The Dog as a Model for Peri-Implantitis. A Review

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ABSTRACT

Objective: To analyze the current available experimental canine models for peri-implantitis. Material and Methods: Electronic databases of the PubMed, EBSCOhost, and Cochrane Library were searched for dog studies on peri-implantitis induction methodology, until October 31, 2012. The eligibility of the studies for this review was based on the screening of two independent reviewers. Results: After screening, 50 publications were eligible for review. The most used animal model was the Beagle (n = 23). The bilateral mandible four premolar were the most extracted group of teeth (n = 20) and the majority of the studies had the placement of six implants in the jaw with only five (n = 5) of them reporting on interimplant distance. All publications reported peri-implantitis induction using ligature during a variable period of time and with a subsequent heterogeneous loss of peri-implant bone. The ligature placement and maintenance around the implant varied greatly between the publications. The constant use of ligatures, sometimes traumatically forced to the peri-implant sulcus, may influence the degree of bone loss during canine experimental peri-implantitis overlapping the contribution of implant surface to the onset and development of this pathology. Conclusions: A great heterogeneity exists among the studies reporting on the induction of peri-implantitis in canine. Experimental peri-implantitis model has suffered a change through the last years, from an exclusive ligature-induced to a ligature-induced and nonligature induced progression, thus approaching the natural occurrence of this pathology. The ideal canine peri-implantitis induction model would be a naturally occurring peri-implanititis induction without the action of any ligature.

Keywords: peri-implantitis; canine model; experimental model; ligature-induced; nonligature induced; review

INTRODUCTION

At the beginning of the 21st century more than 2 million implants were installed per year and this number is expected to rise in the approaching years [1]. It seems evident that the placement of oral implants will become a routinely carried out procedure in order to restore oral esthetic and function. With the increasing number of implants installed per year, one might assume that the number of associated complications will also increase.

The prevalence of peri-implantitis with implants in an average function of time between 9–11 years has been addressed in several publications [2–6]. At a subject level Fransson et al. (2005, 2008) on a cross-sectional study reported a peri-implantitis prevalence of 28% in implants which have been installed for 5–20 years [4, 5]. Roos-Jansaker et al., in a cross-sectional study including 216 patients followed for 9–14 years, concluded that peri-implantitis prevalence was at least 56% on a subject basis [6]. In a very recent prospective cohort study involving 172 patients, Pjetursson et al. concluded that 38.6% of the patients had one or more implants affected by peri-implantitis [7].

Lack of oral hygiene has been mentioned as a risk factor for peri-implant diseases with an odds ratio (OR) of about 14.3 [8]. Bacteria and biofilm formation plays an essential role in the etiology of peri-implantitis [9]. However, it is presently unknown to what extent bacterial and nonbacterial residues have to be removed from the implant surface to obtain a predictable, stable clinical result after treatment [10, 11]. Consequently, there appears to be no firm, evidence-based recommendation for the surgical treatment of peri-implantitis [10].

Therapeutic approaches require the development of animal and experimental models that mimic the human naturally occurring peri-implantitis with respect...
to onset and progress. Until now the dog has been almost exclusively used as an animal model for this purpose [12]. The purpose of this review is to analyze the available canine experimental models investigating peri-implantitis.

**MATERIAL AND METHODS**

**Search Strategy**

A literature search was carried out through an electronic driven search of publications listed in the Medline (Pubmed), EBSCO Library (EBSCOhost), and Cochrane Library (Cochrane Database of Systematic Reviews) up to October 31, 2012.

The key words and boolean operators used in this search were: (“Peri-implantitis” OR “peri-implantitis (MeSH)” OR “Periimplantitis” OR “Perimplantitis”) AND (“Animal” OR “Models, Animal (MeSH)”)). A total of 153 articles were initially obtained.

Titles and abstracts were used in order to find articles eligible for this review, using the following inclusion criteria: English language, experimental dog studies and studies with data concerning peri-implantitis induction methodology. Two reviewers (Isabel Poiares Baptista) and (João Carlos Ramos) assessed titles and abstract both independently and in duplicate. After this first screening, 73 articles were excluded. The eligibility of the studies for this review was based on the inclusion criteria and reviewers agreement based on title and abstract. All the articles in which the title, keywords, and abstract did not provide sufficient information for their inclusion were full text assessed at a second stage. Disagreement regarding inclusion was resolved by discussion in which the respect of the ARRIVE (Animal Research Reporting of In Vivo Experiments) guidelines by the authors was also taken into consideration [13].

Full text of the studies selected in the first stage was evaluated according to the following exclusion criteria: peri-implant osseous defects created surgically (due to the lack of a chronic infection) and inclusion of less than two animals. Ultimately, 50 articles were considered eligible for this review.

**RESULTS**

A total of 153 articles were collected during the initial electronic search. After the first and the second stage evaluation, a total of 103 articles were excluded. A total of 50 articles were selected for the final analysis.

