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Review

Experimental rat model – is it still used? – review article

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Abstract. Periodontitis is a chronic inflammatory disease with a high prevalence in today practice. Its evolution leads to the destruction of the supporting tissues of the teeth by a progressive loss of connective attachment level and alveolar bone resorption. Experimental models for studying periodontitis treatment effects are of high demand for understanding the biological concepts and the evolution of certain treatments in humans. Animal models are considered to be a better alternative to in vitro studies thus are highly important, representing an essential link between a hypothesis and its relevance to human patients. There is a wide range of animals that are suitable for inducing periodontal inflammation and for testing treatments as well. The animal model should be carefully chosen depending on the main purpose of the study and the laboratory constrains. The purpose of this paper is to highlight the advantages and disadvantages of different species used for studying periodontal disease with a main focus on the rat model which is considered by the literature one of the most relevant model available.

Key Words: periodontitis, rats, experimental animal models, histological aspects, systemic inflammation.

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Introduction

According to the literature (Ferreira et al 2017), periodontal disease is a chronic inflammatory pathology caused by an opportunistic infection. Its evolution leads to the destruction of the supporting tissues of the teeth by a progressive loss of connective attachment level and alveolar bone resorption. The pathogenesis of periodontal disease is multifactorial and can be summarized by a series of complex connections between microorganisms in dental plaque and the immuno-inflammatory response of the host.

The dental plaque microorganisms act on the periodontal tissues by direct and indirect mechanisms. On one hand, they release substances that injure the periodontal tissue directly. On the other hand, they can induce the tissue destruction by activating the host immuno-inflammatory responses as shown by Fernandes et al (2010). Also, it was demonstrated that systemic factors such as diabetes, smoking, alcohol consumption and stress are directly associated with severe periodontitis (de Souza et al 2006; Petruţiu et al 2014). Different pathogenic links between periodontitis and some systemic diseases have been reported. At a molecular level, there has been demonstrated an inflammatory response correlated with active periodontitis that can affect the general homeostasis of the patient. This can lead to general manifestations far away from the oral cavity as shown by Ionel et al (2017). Concluding the aforementioned, periodontal disease plays an important role factor in affecting the systemic health having in the meantime an important negative impact on the quality of life and essential emotional, social and functional dimensions (Meusel et al 2015; Ferreira et al 2017).

The periodontal treatment aims to stop the evolution of the periodontal disease by removing the direct etiologic factor and to rehabilitate the oral functions. However, the final goal of the periodontal therapy is to regenerate lost periodontal structures, which, unfortunately, remains an occasional event due to the model of destructions and to the complexity of the regenerative phenomenon.

The therapeutical protocols for periodontitis have changed a lot in the past period. New therapies, novel biomaterials and sophisticated tissue engineering approaches have been introduced in order to diminish the disastrous effects of periodontal diseases. The best way to evaluate the effect of these therapies before clinical implementation is by applying them on animal models. Animal models need to be used in the research field prior to clinical trials when we talk about new therapies or materials for treating periodontal disease according to Struillou et al (2010). Beside clinical evaluation of the effect of a certain treatment, animal model allows to provide histological outcomes relevant for regeneration.

Experimental models for studying periodontitis treatment effects are of high demand for understanding the biological concepts and the evolution of a certain treatment in humans.

Either the situation, in order to quantify the efficacy of one treatment or another we have to evaluate some biological parameters beside the clinical evaluation. In periodontology, the aim of the treatment is to obtain periodontal regeneration. in order

