerostomia with ligature, Xerostomia without ligature	4-0 silk	4 wk
Li et al. [27]	Healthy implant control, Diabetic implant without glycemic control, Diabetic peri-implantitis without glycemic control, Diabetic peri-implantitis with blood glucose control, Diabetic peri-implantitis with poor glycemic control, Diabetic peri-implantitis with peri-implantitis prevention without glycemic control	7-0 silk	3 wk

PI: peri-implantitis, TLR-2 KO: Toll-like receptor 2 knockout, TLR-4 KO: Toll-like receptor 4 knockout, TLR-2/4 KO: Toll-like receptor 2 and 4 knockout, RANKL: receptor activator of nuclear factor kappa-β ligand.

Table 4. Methodology for PI induction and analysis: Lipopolysaccharide

Author	Groups	LPS source	Dose, vehicle	Delivery, frequency	Duration of PI
Pirih et al. [29]	Non-injected control group, Vehicle-injected control group, LPS-injected experimental group	*P. gingivalis*	2 μL of 10 mg/mL (PBS)	Injections, twice a week for 6 wk	6 wk
Takamori et al. [19]	Untreated baseline group, Immunized and LPS-applied group, Immunized and PBS-applied group, Non-immunized and LPS-applied group, Non-immunized and PBS-applied group	*E. coli*	3 μL of 50 μg/mL (PBS)	Topical administration 7 times with 5 min interval daily within 30 min. Carried out thrice with 1 d between applications.	5 d
He et al. [17]	Control, Type 2 diabetes mellitus, Peri-implantitis, Type 2 diabetes mellitus with peri-implantitis	*P. gingivalis*	50 μL of 1 mg/mL (PBS)	Injections repeated every 2 d for 4 wk	4 wk
Wu et al. [12]	Control group, Vehicle group, Melatonin 20 μg/mL group, Melatonin 40 μg/mL group	NR	10 μL of LPS 1 mg/mL (NR)	Injections performed every 3 d for 5 times	18 d

LPS: lipopolysaccharide, PI: peri-implantitis, PBS: phosphate-buffered saline, NR: not reported.

https://doi.org/10.5051/jpis.2200900045

Table 5. Methodology for PI induction and analysis: Microbial infection

Author	Groups	Microbes	Dose, vehicle	Frequency	Duration of PI
Koutouzis et al. [25]	Group A (polymicrobial infection), Group B (sham-infected controls)	*P. gingivalis*, *T. denticola*, *T forsythia*	0.5 mL of the polymicrobial mix (3.3×10^9 cells each) with 4% CMC	4 consecutive days per week for 6 alternate weeks	13 wk
Tzach-Nahman et al. [14]	Implant treated mice that were infected, Implant treated mice that were not infected	*P. gingivalis*	5×10^9 CFU/mL in 0.2 mL PBS with 2% CMC	3 times with 48hr interval	47 d
Varon-Shahar et al. [13]	Early and delayed groups with control and infectious subgroups, SLA-coated and smooth surface groups	*P. gingivalis*, *F. nucleatum*	400 μL of 1:1 (10^9/mL) in PBS with 2% CMC	Gavage 3 times at 2-day intervals	48 d
Ozawa et al. [16]	Control group, Implantitis group, Implantitis + nRIG group, Implantitis + RIG group	*P. gingivalis*	0.25 mL of 3×10^{10} cells/mL with 5% CMC	Gavage on days 11, 13 and 15 from implant placement	25 d
Sun et al. [11]	Untreated group, Bacteria group, Control group	*S. oralis*, *A. actinomycetemcomitans*	3% sucrose in PBS	Daily gavage of *S. oralis* for 1 month followed by daily gavage of both microbes for another 2 mo	84 d

PI: peri-implantitis, SLA: sandblasted and acid-etched, RIG: redox injectable gel, nRIG: non-nitroxide radical-containing injectable hydrogel, CMC: carboxymethyl cellulose, CFU: colony forming unit, PBS: phosphate-buffered saline.

Table 6. Methodology for PI induction and analysis: Titanium particle

Author	Groups	Concentration, vehicle	Delivery, frequency	Duration of PI
Wang et al. [24]	Control group, Ti + LlipClod group, Ti + Lip group, Ti + PBS group	20 mg of titanium particles in 100 μL (PBS)	Single injection	8 wk

PI: peri-implantitis, PBS: phosphate-buffered saline, Ti: titanium-injected, LlipClod: clodronate liposome, Lip: empty liposome.