**Animal Model**

The animal model analyzed in this review was the canine model. The experimental animals presented in the selected studies belong to different species: Beagle [14–36], Labrador [37–46], and Mongrel dogs [47–60]. The different dogs present different characteristics. The Beagle is routinely used in scientific experiments because of well-documented physiological responses [61]. It is a relatively small size breed with docile temperament [62]. Most (although not all) canines spontaneously develop periodontitis following accumulation of bacterial plaque biofilm and calculus [63]. The Beagle is highly affected by spontaneous development of periodontitis and the prevalence increases with age and is high at the age of two years [64]. However, periodontitis prevalence varied markedly among different breeds. Despite some studies reporting high periodontitis prevalence in breeds like the Beagle, this prevalence was smaller among other breeds such as the Labrador and Mongrels [65, 66].

The great majority of studies recruited relatively small numbers of animals. Only four studies included 10 or more dogs [14, 20, 21, 24]. Most of them included five [15, 17, 27, 31, 32, 34, 36, 38, 40–42, 47–51, 55] or six dogs [28, 33, 43–46, 53, 54, 57–59].

During the mandible preparation, heterogeneity in groups of extracted teeth was noticed. The bilateral removal of first, second, third, and fourth premolar were the most common extracted group of teeth [23, 25–27, 30, 34, 35, 48, 49, 51, 59]. Other studies also referred to the extraction of first [18, 19, 22, 29, 32, 37, 38, 40–42, 56, 60] and second molars [33]. Despite the majority of studies reporting only mandible extractions, some authors also extracted maxillary teeth [33, 43–52, 53–55, 57, 58]. These extractions from the upper jaws were intended to avoid any trauma related to the occlusion and not foreseen for maxillary implant placement. Some articles did not specify which teeth were extracted and only referred to the “premolar and molar region” [28], “mandible and maxilla premolars” [53], and “maxillary premolars” [54, 55, 57, 58]. In one article only one quadrant of teeth were extracted [24].

**Experimental Model**

**Implants**

Each dog underwent the placement of 2–10 implants on the mandible, but in the majority of the studies the dogs had six implants. The distance between implants in each quadrant was reported to be 10 mm [27, 33, 57], 8 mm [31], or 4 mm [17].

Several experimental studies included immediate postimplant oral hygiene maintenance between 2 weeks and 6 months. The oral hygiene frequency before and after implant placement also varied between daily and weekly. Some authors made no reference to the postimplant oral hygiene program [18–21, 25, 26, 29, 35–37, 39, 43, 44, 47, 48, 51, 53, 54, 56, 57, 59, 60, 67–69].
Peri-implantitis Induction

All the selected studies induced peri-implantitis by means of ligature placement in a submarginal position around the implant. Most of the studies indicated without further details a soft diet association in order to augment plaque accumulation and reduce immediate trauma influence.

The ligature materials used in the peri-implantitis induction were mainly cotton [14, 15, 20, 21, 23, 26–32, 34–38, 40–55, 57, 58, 60, 68, 69] and silk [16–19, 22, 24, 25]. One study reported polyfiber polyester sutures under wire ligatures [56] and another one reported gauze and wire [59]. Two studies made no reference to the nature of ligature material used [33, 39]. Remarkable discrepancies existed within ligature placements and maintenances. Sometimes ligatures were kept during the whole course of the experimental period, or were kept sutured to peri-implant mucosa and replaced at different intervals (between two weeks and monthly).

Finally, studies exist where new ligatures were inserted over the previous ones [17–19, 22, 53–55, 57, 58]. The peri-implantitis induction period with ligatures varied between 1 [40, 48, 49, 51] and 12 months [35]. Two studies [36, 67] were nonspecific regarding this topic. Also, the amount of peri-implant bone loss associated with this peri-implantitis induction had considerable amplitude, between 20% (during 6–8 weeks) [42] and 60% (during a 4-months period) [33].

DISCUSSION

The most common animal models for periodontitis research are dogs and nonhuman primates [70]. There is a greater incidence of naturally-occurring periodontal disease in canines than in monkeys or swine. Periodontitis lesions in dogs are more closely related to humans than other laboratory animals [62]. Beagles were historically recruited for dental research dealing with periodontal disease progression, guided bone regeneration, tissue wound healing and dental implants. If bacterial plaque is freely left to accumulate in Beagle dogs, signs of gingivitis will develop rapidly and eventually periodontal tissue breakdown appears [63]. In Beagles, induced gingivitis may progress to periodontitis simply by allowing additional plaque to accumulate [71] which seems to be less the case in larger dogs (Labrador, Foxhound, Mongrel) which were far less investigated. Our research results did not include studies with Foxhounds used for peri-implantitis induction, however, this breed is already used in implant research [72]. If the hygienic maintenance procedure is not perfectly implemented all these animals will accumulate plaque at different degrees. This predisposition to gingivitis/peri-implant mucositis and subsequent periodontitis makes the Beagle suitable for studies for biofilm deposition and occurrence of peri-implantitis [73, 74]. The initial soft tissue biofilm deposition around implants results in the development of an inflammatory response of the peri-implant mucosal tissues, e.g., peri-implant mucositis [75]. According to Lindhe et al. the clinical signs of tissue destruction and the size of soft tissue lesions are more pronounced in implants than in teeth [76]. After abandoning plaque control measures peri-implant mucositis is established and characterized by an infiltrated connective tissue found in the marginal portion of the soft tissue adjacent to the implant surface. This collagen poor and cell rich infiltrate is separated from the implant surface by a pocket epithelium which contains numerous PMN cells, macrophages, and lymphocytes [77]. The extension of the infiltrated connective tissue is found to reside within the dimensions of the barrier epithelium [27, 77].