to evaluate the effect of some new therapies we need to evaluate the starting and the ending point. Histological assessment is therefore needed before and after applying the treatment in the research phase.
Also, the immune inflammatory profile is of high relevance in periodontitis taking into account the important role that inflammation plays in the evolution of the disease.
The use of healthy animals for treatment or drug assessment has many advantages. They are standardized and accepted by regulatory authorities. Inter-laboratory results can be compared and new results can be better interpreted as there is more data on such animal models that we could obtain on humans due to safety and ethical reasons according to Graves et al (2008). Animal models are considered to be a better alternative to in vitro studies and are highly important, representing an essential link between a hypotheses and its relevance to human patients. Animals have been the standard testing ground for treatments and drug applications and also for inducing and observing the modification of different disease patterns as shown by the literature (Jacob & Nath 2013).
Testing and validating different therapies used in periodontology require adequate experimental animal models. Their histological particularities have to allow the extrapolation of the results in humans. Animal studies are of a real help and complementary to in vitro tests before releasing into market some new treatments. This help resides in the fact that histologically evaluation it's not accepted in humans.
There is a wide range of animals that are suitable for inducing periodontal inflammation and for testing treatments as well. The animal model should be carefully chosen depending on the main purpose of the study and the laboratory constrains. Primates and canines are an excellent model for inducing periodontitis and afterwards applying different treatments due to their similarities with humans and because of their size, but for ethical reasons they're use is highly limited according to the literature (Madden & Caton 1994; Selvig 1994). From this point of view, smaller animals like rats or hamsters could be an easier option, but their physiopathology may not be similar to humans. In the meantime, experimental animal models need to be reproducible to obtain relevant results and thus choosing the best animal alternative could be a difficult task.
The animals mentioned before, have some differences regarding the anatomy, dentition and the structures of the periodontium. The inducing of the inflammation and the host response to treatments can vary among species as shown by Struillou et al (2010).

1) Non-Human Primates
The major advantage of the monkeys is the similarity to humans. Non-human primate species can be obtained in different sizes. Most of the large primates have the same dental formula as humans (1 central incisor, 1 lateral incisor, 1 canine, 2 premolars and 3 molars). The teeth and roots anatomy is very similar to humans but they have smaller dimensions.
Some of the primates can develop periodontitis at an older age (Schou, Holmstrup, Kornman 1993). They present similarities to humans in the histological structure of the periodontium as well as in the inflammatory pattern of the periodontium. The inflammation consists in a plasma cell infiltration in the connective tissue with lymphocytes and neutrophils (Page and Schroeder 1982). Although this model has a lot in common with humans, it is rarely used due to ethical regulations. Also, the laboratory conditions should be fulfilled having in mind the sizes of these species and the conditions in which they should be kept (Struillou et al 2010).

2) Dogs (Canines)
There are a lot of studies related to periodontitis conducted on dogs because the anatomy of teeth and periodontium is quite similar to humans. The dental differences between dogs and humans are mostly of occlusal nature like the absence of laterality and no contacts in the premolars. The sulcus and crevicular fluid are frequently absent. Also, the periodontal plaque and calculus composition differs from the one found in humans as demonstrated by Sorensen, Löe, and Ramfjord (1980). All dogs are diphyodont (they have a temporary and permanent dentition). Their dental formula is different from humans (3 incisors, 1 canine, 4 premolars and 2 or 3 molars on one side of the mandible/maxilla). Most of the canine species are susceptible to periodontitis as adults. Like in humans, the tissues can be maintained healthy by adequate plaque control. Gingivitis and periodontitis is more prevalent and severe with age. The modifications occur more rapidly than in humans but the etiologic factors seem to be the same.
According to the literature (Egelberg 1965; Lindhe, Hamp, and Löe 1973) ,gingivitis in the canine model is accelerated by a soft diet, which enhances the accumulation of plaque and calculus. In the early stages of gingival inflammation, the neutrophils and monocytes are mostly present in the junctional epithelium leaving the connective tissue intact. Later on, false pockets are formed due to epithelial breakdown and the infiltration on the connective tissue. Periodontal disease in dogs is always preceded by gingivitis.

3) Hamsters
As for the majority of the rodents, periodontitis doesn't occur spontaneously but it can be induced experimentally. The most commonly used hamster is the golden Syrian. The dental formula is the same as for rodents (1 incisor, no canines nor premolars and 3 molars). The periodontal anatomy has a lot of similarities to that of rats (Eggert, Germain, and Cohen 1980) but the interdental septum is narrower than in rats due to its smaller size. Periodontal disease can be induced by shifting the diet to high concentrations of carbohydrates as exemplified by Lallam-Laroye et al (2006). As a result of this diet the plaque has the tendency to accumulate more on the oral sites rather than the buccal ones. The gingival pockets are observed after the plaque accumulation. The breakdown is located at the junctional epithelium. The inflammatory response consists principally of neutrophils. Osteoclastic activity is significantly higher on the oral and interproximal sides of the molars. The bone resorption pattern is mostly horizontal with the degradation of the interradicular spaces as Baron and Saffar (1978) described. To conclude, the inflammatory response in hamsters is approximately the same to that observed in rats but very different from humans (Struillou et al 2010).