Table 7. Summary of the histomorphometric measurements of peri-implant bone levels and supracrestal soft tissue alterations

Histomorphometric measurements	Author	Measurement	Groups (sample size)[a]	Outcomes[b]
Peri-implant bone levels	Nguyen Vo et al. [22]	Distance from the bone crest to the implant apex	Before ligature (n=12/12)	Buccal: 0.9±0.06 mm Palatal: 0.84±0.09 mm
			After ligature (n=12/12)	Buccal: 0.53±0.03 mm Palatal: 0.45±0.04 mm
	Takamori et al. [19]	Distance from the first thread of the implant to the bone crest	Baseline (n=5/5)	337.2±24.93 μm
			Non-immunized + LPS (n=5/5)	274.51±49.88 μm
	Ding et al. [15]	Distance from the bone crest to the implant apex on mesial and distal aspects	Hydroxyapatite after ligature (n=5/5)	Mesial: 0.73±0.05 mm Distal: 0.57±0.06 mm
			Doxycycline after ligature (n=5/5)	Mesial: 0.82±0.04 mm Distal: 0.73±0.07 mm
	Sun et al. [11]	Distance from the most coronal part of head of implant to the bone crest	Untreated (n=10/10)	2.46±0.27 mm
			Antibiotic (n=10/10)	2.29±0.32 mm
			Bacteria (n=10/10)	2.60±0.39 mm
	He et al. [17]	Distance from the bone crest to the implant apex	Control (n=6/8)	1.39±0.09 mm
			Peri-implantitis (n=7/8)	0.91±0.05 mm
Supracrestal soft tissue alterations	Takamori et al. [19]	Distance from the gingival crest to the first thread of the implant	Baseline (n=5/5)	840.3±74.58 μm
			Non-immunized + LPS (n=5/5)	783.18±60.87 μm
		Distance from the apical part of junctional epithelium to the first thread of the implant	Baseline (n=5/5)	542.52±42.45 μm
			Non-immunized + LPS (n=5/5)	517.17±47.03 μm
	He et al [17]	Distance from the crest of the mucosa to the bone crest	Control (n=6/8)	1.25±0.12 mm
			Peri-implantitis (n=7/8)	1.67±0.10 mm

LPS: lipopolysaccharide.
[a]Number of implants that survived experiment/initial sample size; [b]Mean ± standard deviation.

bone volume (n=2) were reported with experimental peri-implantitis, a meta-analysis was not feasible as the definition of the volume of interest (VOI) varied. In contrast, 12 of the 15 studies that performed linear measurements of MBL were included in the meta-analysis (**Table 8**). Among the 12 studies, the data were extracted from the reported figures in 4 studies [16-18,26]. Two of the excluded studies [29,30] did not report the sample size after accounting for implant failure during the osseointegration phase, while the last study did not report the exact MBL measurements for both the control and experimental peri-implantitis groups [14].

