

# Animal Models in Periodontal Research: A Mini-Review of the Literature

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## Abstract

Introduction: Animal models have been extensively used in periodontal research to investigate the pathogenesis of periodontal disease, use of dental implants, periodontal tissue regeneration and other procedures. However, there is in the literature a lack of information regarding the frequency of using animal models in periodontal research.

Aim of the study: To address the most preferred animal models demonstrated in the literature within the field of periodontal research.

Methods: A search of the literature in PubMed was performed between March 1967 and February 2008. The search strategy included the combination of the terms "Animal Models" AND "Periodontology". Inclusion and exclusion criteria of studies were set. Eight subsections of studies were defined; Periodontal Tissue Regeneration Studies, Peri-implant Tissue Studies, Bone Healing Investigations, Periodontitis Model Descriptions, Laser Application, New Animal Model Description, Implant Studies and Bone Regeneration Investigations.

Results: Of the 107 studies addressed, only 82 studies met the inclusion criteria. Dogs were the most animal models used (31.16%), monkeys came at the second level (15.58%), and then rats (10.66%), pigs, ferrets and sheep (1.64%) and finally goats (0.82%).

Conclusion: Dogs showed the most animal model used in periodontal research, especially in the periodontal tissue regeneration studies and as periodontal disease models. Monkeys came at a second level and, at last, came other animals. A gold animal model in periodontology does not exist since every application requires a model that fills specific needs.

This work was done in the department of Periodontology - Faculty of Dental Medicine – Witten/Herdecke University.

## INTRODUCTION

Animal models have been used to evaluate the pathogenesis of periodontal diseases and various periodontal treatment modalities. Human longitudinal studies of periodontal diseases pose many problems such as determining the level of disease activity, individuals at risk, and susceptibility to disease progression.

From the viewpoint of comparative biology, non-human primates are similar to humans, having comparable periodontal tissue structures and healthy and diseased periodontal states, as observed in humans (1). However, most non-human primates used for research purposes are large, expensive, and difficult to handle. Furthermore, the

genetic background of many of these animals has not been established, because animals used in research are often wild-captured animals, with heterogeneity in age, body weight, and oral and general health conditions (1). Among the species of non-human primates, squirrel monkeys and marmosets are small in size and relatively easy to handle, but unfortunately do not exhibit an inflammatory profile characteristic of human periodontal disease. Periodontal tissue specimens from these animals, unlike humans, exhibit very limited numbers of lymphocytes and plasma cells (2-4).

Rodents, belonging to the cohort Glires, such as mice, rats, and hamsters, have been used widely for periodontal research because of specific advantages such as small size, low cost, known age and genetic background, controllable microflora, and ease of handling and housing (5). However, anatomical structures of periodontal tissues and

histopathological features of periodontal disease of rodents are different from those of humans (5). For example, oral sulcular epithelium is keratinized in rodents, but not in humans (6). Neutrophils appear to be the only infiltrating cells in periodontal lesions of rodents. In contrast, periodontally involved human tissues show a complex infiltrate of lymphocytes, plasma cells, macrophages and Neutrophils (5). Suggested reasons for these histological variances include the possibility of some fundamental differences in host responses, or at least in part, some divergence in the reaction of tissues to specific challenges between rodents versus humans (5, 7). Thus, it is clear that efforts to find new animal models which better represent the periodontal disease state in humans would be advantageous for researchers focusing in this area.

The aim of this mini-review was to find out the most preferred animal models demonstrated in the literature in the field of periodontal research during the last two decades.

### **REVIEW METHODS**

Studies concerning the use of animal models in periodontal research were identified by reviewing the appropriate Medical Subjects Heading (MESH) keywords in the period between March 1967 and February 2008. Standardized methodological filters were used to identify analytical studies included the following keywords: (Animal Models) AND (Periodontology). We also searched reference lists of identified articles and abstracts.

### **INCLUSION CRITERIA**

To be eligible for inclusion in the review, studies had to:

- be pilot studies, cohort studies, description papers or in vivo investigations
- be in English language
- consider one or more animal model to investigate one or more subject in the field of periodontology.

### **EXCLUSION CRITERIA**

Non-English articles, in vitro studies, reviews, case reports, reports of workshops and studies performed on human patients were all excluded from this review. Studies which were addressed without identified texts were also excluded.

To simply arrange the results extracted, we defined 8 subsections of studies as follows:

1- Periodontal Tissue Regeneration Studies (PTRS): contain studies considering growth factors, bone grafts/materials, guided tissue/bone regeneration, Enamel Matrix Derivative (EMD) application, collagen/synthetic membranes, Bone Morphogenetic Proteins (BMPs) application, periodontal tissues' regenerative factors and osteogenesis by means of biological cells.