4) Ferrets
Ferrets are diphyodont animals and their permanent dental consists in 2 incisors, 1 canine, 4 premolars and 2 molars on each side upper and lower.

In this experimental model, periodontitis can be ligature-induced within 4 weeks (Harper, Mann, and Regnier 1990; Mann, Harper, and Regnier 1990).
There are reported similarities to humans regarding the evolution of periodontal lesions. The calculus deposits increased as the disease progressed.
The signs of inflammation are present at the gingival level. There are some similarities to hamsters regarding the pattern of pocket formation after gingival breakdown. On the histological sections a large number of neutrophils, plasma cells and lymphocytes are present in the connective tissue and there is also a 50 % rate of bone resorption after 4 weeks (Weinberg and Bral 1999; Struillou et al 2010).

5) Minks
The dental formula of the adult mink is 3 incisors, 1 canine, 3 premolars and 1 or 2 molars. Periodontitis can occur spontaneously and its age and plaque dependent. In very old animals the extent of periodontitis can be really severe. Bone resorption may vary and is associated with the formation of bony craters and furcation lesions. This is of course correlated with the extent of gingival inflammation. The inflammatory response, assessed histologically, is quite different to what occurs in humans. There is abundant vascular proliferation associated. The blood vessels proliferation and neutrophilic invasion is also observed at the gingival margin level. Due to the anatomical extension of the epithelium in the connective tissue there is a dramatically decrease in the space available for the connective tissue. Plasma cells and lymphocytes are almost absent. Concluding the aforementioned, the minks experimental model can be interesting in the field of research on the etiology and treatment of periodontal disease. The biggest disadvantage of this model is the difficulty of housing this animal and they also require specific authorizations (Lavine, Page, and Padgett 1976; Struillou et al 2010).

6) Mice
There are a lot of differences between mice and humans regarding periodontal disease. The permanent dental formula of mice is 1 incisor, no canines nor premolars and 3 molars similar to that found in other rodents. The incisors grow continuously while the molars suffer multiple modifications and alterations in time. The apical part of the roots presents a continuous apposition of cementum which leads to hypercementosis (Gilmore and Glickman 1959). Periodontal modifications are defined by bone loss which, like in the other rodents, is more severe on the oral side of the molars rather than buccal side. There are also observed crater-like defects in the interdental and interradicular spaces. Another big drawback of this model is that periodontitis doesn't occur in mice less than 1 year old. The inflammatory reaction is poor and the modifications that occur in time in the position and physiology of the teeth don't put this model in the best place to use for periodontal research (Lavine, Page, and Padgett 1976; Struillou et al 2010).

7) Sheep
Seeps have been used as well for periodontal research. Their dental formula consists of a total of 32 teeth. Because of their short root, the incisors in this species have a physiological mobility. These teeth are frequently affected by periodontitis and this can rapidly form deep periodontal pockets and determine severe bone loss. Epithelium usually covers the pocket wall. Plasma cells invade the connective tissue underneath. There is a high neutrophilic infiltration in the connective attachment. (Cutress and Schroeder 1982; Struillou et al 2010). Their housing and the manipulation is hard so they are not used as often.

8) Rabbits
Rabbits have been used for biomaterial testing or for validating treatment protocols of peri-implantitis (Johnson et al 1997). They are a very interesting model for testing the bone healing (Struillou et al 2010). Rabbits are naturally resistant to periodontitis but the disease can be induced by bacterial inoculation (Weishan, Dechao, and Rongrong 2016). This is an expensive method, probably this is the reason why it is not used that often.

