Clinical Medicine Research
2025, Vol. 14, No. 5, pp. 203-209
https://doi.org/10.11648/j.cmr.20251405.17

Research Article

Construction of Animal Models for Periodontal Disease

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Abstract

Background: Periodontal disease, the most prevalent chronic inflammatory condition in dentistry, not only causes periodontal attachment loss, tooth mobility, and tooth loss, impacting mastication, aesthetics, and phonation, but also serves as a significant risk factor for various systemic diseases, posing a serious threat to overall human health. Consequently, investigating the pathogenesis of periodontal disease and developing effective preventive and therapeutic strategies are critical tasks in clinical dental research. Objective: To establish and evaluate experimental animal models applicable for periodontal disease research, and to systematically compare the advantages and disadvantages of different modeling methods, thereby providing a reference for related mechanistic studies and the development of therapeutic interventions. Methods: Through a literature review, we systematically summarized current common methods for constructing animal models of periodontal disease. This included the selection of small and large animal species, and various modeling techniques such as molar ligation, local gingival injection of lipopolysaccharide (LPS), local inoculation with periodontal pathogens, high-sugar diet induction, and chemical induction. Results: Different modeling methods possess distinct characteristics suitable for varying research objectives. Molar ligation is straightforward and reproducible but may cause mechanical damage; bacterial inoculation models more closely mimic the human disease process but require controlled infection conditions; dietary and chemical methods can simulate specific pathological conditions but often involve longer experimental periods. A comprehensive comparison provides a basis for model selection. Conclusion: Animal models are indispensable tools for studying the pathogenesis of periodontal disease and evaluating new therapies. The appropriate selection of a modeling method based on specific research needs enhances experimental reliability and applicability, thereby advancing research in the prevention and treatment of periodontal disease.

Keywords

Periodontal Disease, Animal Models, Modeling Methods, Alveolar Bone Loss

1. Introduction

Periodontal disease is a common chronic oral infection characterized clinically by gingival inflammation, periodontal pocket formation, alveolar bone resorption, and tooth loss, which collectively impair oral function and aesthetics. Furthermore, it is closely associated with systemic conditions such as diabetes, significantly affecting overall health. Research on periodontal disease remains a major focus in dentistry, where the choice of research models is

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Received: 8 October 2025; **Accepted:** 17 October 2025; **Published:** 31 October 2025

critical. While in vitro cell cultures can be used to study certain physiological processes involved in the pathogenesis of periodontal disease, they fail to replicate the complex inflammatory microenvironment of the periodontium. Therefore, experimental animal models serve as essential tools for investigating disease mechanisms and exploring new therapeutic approaches [1]. This article discusses the selection of animal species and modeling methods for periodontal disease, elaborates on the advantages and limitations of different models, and describes the principles, procedures, and relative merits of various modeling techniques. It also summarizes the application of combined modeling strategies, aiming to provide a useful reference for further research into the pathogenesis of periodontal disease, evaluation of treatment methods, and the development of more ideal animal models.

1.1. Types of Animal Models

Animal models for periodontal disease are primarily categorized into large animals (e.g., primates, miniature pigs, dogs) and small animals (e.g., rats, mice, hamsters) [2] (Figure 1). While these models have yielded substantial research data, a simple, reproducible model that accurately recapitulates the pathogenesis of human periodontal disease remains elusive [1].

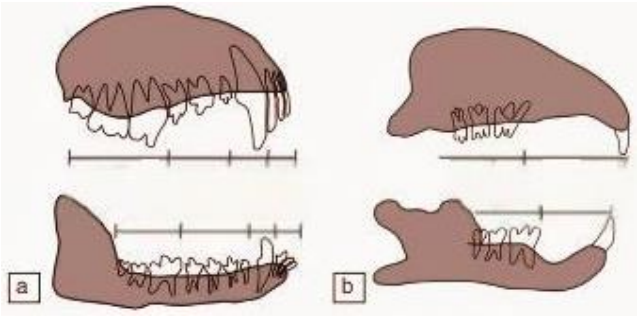

Figure 1. *Periodontal animal models using (a) dog (large animal) and (b) rat (small animal).*

Each animal species presents distinct advantages and limitations in periodontal research [3]. Although certain animals, such as non-human primates, most closely replicate the pathogenesis of human periodontal disease, their application in modeling is constrained by practical challenges, including high maintenance costs. In contrast, rodents—notably rats and mice—are the most widely utilized models, owing to their low cost, ease of husbandry, high survival rate, and the structural and histopathological similarities between their molar periodontium and that of humans [2]. Nevertheless, rodent models remain imperfect, as they cannot fully recapitulate all aspects of human periodontal disease progression.

