Cumhuriyet Dental Journal 2017;20(1):62-71
Doi: 10.7126/cumudj.307312 *REVIEWS*

ANIMAL STUDIES IN FIELD OF PERIODONTOLOGY: EXPERIMENTAL PERIODONTAL AND PERIIMPLANT DISEASE INDUCTION

Periodontoloji Alanında Hayvan Çalışmaları: Deneysel Periodontal ve Periimplant Hastalığın İndüksiyonu

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Makale Kodu/Article code *: 83954*
Makale Gönderilme tarihi *: 01.04.2016*
Kabul Tarihi *: 06.10.2016*

ABSTRACT

Preclinical studies are crucial in studying the etiology and pathogenesis of human diseases especially diseases with multifactoriel etiology such as diabetes, cardiovascular diseases and periodontitis. Studies in animal models are complementary to in vitro experiments prior to clinical trials. Every model has its own advantage and disadvantage and there is not any model suitable for all kinds of studies. To find the optimal experimental model and animal species is a major issue for researchers. In this mini-review I aimed to review the animal models used in the field of periodontology and a relatively novel field implantology and though very little, to provide guidance for researchers.

Key words: Experimental model, animal study, animal model.

ÖZ

Preklinik araştırmalar, özellikle diyabet, kardiyovasküler hastalıklar ve periodontitis gibi multifaktoriyel etiyolojiye sahip insan hastalıklarının etiyoloji ve patogenezinin araştırılması için oldukça önemlidir. Hayvan modellerinde yapılan araştırmalar, in vitro deneylerle birlikte klinik araştırmalardan önce gerçekleştirilmelidir. Her deney modelinin kendine özgü avantaj ve dezavantajı bulunmaktadır ve hiçbir model, tüm araştırma konularının hepsi için tek başına elverişli değildir. En uygun deneysel modeli ve hayvan türünü belirleyebilmek, araştırıcılar için zor bir durumdur. Bu mini derlemede, Periodontoloji alanında ve nispeten daha yeni bir alan olan İmplantoloji alanında kullanılan hayvan modellerinin derlenmesi ve çok az da olsa, araştırıcılara rehber olabilmek amaçlanmıştır.

Anahtar kelimeler: Deneysel araştırmalar, Hayvan çalışmaları, Hayvan modelleri.

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INTRODUCTION

Preclinical studies are crucial in studying the etiology and pathogenesis of human diseases especially diseases with multifactoriel etiology such as diabetes, cardiovascular diseases and periodontitis. Animal studies are complementary to in vitro experiments prior to clinical trials. In addition, experimental animal models of human diseases allow us to investigate individual factors contributing pathogenesis of the disease and discovery of new therapeutic approaches. The first example of the animal studies available online was written by Wakeman[1] in 1905 and was about phosphorus poisoning in dogs. Forty two years after, the first animal study in field of periodontology was published in 1947 by Sognnaes[2] and it was the very first study of experimental periodontal disease. Since then, numerous papers were published and so many animals were used in diverse kinds of studies.

Different animal species were used in experimental study models in periodontology including rats, hamsters, rabbits, ferrets, dogs, pigs and primates. All of these animals were used in order to mimic human periodontal diseases in an attempt to reveal pathogenetic mechanisms of periodontal disease and find cure. However, not every animal is suitable for studying periodontal disease as both the anatomy and physiopathology of animals are different from those of humans. There are some important aspects to be considered in finding the best way of reflecting human periodontal diseases. These are standardization, reproducibility and common characteristics with human disease such as anatomy, etiology and pathophysiology. Furthermore, availability, simplicity of handling, ethical issues and cost are also important factors. Therefore, selection of the appropriate animal model is important and depends on not only the similarity of the nature of the disease to that of humans but also aforementioned criteria. In this mini-review I aimed to review the animals used in experimental models in field of periodontology beginning from the small-sized animals to large-sized ones.

Rats and mice

Rodents have been used in periodontal research due to their advantages such as their small size, low cost, availability, handling and housing and detailed knowledge about their genetic structure. Rats are the most extensively studied animals for the pathogenesis of periodontal diseases. Rats have 1 incisor and 3 molars in each quadrant and incisors are rootless.[3] One of the most successful study approaches, germ-free or gnotobiotic rats, made it possible to study dental plaque and bacterial biofilm in periodontal research. Gnotobiotic rats of the Spraque-Dawley strain have been very useful in the understanding of periodontopathogenic bacteria.[4] There are a few ways of inducting periodontal diseases in rats. These are

- Ligation model
- Bacterial infection and/or inoculation models
- Lipopolysaccaride injection model
- Calvariel model
- Critical size defect model