2- Peri-implant Tissue Studies (PiTS): contain studies considering peri-implant soft and/or hard tissue alterations, peri-implantitis, peri-implant tissue inflammation and treatment of peri-implantitis.

3- Bone Healing Investigations (BHIs): contain studies considering bone healing of artificial defects.

4- Periodontitis Model Descriptions (PMDs): contain studies considering evaluation of assessments in periodontal defects, experimental/induced periodontitis or gingivitis, inflammatory mediators in gingivitis or periodontitis, any animal model of new treatment methods, comparisons between human and animal in terms of periodontal pathogenesis and oral pathology investigations.

5- Laser Application (LA): contain studies considering all applications related to laser.

6- New Animal Model Description (NAMD): contain studies considering evaluation of animals as suitable models in periodontal research and for pioneer treatment ideas.

7- Implant Studies (IS): contain studies considering evaluation of different types of dental implants.

8- Bone Regeneration Investigations (BRIs): contain studies considering bone inducing materials.

### **RESULTS**

The electronic searching system addressed 107 studies, of which, only 82 studies met the inclusion criteria (8), (9), (10), (11), (12), (13), (14, 15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (26), (27, 28), (29), (30), (31), (32), (33), (34, 35), (36, 37), (38-40), (41, 42), (43, 44), (45), (46), (47), (48), (49), (50), (51), (52), (53), (54), (55), (56), (57), (58), (59), (60-62), (63, 64), (65), (66), (67), (68-70), (71), (72), (73), (74), (75), (76), (77), (78), (79), (80), (81), (82), (83), (84), (85), (86), (87), (88, 89) and 25 studies were excluded (90), (91), (92), (93-95), (96, 97), (98), (99, 100), (101, 102), (103, 104), (105), (106), (107-109), (110), (111, 112), (113, 114) (Tables 1 and 2).

Within the 82 studies mentioned, dogs were used as animal

models in 38 studies (8), (10), (11), (12), (14, 15), (17), (18), (20), (22), (24), (25), (26), (28), (29), (30), (31), (34, 35), (9), (13), (23), (32), (16), (19), (21), (33), (36, 37), (38), (40), (41), (42), (43), (44), (45), (27), (39).

At the second level, monkeys were used as animal models in 19 studies (46), (47), (53), (56), (60), (48), (54), (52), (49), (55), (59), (62), (61), (63, 64), (51), (58), (57), (50).

Rats came at the third level and were used in periodontal tissue regeneration studies (68-70), (71), (72), (74), (77), in bone healing investigation studies (67), (65) and to describe periodontitis models (75), (76), (66), (73).

Pigs were only mentioned under Peri-implant Tissue Studies (78), (79).

Rabbits were used as animal models in periodontal tissue regeneration studies (80), (82), (83), in laser application (81). Indeed, rabbits were used to describe a new animal model (84).

Ferrets were used to describe periodontitis model in two studies (88, 89).

Sheep were used to describe a new animal model in periodontology (86), (85).

Finally, only one study considered goats in the field of bone regeneration (87).

**Figure 1**

Table 1: Studies used animal models in periodontal research and the field of application

	PTR	PI Ts	BHIs	PMDs	LA	NAMD	IS	BRIs
Dogs	(8), (10), (11), (12), (14, 15), (17), (18), (20), (22), (24), (25), (26), (28), (29), (30), (31), (34, 35), (39)	(9), (13), (23), (32)	(16)	(19), (21), (33), (36, 37), (38), (40), (41), (42), (43), (44)	(27)	(45)		
Monkeys	(50), (46), (47), (53), (56), (60), (48)	(54), (52)		(49), (58), (62), (81), (63, 64), (51)		(58), (55)	(57)	
Rats	(68-70), (71), (72), (74)		(67), (65)	(75), (76), (66), (73), (77)				
Pigs		(78), (79)						
Rabbits	(80), (82), (83)				(81)	(84)		
Ferret				(88, 89)				
Sheep						(86), (85)		
goats								(87)

**Figure 2**

Table 2: Excluded studies

In vitro studies	(91), (97), (98)
Studies on human patients	(92), (95), (101), (113)
Text not found	(93), (112)
Non-English articles	(90), (94), (99), (109), (108), (110), (114)
Reviews	(96), (100), (103, 104), (105), (106), (107), (111)
Reports of workshops	(102)

## DISCUSSION

In designing any medical or dental animal study, it is often advantageous to select an animal that is phynogenetically similar to humans. The wide range of animal species allows appropriate selection of bio-models for different investigations. Each species has unique similarities and dissimilarities to humans.