9) Other animals
Some other studies used cats or mini pigs as animal models (Takahashi et al 2005; Craig et al 2006). These studies are in low number and the reproducibility of the model is not demonstrated. Although having in mind the advantages and disadvantages of the models described it is a matter of study purpose and housing conditions in order to determine the model one should us
As mentioned before depending on the purpose of the study, is more likely and easy to use small animals like rats or hamster due to ethical reasons and of course financial aspects related to housing, feeding, manipulation etc. Periodontal disease can be induced spontaneously, experimentally or both depending on species (anatomy, immune response etc.)
The experimental animal that should be used is the one that has patterns for the disease process that are similar to those encountered in humans in order to be able to assess the role of bacteria, diet and treatment results in periodontal inflammation at the histological level.
The used parameters in experimental etiopathogenics studies should be similar to those used in clinical practice. It should then be evaluated the calculus index, gingival index, probing depth of the pockets, the attachment loss, the free gingival margin level, tooth mobility, the presence or absence of the furcation. These clinical references can be than completed by computed tomography scans, radiographs, bacteria determination, and blood immunology and histology analysis (Struillou et al 2010).

Experimental rat model for periodontitis

Due to all the advantages and similarities to humans, the rat experimental model is of high relevance nowadays for studying periodontal disease. This is the reason we focused on this model in order to evaluate all the pros and cons. We will describe this model's particularities and the ways to induce experimental periodontitis in order to answer the question: "Is the experimental rat model a proper choice for studying periodontal disease?"
Rats obey all the ethically principles regarding the experimental animal manipulation which makes them proper models to experimental induce, treat and assess periodontal disease. The most frequently used strains are Wistar or the Spraque-Dawley. The anatomy observed in the dental gingiva is very much alike to that described in humans (Yamasaki et al 1979) but the prevalence of periodontitis is very low compared to humans. This pathology can be induced though, by inoculating bacteria and giving a diet rich in carbohydrates. A particular way to induce

periodontitis in rats is by fixing ligatures around the teeth. This method also eases the systematic shift from gingivitis to periodontitis (Lindhe and Ericsson 1978; Soames and Davies 1980). Although there are reproducible methods to induce periodontitis in rats this model is used mainly for microbiological and immunological studies. It is really difficult to evaluate the progression of the disease in this model due to anatomical changes and dimensional modifications that occur with aging (Lallam-Laroye et al 2006; Peruzzo et al 2008).

Rats dental anatomy

Typical rodent dentition is Incisors 1/1, Canines 0/0, Premolars 0/0, Molars 3/3 on one side of the arch. The incisor is rootless and grows continually. If they do not have material to chew or if they have a malocclusion, the incisors will not wear normally leading to problems regarding mouth closure. Molars are fully erupted when the rats are 5 weeks old (Jacob and Nath 2013).
The periodontal similarities resume to a shallow gingival sulcus with the presence of an oral gingival epithelium, oral sulcular epithelium, junctional epithelium, periodontal collagen fibers, acellular and cellular cementum, and alveolar bone and junctional epithelium attachment to the tooth surface.
There are also some differences in the gingival anatomy:
1. The internal sulcular epithelium in rats is keratinized
2. Gingival and junctional epithelium have a desmosome contact between the most superficial cells of the gingival epithelium and the non-keratinized cells of the junctional epithelium (Listgarten 1975).
Regarding this difference although some might think that this particular gingival anatomy prevents the breakdown of the attachment it seems that the junctional epithelium is a path for irritant substances, bacterial end products and inflammatory cells, quite similar with the processes occurring in humans (Struillou et al 2010).
As rats age, there is a physiologically wear on all their occlusion surfaces that leads in crown attrition compensated by a permanent root growth. Therefore, the physiological wear leads to a permanent eruption of the teeth with continuous apposition of bone and cellular cementum. These modifications result in a progressive movement in an occlusal direction accompanied as well by a distal and buccal shift. This process is opposite to what happens in humans where the movements are in an occlusal-mesial direction) (Page and Schroeder 1982). These modifications should be carefully taken into consideration when interpreting the data obtained in experimental model disease.
After inducing the experimental periodontal disease, the first modifications observed are the edema and ulceration of the free gingival margin resembling gingivitis. Following these modifications, we observe the formation of deep pockets filled with hair and debris. Untreated, this condition leads to bony lesions of the interradicular and interdental spaces with severe alveolar bone resorption and gingival retraction (Page and Schroeder 1982). The bone loss appears different in time depending of the protocol used for inducing periodontitis, as will be described in next paragraphs.