https://doi.org/10.5051/jpis.2200900045

Table 8. Summary of the radiographic measurements of marginal bone loss

Author	Micro-CT linear bony measurement		
	Measurement	Groups (sample size)[a]	Outcomes[b]
Pirih et al. [28]	Average of the distances from junction of head and shaft of the implant to the bone crest at the mesial, distal, buccal, and palatal surfaces.	Control (n=8/8) Ligature (n=6/10)	0.226±0.045 mm 0.422±0.047 mm 0.579±0.155 mm[c]
Koutouzis et al. [25]	Distance from the implant platform to the first bone to implant contact.	Polymicrobial infected (n=4/8)	0.80±0.37 mm
Nguyen Vo et al. [22]	Distance from the bone crest to the implant apex at the mesial and distal surface.	Before ligature (n=12/12) After ligature (n=12/12)	Mesial: 0.81±0.04 mm Distal: 0.84±0.03 mm Mesial: 0.37±0.03 mm Distal: 0.37±0.07 mm
Wong et al. [20]	Average distance from the implant head to the bone crest, at the mesial, distal, buccal, and palatal surfaces.	Control (n=4/4) Ligature-removed (n=4/4)	0.218±0.024 mm 0.375±0.028 mm
Wong et al. [26]	Distance from the implant head to the bone crest	Control 14 days (n=3/3) Ligature removed 14 days (n=4/4)	0.175±0.038 mm 0.354±0.072 mm
Ding et al. [15]	Distance from the bone crest to the implant apex at the mesial, distal, buccal, and palatal surfaces.	Hydroxyapatite before ligature (n=5/5) Hydroxyapatite after ligature (n=5/5)	Buccal: 1.00±0.13 mm Palatal: 1.06±0.04 mm Mesial: 0.97±0.09 mm Distal: 0.92±0.11 mm Buccal: 0.74±0.06 mm Palatal: 0.72±0.08 mm Mesial: 0.72±0.09 mm Distal: 0.76±0.08 mm
Varon-Shahar et al. [13]	Distance from the coronal-most part of implant to the residual bone adjacent to the implant.	Control + SLA (n=22/28) Early infection + SLA (n=18/30) Delayed infection + SLA (n=20/20) Control + smooth surface (n=6/6) Early Infection + smooth surface (n=4/6)	0.0115±0.113 mm 0.0313±0.225 mm 0.0378±0.268 mm 0.0349±0.105 mm 0.051±0.064 mm
Wang et al. [24]	Average distance from the coronal most position of the marginal bone to the apical point of implant head, at the mesial, distal, buccal, and palatal surfaces.	Control (n=4/4) Ti + PBS (n=4/4)	0.13±0.04 mm 0.44±0.15 mm
Ozawa et al. [16]	Distance from the implant head to bone	Control (n=4/4) Implantitis (n=4/4)	1.07±0.26 mm 1.52±0.51 mm
Yamazaki et al. [21]	Average distance from the implant shoulder to the first bone to implant contact at the mesial, distal, buccal, and palatal surfaces.	Control with ligature (n=10/10) Control without ligature (n=10/10)	With ligature: 0.62±0.07 mm Without ligature: 0.29±0.08 mm
He et al. [17]	Distance from the top of the implant to the alveolar bone crest	Control (n=6/6) Peri-implantitis (n=7/7)	0.49±0.045 mm 0.69±0.052 mm
Hori et al. [18]	Distance from the implant shoulder to the first bone-implant contact	Control without ligature (n=9/9) Control with ligature (n=10/10)	0.34±0.21 mm 0.55±0.11 mm

CT: computed tomography, SLA: sandblasted and acid-etched, Ti: titanium-injected, PBS: phosphate-buffered saline.
[a]Number of implants that survived experiment/initial sample size; [b]Mean ± standard deviation; [c]Bone loss was equated to the length of the implant (1 mm) when the implants were lost to peri-implantitis.

Synthesis of results (meta-analysis)

Twelve studies with high pooled heterogenicity (I^2=92.0, P<0.01) were included in the meta-analysis of the linear MBL (micro-CT) (**Figure 2**). An overall MBL of 0.26 mm (95% CI, 0.19–0.33 mm) was estimated. For mice and rats respectively, an MBL of 0.25 mm (95% CI, 0.14–0.36 mm) and 0.26mm (95% CI, 0.19–0.34 mm) were estimated. A subgroup analysis was performed for the respective experimental protocols for each species. In mice, an overall MBL of 0.29 mm (95% CI, 0.19–0.38 mm) was estimated for ligature-induced peri-implantitis, whereas the MBL for oral infection models was based on 1 study [13]. For rats, an overall MBL of 0.29 mm (95% CI, 0.17–0.40 mm) and 0.20 mm (95% CI, 0.15–0.25 mm) were estimated for the ligature and oral infection models respectively, whereas the MBL in the titanium particles model was based on 1 study [24]. Meta-regression, which was used to investigate potential sources of variability among study characteristics, revealed that neither