Choosing a gold animal model which suits all fields of application is a current goal in research though seems to be very difficult or impossible.

It was the aim of the current mini-review to address the most frequent animal model used in periodontal research within its different divisions.

According to the electronic search, it was shown that dogs were most used in periodontal research as biological models (31.16%). In view of their docile temperament and natural susceptibility to periodontal disease, dogs, particularly beagles, are used in dental research for the study of periodontal disease progression, guided tissue regeneration, tissue wound healing, and dental implants. The etiologic factors of periodontal disease seem to be identical in humans and dogs (115). Dogs may therefore be of value as a model for experimental gingivitis. In our review, the most frequent use of dogs in the addressed studies was in the field of periodontal tissue regeneration and as models for induced periodontitis. On the other side, dogs were not preferred in implant studies and bone regeneration investigations.

Monkeys came at a second level after dogs (15.58%) and were most considered in periodontal regeneration studies and to investigate periodontitis and/or gingivitis models.

Monkeys have been used widely as an animal model for studying periodontal surgical procedures. Periodontal lesions in these animals are also suitable for evaluating periodontal regenerative procedures (1), especially since histometric analysis needed to quantify the amount of new cementum, periodontal ligament and alveolar bone formed as the result of regenerative periodontal surgery (116), can only be done with animals, usually monkeys or dogs.

Due to the possibility of obtaining block biopsies, the rhesus monkey, cynomolgus monkey, and baboons have been used to study osseointegrated oral implants. Fritz et al. (52) suggested that ligature-induced periodontitis around teeth and ligature-induced peri-implantitis follow similar destructive patterns, namely alteration of microbiological flora.

Although various species of non-human primates are adequate for studying different aspects of periodontal diseases, monkeys are expensive to purchase and maintain and are ferocious (100). However, in the fields of bone healing investigations, laser application and bone regeneration investigations, monkeys were not preferred as resulted in our review.

The laboratory rat, although an acceptable model for studying calculus and caries, has limitations as a model for periodontal disease. That is because periodontal disease in rats is different from that of humans.

In our review, rats came at the third level (10.66%) and were used in periodontal tissue regeneration studies, in bone healing investigation studies and to describe periodontitis models. For other applications, rats were not frequently recommended.

Rabbits came at the forth level (4.1%) and were most used in periodontal tissue regeneration studies. One study considered rabbits in the field of laser application (81). Other study (84) introduced the rabbit as a new animal model and showed that this animal model can be efficiently used for the testing of various bone grafting materials.

Pigs, ferret and sheep came at the fifth level as animal models in periodontal research (1.64%). Pigs were used in peri-implant tissue studies (78, 79) and ferrets were used in two studies to evaluate the clinical and histological characteristics of ligature induced periodontitis (88, 89).

Use of the domestic ferret as an animal study model in periodontics was originally described in the 1940s by King et al., who documented that the occurrence of periodontal disease in ferrets was similar to that occurring in humans (117). The ferret is a suitable model for the study of calculus because of its resemblance to human calculus and the fact that formation of calculus is not diet dependent as in the rat and hamster.

Further research is still needed to ascertain the role of ferrets as a model in the pathogenesis of periodontal disease.

Two studies introduced sheep as new animal models; one of them (85) described a model suitable for training for several periodontal surgical methods and showed that the sheep mandible seems to be a feasible training model for the demonstration and exercise of various periodontal surgical techniques for the treatment of periodontitis. The other study (86) evaluated the sheep as a suitable animal model in which to compare periodontal wound healing after furcation defects were treated with different guided tissue regeneration membranes and showed a successful use of the sheep animal model for guided tissue regeneration research.

Within the results obtained in the current study, only one study (0.82%) (87) used goats to evaluate the clinical applicability and biological behavior of a newly developed injectable calcium phosphate (Ca-P) cement as bone filler for gaps around oral implants.

## CONCLUSION

According to the mini-review of literature achieved in the current study, it could be stated that dogs showed the most animal model used in periodontal research, especially in the periodontal tissue regeneration studies and as periodontal disease models. Monkeys came at a second level and then came rats, rabbits, pigs, ferrets, sheep and goats, each of which was used in a specific field in periodontal research.

This study could have certain limitations due to the research methods used. That is why it was referred to as “mini-review”. However, it is still of importance since no similar reviews has yet been made.

A gold animal model in periodontology does not exist since every application requires a model that fills specific needs.

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