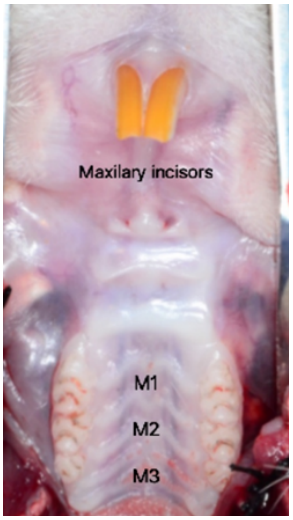

Figure 1. Rat maxillary anatomy

Gram-negative infection model

In rats, periodontitis has been described as an infectious process. Inoculations of specific bacterial strains such as Prophyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Capnocytophaga, Eikenella corrodens, Actinomyces viscosus, and Streptococus sobrinus can induce periodontitis (Klausen 1991).
The modifications in the periodontal tissue take place rapidly after bacteria inoculation. This infection produces a superficial inflammatory response opposite to humans. The cell population at the infection site consists mainly in neutrophils, few lymphocytes but the plasma cells are absent in the gingival tissues becoming more prominent as the destruction progresses (Garant, Paik, and Cho 1983). Like in humans, the response of the host is different from an animal to another and most important dependent on the inoculated bacterial agent. Gingivitis though in rats is not always a precursor of periodontitis. In the early stage, the inflammation is only located at the junctional epithelium level and it can be quantified by an intense phagocytic activity and the presence of the neutrophils that form a protective layer of the under periodontal structures. Regarding the bone modifications, the resorption is inconstant, depending on the individual. There are some studies that show that only 10% of animals up to 100 days of age presented osteoclastic activity although clinically there was a severe interdental inflammation with the presence of on ulcerated junctional epithelium and a neutrophilic infiltration of the connective tissue above the alveolar crest (Garant and Cho 1979I, Garant and CHO 1979II). Regarding the osseous defects, they were crater-like defects. The true periodontal pocket was filled with bacteria and the connective tissue nearby was infiltrated by neutrophils, macrophages and lymphocytes. These modifications occur more rapidly in the maxilla than the mandible. An important finding was that the destructive process related to Gram-negative bacteria inoculation can also occur in the absence of cell-mediated immune response. (Listgarten et al 1978).

Rat ligature model

Ligature placement around the teeth for inducing periodontitis is an interesting model that was applied to different types of animals from rats to non-human primates. This mechanical irritation leads to micro ulcerations of the sulcular epithelium. This breakdown leads to bacterial invasion into connective

tissue and promoting the periodontal damage. Loss of periodontal attachment in rats occur predictably in a 7-day period (Xie, Kuijpers-Jagtman, and Maltha 2011; Graves et al 2008). Although this model doesn't include bacterial inoculation the progression of periodontal disease it is still caused by bacterial infiltration of the ulcerated epithelium. The role of bacteria in this model is demonstrated by topical application of antiseptics which reduces the alterations regarding the attachment level and bone resorption (Kenworthy and Baverel 1981; Luan et al 2008). Opposite to gram negative bacteria inoculation in this model the stimulation of the host response enhances the periodontal destruction similar to humans (Györfi et al 1994). The host response is demonstrated by the lower periodontal destruction if the immunological response is reduced either by inducing endotoxin tolerance or by application of prostaglandins inhibitors (Bezerra et al 2000; Samejima, Ebisu, and Okada 1990). The ligature-induced model is also found to be sensitive to some systemic effects, such as smoking or diabetes (César Neto et al 2004; Liu et al 2006). It is that a useful model to study the effect that different antiseptic administration or drugs have on the periodontal alterations or healing.

Besides clinical evaluation, when we talk about an inflammatory disease we must also consider the immuno-inflammatory molecules that are of high relevance when analyzing the progression or resolution of the periodontal inflammatory process. Of course, the aim is to extrapolate the results we obtain on the experimental model to humans. Having that in mind, a comparison of the cytokine profile (human vs rat) is recommended. A comparison such as that was successfully used for the histological evaluation of periapical lesion progression correlated with systemic diseases such as diabetes and osteoporosis. It provided important information that could change protocols regarding treatment of such lesions in daily practice (Berar et al 2016).