https://doi.org/10.5051/jpis.2200900045

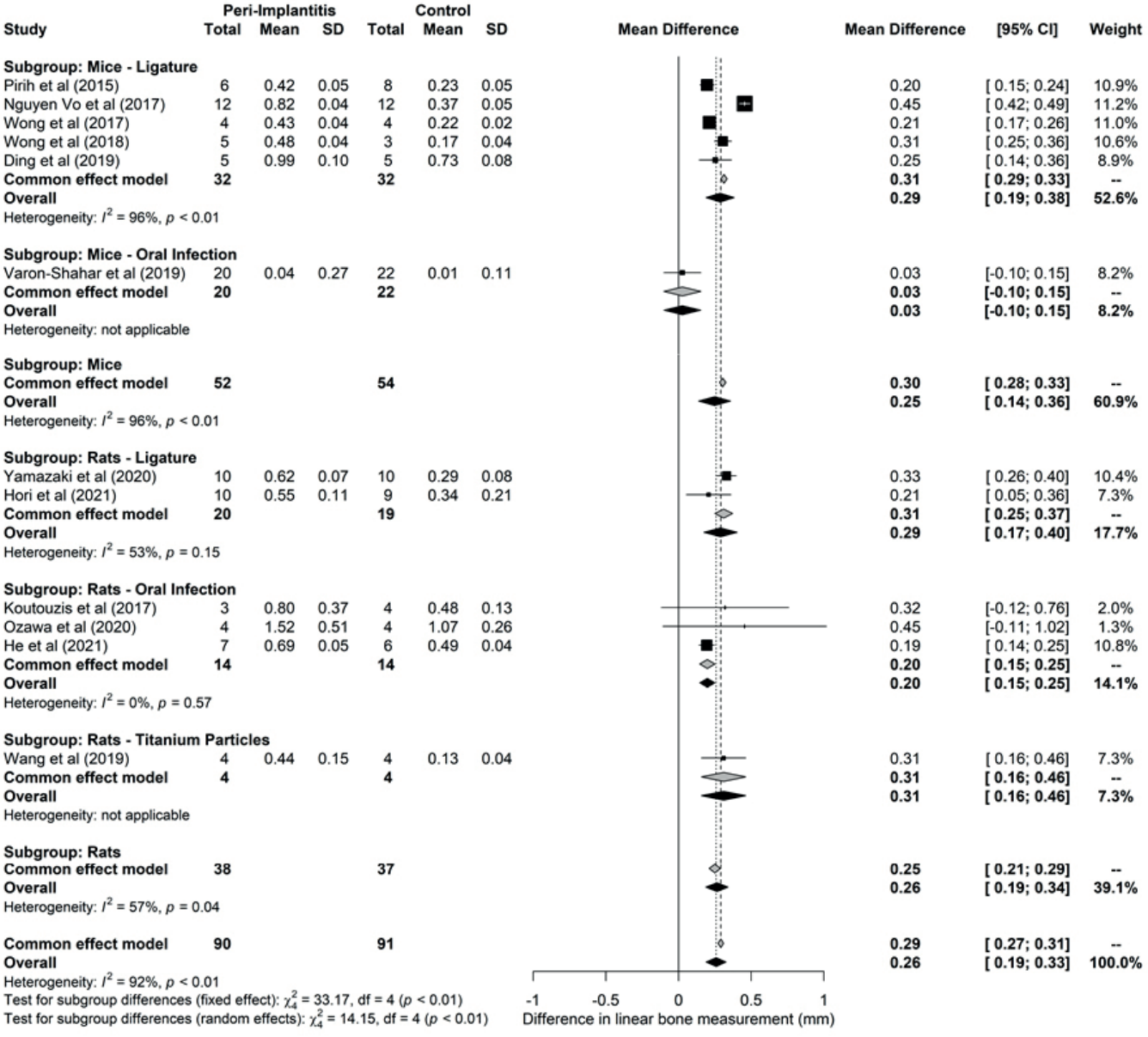

Figure 2. Forest plot of micro-CT analysis for linear MBL.
CT: computed tomography, MBL: marginal bone loss, SD: standard deviation, CI: confidence interval.

the species (mice and rats) nor the method used to induce peri-implantitis was statistically significantly associated with the resulting MBL (**Figure 3**).

Quality assessment of studies

Figure 4 summarizes the analysis of the risk of bias in the included studies. Although the randomization of rodents and implants was reported in 16 studies, only a small proportion specified the method used for sequence generation (17.4%) and maintained allocation concealment (4.3%). The majority (95.7%) of studies had an unclear risk of bias for performance bias due to the lack of randomized housing and blinding of investigators and caregivers. When considering detection bias, although there was generally a low risk of bias for random outcome assessment (91.3%), 56.5% of studies did not perform blinding during