1.2. Selection of Animal Models

The choice of an animal model is largely determined by research objectives and laboratory constraints. Common applications of periodontal animal models include investigating disease etiology/pathology and evaluating therapies, including periodontal regeneration strategies [1, 4].

1.2.1. Etiology and Pathology

While non-human primates are theoretically the optimal model for etiopathological studies due to their close resemblance to humans, their use is limited by ethical concerns and high costs. Currently, rodent models, particularly rats and mice, are extensively employed in bacteriological and immunological research related to periodontal disease [4]. Additionally, miniature pigs and beagle dogs serve as suitable models for evaluating periodontal and peri-implant diseases [5].

1.2.2. Therapeutic Studies

Mice represent the most frequently used model in experimental periodontal disease research for evaluating the efficacy of pharmaceuticals or biomaterials, owing to their low cost, ease of handling, and similar molar anatomy to humans. Periodontal regeneration remains a critical yet challenging therapeutic goal. Since the natural progression of periodontal tissue destruction is relatively slow, surgically created bone defects have become a standard method for studying regeneration.

Although primates represent an ideal model, ethical considerations restrict their application. The small oral cavity of mice also presents significant technical challenges for surgical procedures. Consequently, dogs, especially beagles, are widely adopted in periodontal regeneration studies [6, 7]. In contrast, animals such as rabbits, characterized by rapid tooth eruption, are generally unsuitable for regeneration research as surgically created defects may not be adequately maintained for evaluation [8].

2. Modeling Methods for Periodontal Disease

Several established methods are currently used to induce experimental periodontal disease in animals, including ligature placement, local injection of lipopolysaccharide (LPS) or periodontal pathogens, high-sugar diet feeding, and surgical induction [2]. Each method presents distinct advantages and limitations. However, none can fully replicate all aspects of the initiation and progression of human periodontal disease. A universally accepted model that concurrently exhibits periodontal inflammation and alveolar bone loss remains unavailable.

2.1. Silk Ligature Method

2.1.1. Principle

Ligature placement promotes food debris retention and plaque accumulation, leading to gingival redness, bleeding, and alveolar bone loss. Furthermore, this model allows for the study of inflammatory resolution and healing responses following ligature removal [9]. Consequently, it is the most frequently employed method for inducing periodontitis in animals. Nevertheless, considerations such as potential ligature loss and the selection of appropriate ligature materials are crucial for experimental design [3].

2.1.2. Operative Procedure

(i). Conventional Ligature

This method is relatively straightforward to perform. It involves placing a ligature around the cervical region of specific teeth, typically molars, in the animal. Care must be taken during placement to avoid inadvertent injury to the periodontal tissues (Figure 2).

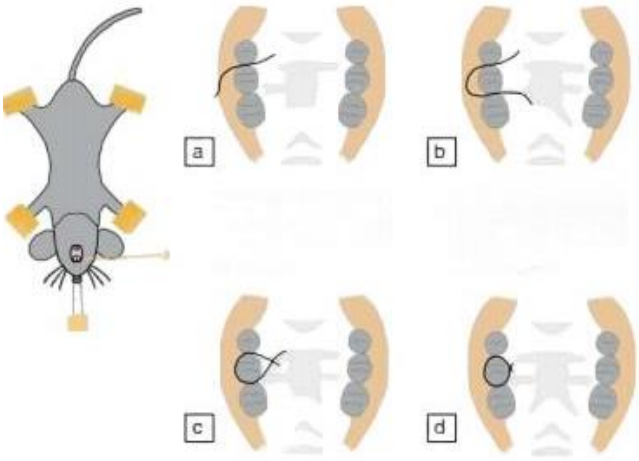

Figure 2. *Representative image of the conventional ligature-induced periodontitis model in mice.*

Commonly used laboratory animals for this purpose include rats and mice, with ligature materials ranging from nylon sutures and silk threads to orthodontic elastics and steel wires. Each material presents distinct trade-offs. For instance, silk ligatures are generally easier to place but are also more prone to premature loss. In contrast, steel wires, though more challenging to position and adapt, typically demonstrate superior retention [10]. A recent study indicated no statistically significant difference between steel wires and silk ligatures in their capacity to induce alveolar bone loss in rats [11]. However, given the limited sample size in that investigation, these preliminary findings require validation through larger-scale studies to confirm their reliability and generalizability. Consequently, the optimal choice of ligature material for periodontal disease modeling remains an area warranting further systematic research.