Signaling molecules, like cytokines are small proteins produced by different cells that can modify the behavior or properties of another cells at a locally or systemically level. There is a high number of biological activities regulated by cytokines like proliferation, development, differentiation, homeostasis, regeneration, repair, and inflammation. Cytokines are divided in: interleukins, interferon, growth factors, cytotoxic factors, activating or inhibitory factors, colony stimulating factors, and intercrines. In healthy tissues cytokines are secreted by resident cells in order to maintain the homeostasis. In diseased areas, the cytokines are also secreted by the infiltrated immunocompetent cells (Graves et al 2012; Kachlany et al 2001).

There have been found similarities between the expression of IL1, TNF and IL8 in humans and rats as a response to periodontal inflammation (Jacob and Nath 2013).

Conclusion

In conclusion, the rat model is a very useful model for periodontal research. It is suitable for evaluating the progression of periodontal disease in different general condition, but it is also a good model to study the effect of new introduced drugs on periodontal tissues even at a molecular level.

Its housing costs and the ability to obtain result in a very short time make it the best choice in a lot of studies. Adding the fact that it can be used in large numbers make it ideal to obtain results with a minimum risk of bias. Also, if subjects are lost during the study, due to secondary reasons, they are easy to be replaced.

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References

Baron R, Saffar JL. A Quantitative Study of Bone Remodeling during Experimental Periodontal Disease in the Golden Hamster. J. Periodontal Res 1978;13(4):309–15.

Berar A, Kui A, Moraru CV, Matros L, Picos A, Lascu L, Campian R. A Quantitative Radiological and Histopathological Study of Periapical Inflammatory Lesions Associated with Experimentally Induced Diabetes and Osteoporosis. HVM Bioflux 2016;8(2):85–91.

Bezerra MM, de Lima V, Alencar VB, Vieira IB, Brito GA, Ribeiro RA, Rocha FA. Selective Cyclooxygenase-2 Inhibition Prevents Alveolar Bone Loss in Experimental Periodontitis in Rats. Periodontol 2000;71(6):1009–14.

Neto C, Batista J, de Souza AP, Barbieri D, Moreno H, Sallum EA, Nociti FH. 2004. Matrix Metalloproteinase-2 May Be Involved with Increased Bone Loss Associated with Experimental Periodontitis and Smoking: A Study in Rats. J. Periodontol 2004;75(7):995–1000.

Craig RG, Kamer AR, Kallur SP, Inoue M, Tarnow DP. Effects of Periodontal Cell Grafts and Enamel Matrix Proteins on the Implant-Connective Tissue Interface: A Pilot Study in the Minipig. J Oral Implantol 2016;32(5):228–36.

Cutress TW, Schroeder HE. Histopathology of Periodontitis ('broken-Mouth') in Sheep: A Further Consideration. Res Vet Sci 1982;33(1):64–69.

Egelberg J. Local effect of diet on plaque formation and development of gingivitis in dogs. i. effect of hard and soft diets. Odontol Revy 1965;16:31–41.

Eggert FM, Germain JP, Cohen B. The Gingival Epithelium of Rodent Molars with Limited Eruption. Acta Anat 1980;107(3):297–306.

Fernandes LA, Martins TM, de Almeida JM, Theodoro LH, Garcia VG. Radiographic Assessment of Photodynamic Therapy as an Adjunctive Treatment on Induced Periodontitis in Immunosuppressed Rats. J Appl Oral Sci 2010;18(3):237–43.

Ferreira MC, Dias-Pereira AC, Branco-de-Almeida LS, Martins CC, Paiva SM. 2017. Impact of Periodontal Disease on Quality of Life: A Systematic Review. J Periodontal Res 2017;52(4):651-665.

Garant PR, Cho MI. Histopathogenesis of Spontaneous Periodontal Disease in Conventional Rats. I. Histometric and Histologic Study. J Periodontal Res 1979;14 (4):297–309.