Ligation Model

Ligature-induced periodontal disease is the most common way of inducting periodontal disease in animals. Many different types of animals ranging from rats to nonhuman primates were used in this model. In rats molar teeth are suitable for induction and evaluation of periodontal disease, both mandible and maxilla can be used but it must be considered that there might be some problems in histological or morphological evaluation of the jaw selected. Mostly silk ligature but any retentive ligature type can be used. Placement of a ligature causes an accumulation of dental plaque and ulceration in the sulcular epithelium facilitating the bacterial invasion into connective tissue. Alveolar bone and attachment loss occur in 7 days after ligation.[5]

In wild-type rats ligation could induce periodontal disease alone but in gnotobiotic rats ligation without bacteria is not enough.[6]

Bacterial infection and/or inoculation models

As periodontitis is an infectious disease, bacterial colonization around teeth and subsequent bacterial invasion into the soft tissues is an important aspect of periodontal disease especially in experimental procedures. A limitation of the infection/inoculation model is that rodents are not natural hosts for many human bacteria and the bacterial infection process in the oral cavity is transient. Different periodontopathogenic bacterial strains have been used such as *Porphyromonas gingivalis.*[7,8] *A. actinomycetemcomitans,*[9] *Tannerella forsythia*[10] and *Treponema denticola.*[11] There is an exception of transient infection in rats. Wild-type *A. actinomycetemcomitans* is a common inhabitant of rice rats. Rice rat (*Oryzomys palustris*), is a native American species that is highly susceptible to periodontal disease, beginning as early as 2 weeks of age.[12]

In infection/inoculation model, typically 10^9 CFU bacteria in a viscous suspension (2% carboxymethylcellulose) are administered orally every other day for 1 week. PCR has frequently been used for detection of bacteria but a limitation of PCR is that PCR does not specify living or dead bacteria. Prophylactic antibiotic use before infection/inoculation and repeating inoculation enhance the chance of inducing periodontal infection. In addition, some strains of mice have different degree of susceptibility to infection.[13]

Lipopolysaccharide Injection Model

The lipopolysaccharide (LPS) is a major component of the cell wall of microorganisms that contributes to inflammatory process in the host. Injection of LPS causes an innate immune response and induces inflammation to stimulate osteoclastogenesis and bone loss. Therefore LPS injection is a good model of inducing periodontal disease in rodents.[13]

Calvarial Model

Calvarial model is not particularly an experimental periodontitis model but was first designed and developed to study the effect of cytokines on osteoclastogenesis.[14] In this model, the soft tissue above the calvaria is stimulated by an injection and with a rapid expansion of pro-inflammatory cytokines in 24 hour, inflammatory process leads to bone destruction.[15]

Rat Critical Size Defect Model

Like calvarial model, the critical size defect model is also not an experimental periodontitis model. It was developed to study bone formation in the mandible and has been very useful in studying the efficacy of different materials such as barrier membranes[16], bone grafts[17], growth factors and hormones[18] in bone augmention procedures.[19]

Hamsters

The dentition formula of the hamsters is identical to rodents and periodontal disease does not occur spontaneously[20] but experimental periodontal disease can be achieved with a diet containing high concentrations of carbohydrates, particularly sucrose.[21] The albino hamster is disease-free but the golden Syrian hamster is the most commonly used for inducing periodontal disease. Keyes and Jordan demonstrated that infectious dental plaque inoculation in albino hamsters induced periodontal disease and this disease transmitted from generation to generation.[22] Diet-induced periodontitis model of hamsters have some similarities with rat model of experimental periodontitis. Both have similar bone destruction pattern with horizontal bone loss, therefore bone loss occurs mostly in horizontal dimension.[3] However, there are certain differences between these two rodent model of periodontitis. Firstly, despite the similarity of periodontal tissue structure, interdental septum is narrower than in rats. Secondly, alveolar bone loss in the buccal surface is lesser than the interdental surfaces.[23,24] In conclusion, this model of periodontal disease

causes a similar bone destruction pattern to those observed in rats infected with Gram-positive bacteria and the disease pattern is different from human periodontal disease.[24]

Rabbits

Rabbits are not the first choice of animal for experimental periodontitis models and mostly have been used to study surgically induced periodontal defect and periodontal regeneration. Critical-sized femoral defects are traditionally the most commonly used models in rabbits.[25] It has also been reported that rabbits were used in implant research.[26] Although not too much, there are some studies[27,28] demonstrating periodontal disease induction in rabbits. In these investigations ligation method along with bacterial inoculation were used to induce periodontitis in New Zealand type white rabbits. In addition, numerous pathogenic bacteria such as *F. nucleatum, P. heparinolytica, Prevotella spp., P. micros, S. milleri group, A. israelii,* and *A. haemolyticum* were found in oral flora of the rabbits.[24,29]