https://doi.org/10.5051/jpis.2200900045

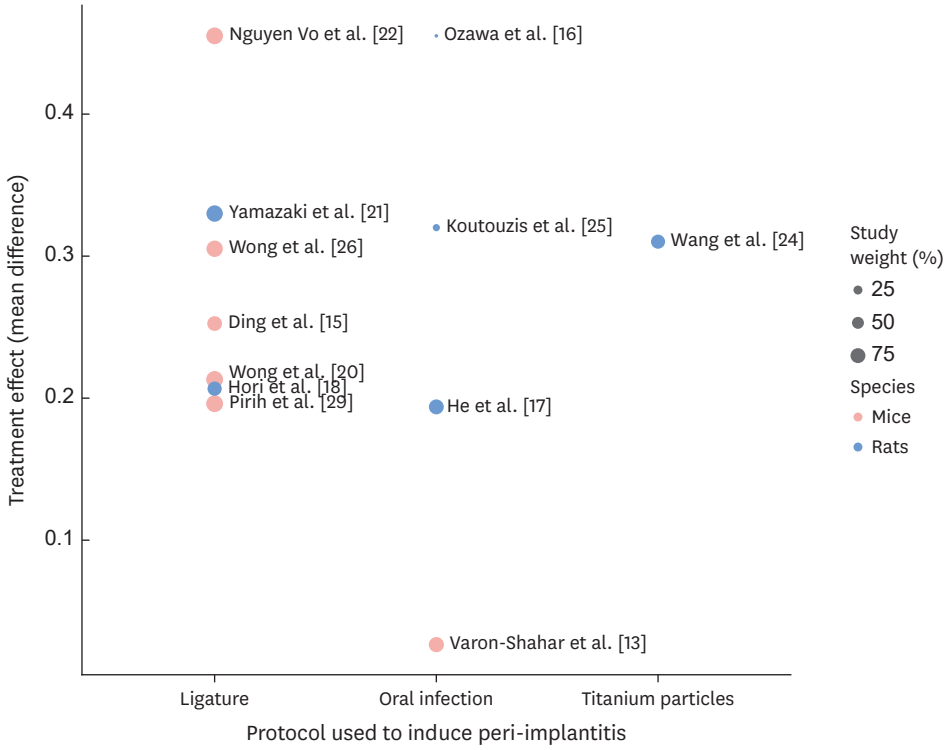

Figure 3. Bubble plot depicting the effects of species (mice and rats) and the protocol used for inducing peri-implantitis on the MBL.
MBL: marginal bone loss.

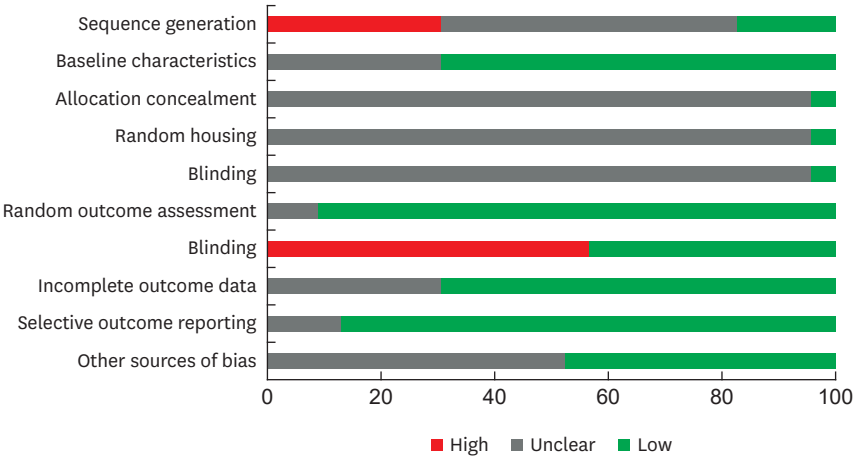

Figure 4. ROB evaluated using the SYRCLE RoB tool, reported as the percentage per criterion.
RoB: Risk of Bias, SYRCLE: Systematic Review Center for Laboratory animal Experimentation.

outcome assessment. An unclear risk of attrition bias was observed in 30.4% of studies, as they failed to account for sample attrition due to implant loss during the osseointegration phase. A low risk of reporting bias was observed in 87.0% of studies, with 3 studies having unclear risk. Twelve studies had an unclear risk of bias from other sources, while the remaining 11 were found to be of low risk.

https://doi.org/10.5051/jpis.2200900045

DISCUSSION

To improve the management of peri-implantitis, additional insights into its etiology, disease processes, and systemic implications. While such mechanistic studies have been traditionally performed in larger animals, rodent models have emerged as a potential alternative in the last decade. However, the validity of these models remains controversial due to the lack of consensus regarding their histological, morphological, and biochemical characteristics. To address this issue, 23 studies were systemically identified and analyzed to characterize the morphological changes following experimental peri-implantitis in rodents.