Garant PR, CHO MI. Histopathogenesis of Spontaneous Periodontal Disease in Conventional Rats. II. Ultrastructural Features of the Inflamed Subepithelial Connective Tissue. J Periodontal Res 1979;14 (4):310–22.

Garant PR, Paik KS, Cho MI. The Distribution of Plasma Cells in Naturally Occurring Periodontitis Lesions in Rats. A Light and Electron Microscopic Study. J Periodontol 1983;54 (4):227–35.

Gilmore ND, Glickman I. Some Age Changes in the Periodontium of the Albino Mouse. J Dent Res 1959; 38:1195–1206.

Graves DT, Fine D, Teng YT, Van Dyke TE, Hajishengallis G. The Use of Rodent Models to Investigate Host-Bacteria Interactions Related to Periodontal Diseases. J Clin Periodontol 2008;35(2):89–105.

Graves DT, Kang J, Andriankaja O, Wada K, Rossa C Jr. 2012. Animal Models to Study Host-Bacteria Interactions Involved in Periodontitis. Front Oral Biol 2012; 15:117–32.

Györfi A, Fazekas A, Suba Z, Ender F, Rosivall L. Neurogenic Component in Ligature-Induced Periodontitis in the Rat. J Clin Periodontol 1994;21(9):601–5.

Harper DS, Mann PH, Regnier S. Measurement of Dietary and Dentifrice Effects upon Calculus Accumulation Rates in the Domestic Ferret. J Dent Res 1990;69(2):447–50.

Ionel A, Lucaciu O, Tăbăran F, Berce C, Toader S, Hurubeanu L, Bondor C, Câmpian RS. 2017. Histopathological and Clinical Expression of Periodontal Disease Related to the Systemic Inflammatory Response. Histol and Histopathol 2017;32 (4):379–84.

Jacob SP, Nath S. Rat Gingival Model for Testing Drugs Influencing Inflammation. IeJSME 2013;7(2):8–16.

Johnson MW, Sullivan SM, Rohrer M, Collier M. Regeneration of Peri-Implant Infrabony Defects Using PerioGlas: A Pilot Study in Rabbits. J Oral Maxillof Implants 1997;12(6):835–39.

Kachlany SC, Planet PJ, DeSalle R, Fine DH, Figurski DH. "Genes for Tight Adherence of Actinobacillus Actinomycetemcomitans: From Plaque to Plague to Pond Scum." Trends Microbiol 2001;9(9):429–37.

Kenworthy R, Baverel M. Studies of a Periodontal Tissue Lesion in the Rat, Untreated or Treated with Chlorhexidine Digluconate. J Clin Periodontol 1981;8(4):349–58.

Klausen B. Microbiological and Immunological Aspects of Experimental Periodontal Disease in Rats: A Review Article. J Periodontol 1991;62(1):59–73.

Lallam-Laroye C, Escartin Q, Zlowodzki AS, Barritault D, Caruelle JP, Baroukh B, Saffar JL, Colombier ML. Periodontitis Destructions Are Restored by Synthetic Glycosaminoglycan Mimetic. J Biomed Mater Res A 2006;79(3):675–83.

Lavine WS, Page RC, Padgett GA. Host Response in Chronic Periodontal Disease. V. The Dental and Periodontal Status of Mink and Mice Affected by Chediak-Higashi Syndrome. J Periodontol 1976;47(11):621–35.

Lindhe J, Ericsson I. Effect of Ligature Placement and Dental Plaque on Periodontal Tissue Breakdown in the Dog. J Periodontol 1978;49(7):343–50.

Lindhe J, Hamp S, Löe H. Experimental Periodontitis in the Beagle Dog. J Periodontal Res. 1973;8(1):1–10.

Listgarten MA. Similarity of Epithelial Relationships in the Gingiva of Rat and Man. J Periodontol 1975;46(11):677–80.

Listgarten MA, Johnson D, Nowotny A, Tanner AC, Socransky SS. Histopathology of Periodontal Disease in Gnotobiotic Rats Monoinfected with Eikenella Corrodens. J Periodontal Res 1978;13(2):134–48.