Ferrets

Ferrets (*Mustela putorius*) rarely have been studied in terms of periodontal disease. However, restricted studies have reported some similarities between human and ferret dentition and periodontal physiology.[30] Unlike rodents, ferrets naturally develop calculus and periodontal disease similar to humans regardless of the diet and have a deciduous and permanent dentition.[3,30] Because of spontaneously calculus development, ferrets were considered to be a suitable model for studying calculus. Research has shown that ferret calculus has a structure similar to hydroxyapatite and differs from human calculus in terms of degree of calcification.[31] Experimental periodontitis in ferrets could be induced by ligation within four weeks[31,32] and the ferret periodontitis model showed a similar pattern of periodontal destruction observed in humans with a small difference as 50-70% loss of attachment with ligation.[3,30] Ligation also caused large populations of PMNs, plasma cells and lymphocytes. Unlike periodontitis model, ferret model of gingivitis is almost identical to human gingivitis.[30] However, ferrets are difficult to handle and need special care and maintenance.

Dogs

Due to the naturally occurring gingivitis and periodontitis, dog model is quite suitable for periodontal research.[33] Periodontitis is the most prevalent disease in canines older than 2 year old with a percentage of 80%.[34] Periodontal tissues and the size of the teeth are similar to those observed in human. It is reported that, like human microflora, dogs have anaerobic gram negative cocci and rods, *P. gingivalis* and *F. nucleatum* in their subgingival flora.[35,36] The severity of the periodontal disease increases with age and frequently results in loss of tooth in dogs. The beagle is one of the most commonly used due to its size and its extremely cooperative temperament. Several studies have used dogs to evaluate the regenerative procedures, surgical manipulations and different treatment modalities including wound healing and regeneration in periodontal pockets.[35,37] However there are some limitations of studying in dogs. There are quite strict ethical policies regarding dog studies and dogs require special treatment such as exercise, maintenance, daily companionship and requirement of large space.

Pigs

Studies in miniature pigs have been increasing in recent years. Similarities between human and mini pig periodontal anatomy and physiology made it possible to evaluate pathogenesis and treatment outcomes of periodontitis. Like human, mini pigs have both deciduous and permanent dentition. Gingivitis and periodontitis occur spontaneously in mini pigs in early and middle terms of their life span (6 and 16 months respectively).[38,39] Pig model of gingivitis and

periodontitis have similar histopathological process manifested by inflammation and bleeding in gingival tissues, plaque and calculus accumulation and probing depth. However, additional procedures are recommended in order to shorten the time required for disease occurrence. Surgical removal of bone, bacterial inoculations of *P. gingivalis, S. mutans*, and *A. actinomycetemcomitans* and additional ligation of silk sutures are reported to reduce time without affecting course of the disease.[35,40,41]

Non-human primates

Non-human primates are considered to be the closest animal model mimicking human periodontal diseases due to their phylogenetic proximity. The reason is that human and non human primates share common anatomical and physiological features in periodontal tissues and periodontal diseases of both species present similar immunological and microbiological aspects.[3,4] Periodontal diseases in non human primates occur spontaneously in late period of their life span in some species. There are also some limitations of this model. These are the risk of cross infection with human, the diversity in the size of species, handling and housing issues, aggressive temperament and high cost.[3,42] Many studies carried out in monkeys were performed in order to evaluate implant surgery outcomes and periodontal regeneration.[4,43] There are also some ethical issues regarding the use of non human primates. The most preferred non human primates in periodontal research are macaques, baboons, chimpanzees and marmosets. First three have the same dental formula as human while marmosets have a different formula with 3 premolars and 2 molars in a quadrant. In most species, periodontal inflammation and destruction pattern are quite similar to human with plasma cell, lymphocyte and neutrophil infiltration in inflamed periodontium while small sized monkeys such as marmosets have very little inflammation restricting their use in periodontal research.[42] However, as in pig model of periodontitis, an intervention to increase plaque accumulation is necessary. In this regard, orthodontic ligatures, sutures, bone surgery could be used.[35,43]

Experimental periimplantitis models

In this section of this mini-review only the experimental periimplantitis models were discussed. Experimental periimplant mucositis which is characterized by an inflammatory lesion around the soft tissues surrounding implants caused by bacterial challenge is not included. The advantages and disadvantages of animal models used in experimental periodontitis are discussed above. Here, only the difference of experimental periimplantitis model from experimental periodontitis will be discussed.

Periimplantitis is the inflammatory disease of the soft and hard tissues surrounding implants and characterized by bleeding on probing, pus formation and alveolar bone loss.[44] Experimental periimplantitis models are relatively new and unlike periodontitis there is not any established animal model. The pathogenesis of periimplantitis is not fully understood and therefore putting these two diseases in same basket might mislead us in terms of investigating ethiopathogenesis, preventing the disease or finding new treatment modalities. Periimplantitis is a unique disease regarding to its anatomical and physiological structure for it is the disease of living tissues surrounding an inanimate object. Day by day the increase in implant numbers caused an increase in periimplantitis incidence. Because of its unrevealed pathophysiology, studies are rapidly increasing.