The key histological hallmarks of peri-implantitis are inflammation of the supracrestal soft tissue and formation of peri-implant pockets with the underlying circumferential bone loss [2]. These histological features are clinically measured as increased probing depth (≥6 mm), bleeding or suppuration on probing, and radiographic bone loss (≥3 mm) [31]. Considering the rodent's size, and the extent of MBL (0.25 mm in mice and 0.26 mm in rats), it would not be appropriate to directly apply these clinical diagnostic criteria to rodents. Instead, there is a need to identify the underlying histological and morphological characteristics that these clinical parameters represent. Based on the results of the meta-analysis, experimental peri-implantitis resulted in a significantly greater linear MBL than observed in healthy controls in both rats and mice, without species-specific differences. These radiographic findings were consistent with the histomorphometric measurements [15,17,19,22]. The extent of bone loss was comparable for the buccal, mesial, distal and lingual surfaces of the implant, suggesting that MBL was circumferential [19,22]. This was confirmed by a volumetric analysis, which further identified the presence of suprabony and infrabony components [13,14,23,26,30,32-34]. This concurred with the findings reported in dog models and the defect configuration observed clinically [35]. In addition to MBL, the included studies have also reported the apical migration of an ulcerated pocket epithelium [19,22] and expanding inflammatory cell infiltration within the supracrestal connective tissue [19,24]. Moreover, these soft tissue changes also presented as visible signs of inflammation, such as edema and erythema [20,22,25,28,29], consistent with the clinical features of peri-implantitis. Thus, this review confirmed that the histological and morphological hallmarks of peri-implantitis were successfully recreated in rodent models of experimental peri-implantitis, supporting the construct validity of these models. However, construct validity is only one of the many considerations when choosing an animal model, especially since no model can replicate all aspects of peri-implantitis. Therefore, there is a need to discuss rodent models' potential role in peri-implantitis research, while considering their advantages, limitations, and challenges.

Animal research in peri-implantitis can be broadly categorized into studies that focus on the disease processes and those focusing on therapy. The former involve research on the pathogenesis and wound healing of peri-implantitis, and its systemic interactions. Compared to their larger counterparts, rodents have several advantages that make them particularly suitable for such research. Longitudinal observations will be required to investigate the mechanisms involved in the initiation, progression, and resolution of peri-implantitis, translating to a considerable sample size, which is not feasible in larger animals considering the logistics, costs, and ethical concerns. This would be more achievable in rodent models due to their lower costs and shorter healing time [7]. Furthermore, the availability of transgenic and knockout rodents and a wide array of antibodies against rodent antigens would enable researchers to probe the roles played by specific cells, genes, and pathways in

https://doi.org/10.5051/jpis.2200900045

the disease process of peri-implantitis. For example, 2 studies utilized Toll-like receptors 2 and 4 knockout mice to explore the role of pattern recognition receptors in mediating the expression of proinflammatory cytokines and osteoclastogenesis that result in MBL [32]. This study shed light on the differences in molecular features between peri-implantitis and periodontitis, highlighting the rodents' potential utility.

These advantages enable the use of rodents for research on various systemic diseases, giving rise to the availability of various protocols to reproduce these conditions in rodents. Thus, rodent models can be potentially used to explore the interactions between these diseases and peri-implantitis. As discussed in this review, rodent models have been used to determine the impact of diabetes mellitus [17,21,27] and xerostomia [18] on peri-implantitis. While an association between diabetes mellitus and peri-implantitis has been described, this relationship is poorly defined [2]. The rodent studies clarified this by highlighting the effects of hyperglycemia on inflammatory cytokine pathways, linking it to osteoclastogenesis and MBL [17,21,27]. In addition, the negative influence of xerostomia on the oral microbiota, mucosal inflammation, and MBL are novel findings with significant clinical implications [18]. These studies demonstrated rodent models' potential to provide insight into disease processes and systemic interactions that will impact the clinical management of peri-implantitis.