Liu R, Bal HS, Desta T, Krothapalli N, Alyassi M, Luan Q, Graves DT. Diabetes Enhances Periodontal Bone Loss through Enhanced Resorption and Diminished Bone Formation. J Dent Res 2006;85(6):510–14.

Luan Q, Desta T, Chehab L, Sanders VJ, Plattner J, Graves DT. Inhibition of Experimental Periodontitis by a Topical Boron-Based Antimicrobial." J Dent Res 2008;87(2):148–52.

Madden TE, Caton JG. Animal Models for Periodontal Disease. Methods Enzymol 1994;235:106–19.

Mann PH, Harper DS, Regnier S. Reduction of Calculus Accumulation in Domestic Ferrets with Two Dentifrices Containing Pyrophosphate. J Dent Res 1990;69(2):451–53.

Meusel DR, Ramacciato JC, Motta RH, Brito Júnior RB, Flório FM. Impact of the Severity of Chronic Periodontal Disease on Quality of Life. J Oral Sci 2015;57(2):87–94.

Page RC, Schroeder HE. 1982. Periodontitis in Man and Other Animals. A Comparative Review. S Karger Ag, 1982. University of Michigan. ISBN: 380552479X, 9783805524797.

Peruzzo DC, Benatti BB, Antunes IB, Andersen ML, Sallum EA, Casati MZ, et al. Chronic Stress May Modulate Periodontal Disease: A Study in Rats. J Periodontol 2008;79 (4):697–704.

Petruţiu SA, Stratul SI, Soanca A, Roman A, Baciut M, Kasaj A, Bocsan IS. The Impact of Some Behavioral Aspects on Periodontal Disease in a Group of Romanian Students - an Epidemiological Survey. Rev Epidemiol Sante Publique 2014;62(6):367–75.

Samejima Y. Ebisu S, Okada H. Effect of Infection with Eikenella Corrodens on the Progression of Ligature-Induced Periodontitis in Rats. J Periodontal Res 1990;25(5):308–15.

Schou S, Holmstrup P, Kornman KS. Non-Human Primates Used in Studies of Periodontal Disease Pathogenesis: A Review of the Literature. J Periodontol 1993;64 (6):497–508.

Selvig KA. Discussion: Animal Models in Reconstructive Therapy. J Periodontol 1994;65(12):1169–72.

Soames JV, Davies RM. Lymphocyte-Macrophage and Lymphocyte-Lymphocyte Associations in Early Gingivitis in Beagle Dogs. JPeriodontal Res 1980;15(3):341–44.

Sorensen WP, Löe H, Ramfjord SP. Periodontal Disease in the Beagle Dog. A Cross Sectional Clinical Study. J Periodontal Res 1980;15(4):380–89.

de Souza DM, Ricardo LH, Prado Mde A, Prado Fde A, da Rocha RF. The Effect of Alcohol Consumption on Periodontal Bone Support in Experimental Periodontitis in Rats. J Appl Oral Scie 2006;14(6):443–47.

Struillou X, Boutigny H, Soueidan A, Layrolle P. Experimental Animal Models in Periodontology: A Review. Open Dent J 2010;4:37–47.

Takahashi D, Odajima T, Morita M, Kawanami M, Kato H. Formation and Resolution of Ankylosis under Application of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) to Class III Furcation Defects in Cats. J Periodontal Res 2005;40(4):299–305.

Weinberg MA, Bral M. Laboratory Animal Models in Periodontology. J Clinl Periodontol 1999;26(6):335–40.

Weishan L, Dechao L, Rongrong Q. Effects of Porphyromonas gingivalis on interleukin-33 expression in rabbit vascular endothelium tissues. Hua Xi Kou Qiang Yi Xue Za Zhi 2016;1;34(4):354-357.

Xie R, Kuijpers-Jagtman AM, Maltha JC. Inflammatory Responses in Two Commonly Used Rat Models for Experimental Tooth Movement: Comparison with Ligature-Induced Periodontitis. Arch Oral Biol 2011;56(2):159–67.

Yamasaki A, Nikai H, Niitani K, Ijuhin N. Ultrastructure of the Junctional Epithelium of Germfree Rat Gingiva. J Periodontol 1979;50 (12):641–48.

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