Experimental models of the periimplantitis were studied in mostly canine but also nonhuman primates and mini pigs.[39] As the most used big animal models in periodontology, dog, non-human primate and pig (mini-pig, micro-pig) has some advantages over small animal models. The biggest advantages of dog model are that periodontal diseases spontaneously develop and with a good plaque control periodontal health can

be maintained. Docile character, ease of management and maintenance and large size make dog a good animal model for periodontal disease. These also apply in terms of periimplantitis. Bone structure and remodeling process of dogs are quite similar to human and in addition plaque control and maintenance of periimplant lesions are easy.[45-47] Periimplantitis in dog model could be induced by ligature placement around implants and disrupting oral hygiene. The regions suitable for experimental periimplantitis are mandibulary premolars and first molar regions.[24,45]

On the other hand, non-human primate dentition closely resembles the human dentition as they have deciduous and permanent dentition such as humans and the anatomy of the periodontium and periodontal disease in non-human primates and humans share some similarities.[3,4] The advantages and disadvantages of experimental periodontal disease model in non-human primates also apply to experimental periimplantitis.[45] Mini pigs and micro pigs are relatively new in this field than dog and non-human primates. They eliminated disadvantages of the domestic pig model of experimental studies such as body weight, maintenance and management issues and made it easier to study this model in periodontology. Like dogs, pigs have a similar bone composition, structure and remodeling rate to human bone[47] allowing to study periimplant lesions effectively.

In experimental periodontitis, different experimental models are available for different animal models. However, in terms of experimental periimplantitis, regardless of the animal model, the most used method is ligature-induced periimplantitis model. Especially two models of ligature-induced experimental periimplantitis were studied, one of them is dog model[1,48,49] and the other is mini pig model.[45,50] Other than ligature-induced periimplantitis model, miniimplants in rabbits, rats and mice were also studied.[51-55] Small sized animals have a disadvantage of smaller oral cavity and implants replacing teeth are difficult to insert in small animal models.

Ligature-induced periimplantitis model has many discrepancies regarding the method used by the authors.[45,49,56,57] However the procedure can be summarized by following steps:

1. Tooth extraction and healing time (3-4 months),
2. Implant placement and healing time (2-4.5 months),
3. Ligature placement and active destruction period,
4. Some studies removed the ligature and allowed a passive destruction period[48,58] while some studies kept the ligatures in place.[57, 59, 60]

Besides a study reported implant removal and reimplantation.[49] In addition, in a recent study, ligature-induced periimplantitis model was achieved with *P.gingivalis* infiltration to ligatures.[61] With small or big modifications, this model is still being developed by researchers. The protocol is widely different from one to another. However the aim of ligature-induced periimplantitis is to induce periimplant bone destruction in a way seen in humans and establish an optimal treatment modality. Soft diet after implant placement is also suggested in order not to traumatize implants and to allow plaque accumulation.[39]

Other than ligature placement, a study in minipigs reported flapless implant placement and plaque accumulation in order to develop periimplant infection.[62] Not being a periimplantitis model, some researches induced surgical bone defects with or without implants to evaluate bone regeneration.[63]

Two recent studies suggested an immediate ligature-induced periimplantitis model, one in dogs[64] and the other in rabbits.[53] This new method of theirs was different from the

conventional method in terms of immediate implant placement and simultaneous insertion of ligatures.

Although many studies were performed in dogs, Becker *et al.*[65] for the first time described a mice model of periimplantitis. They inserted titanium implants in the median of the palate and induced periimplantitis with ligature placement. Recently, another mice model of ligature-induced periimplantitis was developed by Nguyen *et al.*[55] Their protocol is nearly same as dog or minipig model. Another study by Firih *et al.*[66] described a mice model of experimental peri-implantitis with *P.gingivalis* lipopolysaccaride injection delivered to periimplant soft tissues in the edentulous alveolar bone. A study in rats used *A. actinomycetemcomitans* inoculation around implants and inserted contaminated implants in rat hard palate.[67]

In conclusion, experimental periodontitis models are well established and documented in almost all animal models. Other than genetic innovations such as knock-out models, experimental periodontitis models are nearly same. On the other hand, lack of an established animal model and/or treatment protocol caused a rapid increase in periimplantitis research. Big animal models have their own advantages however cost, handling problems, ethical issues are major problems for their use. In addition, new models such as rat and mice may facilitate experimental procedures and accelerate improvements in this area.

Conflict of interest

There is no conflict of interest in this article.

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