Nonetheless, for studies that seek to develop or test novel therapeutics, larger animal models such as dogs may be a more suitable candidate. The small size of rodents precludes the use of clinical-grade dental implants and biomaterials and limits the possible routes of administering therapeutics to injections and topical applications [16,34,36]. These inherent limitations would affect the utility of rodent models in studies seeking to explore the underlying mechanism of action of these novel therapeutics. Furthermore, the healing potential and regenerative capacity of these models are poorly defined since the majority of the studies were concluded after successfully inducing peri-implantitis. While 2 studies reported that the MBL resulting from ligature-induced peri-implantitis was critical, to the point that spontaneous regeneration was not possible [20,26], their responsiveness to treatment and regenerative capacity remains unexplored. In the current studies, therapeutic interventions were administered before or during the induction of peri-implantitis [12,15,16,33,34]. Thus, the significant reductions in MBL achieved would represent the intervention's ability to prevent peri-implantitis, rather than their therapeutic or regenerative efficacy. Factoring in these limitations, even though rodents can serve as a screening platform, further translational research in larger animal models would still be required.

Nevertheless, for both types of research, rodent models have a fundamental limitation, which is the difficulty in ensuring successful osseointegration. In this review, failure rates of 11.6% and 11.3% were observed for mice and rats respectively. Considering rodents' limited alveolar bone volume, difficulties in achieving primary implant stability may predispose implants to micromotion during healing, resulting in fibrous encapsulation instead of osseointegration [37]. To address these issues, future studies may adopt implants with cutting thread designs that help achieve primary stability or surface modifications that accelerate the process of osseointegration. Furthermore, to avoid confounders arising from the synergistic effects of the experimental peri-implantitis and post-insertion infection during the osseointegration phase [13], at least 28 days should be provided for the healing processes of osseointegration to be completed in both rats and mice [38,39]. These issues will need to be factored in and addressed when planning future studies.

https://doi.org/10.5051/jpis.2200900045

As with most research, this systematic review has its strengths and limitations. This is the first review to systematically appraise the validity of rodent models of experimental peri-implantitis. In addition, this review also summarizes the various experimental peri-implantitis protocols, providing a reference for future studies (**Table 2**). Four different methods for inducing peri-implantitis were identified, including the use of titanium particles, a topic of controversy. While the majority of the literature supports a microbial etiology for peri-implantitis [2], there is limited evidence that peri-implant bone loss could result from foreign body reactions provoked by titanium particles and their corrosion products [40]. Future research will be needed to clarify the individual roles played by and the interactions between biofilms, microbial products, and titanium particles in the disease processes of peri-implantitis. To facilitate this, an inclusive approach was adopted.

This systematic review was limited by the inherent shortcomings of the included studies. Among the included studies, heterogeneous definitions were used for both linear and volumetric measurements. Linear measurements of MBL have been defined as the distance from the bone crest to either the implant's first thread, top, or apex. To account for these variations, the difference in MBL between healthy implants and those with experimental peri-implantitis was first calculated for each study. This difference was then used for meta-analysis. Unfortunately, a similar approach could not be adopted for the volumetric analysis because variations in the horizontal dimension in the VOI precluded a meta-analysis. Since an optimal VOI definition cannot be inferred from the available evidence, future studies will need to report a clear description of their respective VOI definitions to facilitate replication or comparison with other studies.

Another limitation of the available literature was the lack of measures to minimize biases. To improve the quality of pre-clinical evidence, future studies will need to incorporate measures such as clear sequence generation, allocation concealment, and blinding during the experiment and at the time of outcome assessment. In addition, to account for possible implant loss during osseointegration, this attrition should be considered during sample size calculation and changes in the sample size for each experimental group should be reported. Future studies may consider performing randomization only after confirming successful osseointegration, reducing the possible biases before peri-implantitis induction, and ensuring clearly reported and equal sample sizes for the different experimental groups.

In conclusion, the key features of peri-implantitis, including supracrestal soft tissue inflammation, peri-implant pocket formation, and circumferential MBL, have been successfully recreated in rodent models of experimental peri-implantitis. While the current systematic review revealed several limitations and challenges, these models are promising alternatives to larger animals for mechanistic studies pertaining to the disease processes and systemic interactions of peri-implantitis. We propose that future studies standardize their peri-implantitis protocols and improve the reporting of methodology and results, to enable replication and comparisons across the literature.

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