(ii). Modified Ligature Method

The conventional ligature technique requires passing the ligature through two separate interdental spaces (between the first and second molars, and between the second and third molars). This procedure presents significant technical challenges in mice due to their small oral cavity and minute tooth size [12]. To address this, researchers have utilized 3D printing to fabricate a precise auxiliary device—a mouse alveolar process and ligature fixator. Under isoflurane anesthesia, a 2.5 mm double-knotted ligature was successfully placed between two molars using this apparatus, establishing a simplified and effective ligature-induced periodontitis model in mice [12] (Figure 3).

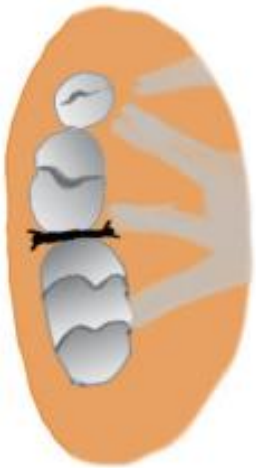

Figure 3. *The modified ligature-induced mouse model of periodontitis.*

Furthermore, while the maxillary second molar is the conventional ligation site, its deep anatomical position presents practical challenges. Recently, researchers have developed an alternative murine periodontitis model utilizing the mandibular first molar [13]. In another methodological refinement, the combined use of a nickel-titanium endodontic file and an orthodontic ligature wire has been reported to facilitate easier and more secure ligature placement, enabling successful induction of periodontitis in mice [14].

2.2. Local Gingival Injection of LPS

2.2.1. Principle

As Gram-negative bacteria are primary periodontal pathogens, lipopolysaccharide (LPS)—a key component of their cell walls—can induce polymorphonuclear leukocyte infiltration, edema, and vascular dilation in periodontal tissues

[15]. Local injection of purified bacterial LPS into the gingival tissues surrounding molars of rodents (e.g., mice or rats) simulates the innate immune response to this bacterial component. Studies have reported observable bone loss as early as 7 days after the initial injection [16]. Advantages of this approach include precise control over the dose and type of LPS administered. However, the method may not fully replicate the natural progression of bacterially induced periodontal disease. Frequent anesthesia required for repeated injections also increases mortality risk [3], while variations in LPS source and purification protocols may affect experimental reproducibility [16].

2.2.2. Process

Injection sites are typically located in the palatal region between the maxillary first and second molars in rats, though some researchers administer LPS into the lingual interdental papilla between mandibular molars. Injections are commonly performed every 48 hours over a period of approximately 6 weeks, depending on experimental requirements [16-20].

2.3. Periodontal Pathogen Inoculation Model

2.3.1. Principle

Also referred to as the oral gavage model, this approach involves oral inoculation with major human periodontitis-associated pathogens (e.g., Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia, Tannerella forsythia, and Treponema denticola) to induce gingival inflammation and alveolar bone loss [21]. P. gingivalis is among the most frequently used pathogens, administered either alone or in combination with other strains [2, 22]. This model is particularly suitable for studying host-microbial interactions in periodontitis, though the time required for successful disease induction remains variable [3].

2.3.2. Procedure

Pathogens may be delivered via direct injection, topical application, or food-borne implantation into the oral cavity [23]. While mono-infection with A. actinomycetemcomitans or P. gingivalis alone can induce periodontitis in mice, mixed-species inoculation tends to result in more severe bone resorption [22].

2.4. High-Sugar Diet

2.4.1. Principle

High-sugar diets provide abundant nutrients for oral bacteria, promoting the production of acidic metabolites and endotoxins that disrupt the oral microbiome. Such diets also impair natural tooth self-cleaning mechanisms, thereby facilitating bacterial proliferation [2]. This method avoids the mechanical trauma associated with ligation, but long-term high-sugar feeding may confound the study of periodontitis in the absence of metabolic disorders [24]. It is particularly suitable for modeling diabetic periodontitis [25].

2.4.2. Procedure

Animals are fed a high-sugar diet in place of standard chow. For example, rice rats fed a high-sucrose, high-casein diet without additional oral interventions developed periodontitis after 24 weeks [26]. Alternatively, a simplified rat periodontitis model has been established by combining localized gingival stripping with high-sugar feed and drinking water. The gingival stripping provides a retention site for high-sugar debris, promoting anaerobic bacterial overgrowth, while the high-sugar diet and drinking water collectively support bacterial growth and virulence [27].

2.5. Chemically Induced Models

Periodic administration of trinitrobenzenesulfonic acid (TNBS) or dextran sulfate sodium (DSS) has been shown to induce time-dependent alveolar bone resorption. DSS primarily acts via the innate immune system, whereas TNBS activates T cell-mediated immune responses. Both models are useful for investigating immune-mediated alveolar bone metabolism [26] and may serve as valuable tools for elucidating immunopathological mechanisms in periodontal disease.

2.6. Surgical Models

Surgical removal of periodontal bone tissue has been used to create standardized bone defects for studying repair mechanisms [28]. For example, Takeuchi et al. [29] extracted the maxillary first molar in rats, allowed healing for 4 weeks, and then surgically created a periodontal defect mesial to the second molar, simulating post-debridement conditions. Padial-Molina et al. [30] generated a fenestration defect in rat mandibles by exposing the lateral bone surface and removing superficial bone and dental tissues adjacent to molar roots. Similarly, our research group created a periodontal fenestration model (5 × 4 × 1 mm) in rat mandibles by exposing and removing buccal alveolar bone, periodontal ligament, and cementum of the first molar [31]. In beagle dogs, class II furcation defects have been induced by raising a mucoperiosteal flap, creating a critical-sized defect, and filling it with polyester mesh before suture closure [7]. While surgically created defects offer significant potential in periodontal research, further standardization and refinement are needed for broader application.

2.7. Combined Modeling Approaches

Although ligature placement alone remains the most common periodontitis induction method [32], combined ap-

proaches are increasingly used to enhance modeling efficiency and severity. Examples include ligature with high-sugar diet, ligature with pathogen inoculation, and more complex protocols such as "gingival mechanical injury + steel wire ligation + rinsing with patient-derived bacterial culture + high-sugar diet," which rapidly induces severe periodontitis in rats [33]. Another model involved inferior alveolar nerve transection—known to exacerbate periodontal destruction [34]—combined with molar ligation and injection of human gingival crevicular fluid, yielding a representative murine periodontitis model [35]. Similarly, application of P. gingivalis LPS to a surgically created alveolar bone defect with simultaneous ligation induced periodontitis within 4 weeks [36].

Combined methods not only improve model stability but also enable the study of contributing co-factors. For instance, ligation of rat molars supplemented with glass ionomer cement added to the occlusal surface secured the ligature while creating occlusal interference [37]. Another study combined bacterial inoculation with composite resin bonding to establish occlusal trauma, generating a combined periodontitis–occlusal trauma model [38]. Such models provide valuable platforms for investigating the interplay between periodontal disease and occlusal factors.

Notably, combining methods does not always yield additive effects. Some studies reported that P. gingivalis inoculation in ligated mice led to less bone loss than ligation alone, possibly due to induced anti-inflammatory and anti-resorptive host responses [39]. In contrast, Eikenella corrodens was found to accelerate ligature-induced periodontitis in rats [40]. Similarly, combining ligature with LPS did not consistently enhance alveolar bone resorption in all experimental settings [28].

3. Conclusion

As the understanding of periodontal disease complexity deepens, animal models continue to play an indispensable role in studying its pathogenesis and evaluating potential interventions. This review has elaborated on various established methods for constructing periodontal disease models, including bacterial inoculation, ligature induction, and application of chemical inducers—each providing unique insights into disease mechanisms. However, to better simulate the multifactorial nature of human periodontitis, ongoing refinement of existing models remains essential. Future efforts should focus on two key directions. First, exploring optimized combinations of existing methods to develop complex composite models—such as those concurrently exhibiting inflammation and bone loss as seen in natural disease progression—could better simulate the clinical course of periodontitis and provide more relevant platforms for therapeutic evaluation. Second, establishing standardized modeling protocols and consistent evaluation metrics will be crucial for improving model reliability and reproducibility. Innovation and refinement of periodontitis animal models will collectively form a critical foundation for developing more effective strategies for the prevention and treatment of periodontal disease.

Abbreviations

LPS	Local Gingival Injection of Lipopolysaccharide
TNBS	Trinitrobenzenesulfonic Acid
DS	Dextran Sulfate Sodium

Author Contributions

Chao Liu: Data curation
Li Xie: Writing – original draft
Baasanjav Nachin: Writing – review & editing
Batbold Baasanjav: Formal Analysis
Hongxing Hai: Project administration

Advantages (Novelty of the Research)

This study summarizes and reviews the comprehensive knowledge points.

Disadvantages (Study Limitations)

This research has limitations and lacks the latest research data.

AI Usage Declaration

No artificial intelligence (AI) technology was employed in this study.

Funding

This study received no financial support.

Conflicts of Interest

All authors of this paper declare that they have no conflicts of interest.

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