The present review about peri-implantitis induction in the dog reveals that the teeth extracted to create edentulous sites varied among studies. The major extracted group was the four bilateral mandible premolars, but some studies also reported first and second molar extractions [16, 18, 19, 22, 28, 29, 31–33, 37, 38, 40–42, 56, 60]. Generally, implants were positioned between the first premolar and second molar. The position occupied by implants in the jaw (e.g., at the first, second, third, fourth premolar, or first or second molar area) may be related to the degree of inflammation and subsequent bone level changes. In a study on experimental periodontitis reported by Lindhe et al. [78], gingivitis was first observed in areas where plaque started to form, that is, the contact area between mandible fourth premolar and first molar. The first significant increase in pocket depth occurred in molar and premolar areas two months after ceasing the plaque control. Afterwards significant loss of fiber attachment was first noticed in molars and then in premolars [79]. In an experimental study by Zitzmann et al. [38] the peri-implant tissue breakdown was analyzed. These authors extracted all mandible premolars and first molar and placed implants with the same surface on a corresponding area. Peri-implantitis was induced over 2 months with the help of ligatures (“experimental periimplantitis”) which were then removed and peri-implantitis allowed to progress for another 12 months, without any plaque control. During this nonligature period, the progressive breakdown of peri-implant bone continued in 16 out of the 21 implants analyzed. As all implants had the same surface one possible explanation for this difference in peri-implantitis progression may be the different implant position held by each implant in the jaw.

Only five articles mentioned the importance of the interimplant distance on the final experimental results. This distance varied from 4 to 10 mm [17, 27, 31, 33, 57]. We speculate that this length may have an influence on the final peri-implant defect configuration since it could contribute to the overlapping and broadening of
adjacent defects. Grunder et al. [14] reported that defect configuration was “in most instances horizontal”, without referring to the interimplant distance. However, our analysis of the X-ray images published in the article allowed us to hypothesize that the dental implants were inserted too near to each other. This proximity between implants will prevent the individual development of peri-implant defects, subverting their original anatomy.

Almost half of the studies included in this review did not give a sufficient description of peri-implant created defect. Schwarz et al. compared the morphology of natural occurring peri-implantitis defects in humans and ligature-induced peri-implant defects in the beagle mandible [32], proposing a classification of those defects. According to this classification, both dog and human peri-implant defects had a CI I (intrabony peri-implant defect) and a CI II (suprabony horizontal peri-implant defect) component. The most frequent peri-implant defect in humans was the CI Ie (circular), with 55.3%, and in dogs was also CI Ie but with 86.6%. The second most common peri-implant defect in humans was CI Ib (interproximal peri-implant defect with buccal dehiscence) (15.8%). Curiously, this defect was not found in dogs. This study represents a very positive step forward in terms of morphological characterization of peri-implant defects but there is still work to be done in order to find an experimental model that simulates human peri-implantitis. The defect configuration, that is, depth and width, has a direct effect on its regenerative potential [80]. Polyzois et al. created artificially circumferential defects around implants and demonstrated that when the width of the gap increased the histological outcome was negatively affected [80]. Tonetti et al. [81] also showed, in a human periodontal intrabony defect, that narrower and deeper defects had a greater chance of clinical improvements. Cortellini et al. [82, 83] demonstrated that the greater number of walls inclosing the defect, the greater the success of the regenerative treatment.

In all included studies, peri-implantitis was artificially induced by the use of ligatures. There was a considerable heterogeneity in ligature material used. Some authors recommended forcing the ligatures in the peri-implant sulcus [31], disrupting the peri-implant soft-tissue seal. It can be considered that this traumatic action, which does not really mimic any etiological factor of the human peri-implantitis, could be responsible for an over growing inflammatory response. Several authors replaced the ligatures [14, 15, 27, 30–35, 38, 43–46]. According to Shibli et al. [53], the number of pathogens detected following the ligature tissue-breakdown increased. Furthermore, the severity of the peri-implant destruction is closely associated with the quality and quantity of the bacterial attack [20]. If ligature presence was only related to additional plaque accumulation, and not to a traumatic action, it would make no sense to remove the ligatures as the associated established plaque would also be removed and would disrupt the installed biofilm. However, when a new “pristine” ligature is placed in a submarginal already inflamed position, this will cause a traumatic action on the surrounding tissues. This ligature placement could produce a peri-implantitis of traumatic origin [57] and induce a foreign body reaction different from peri-implant diseases [58]. In experimental periodontitis, the trauma due to ligature placement has been implicated as a cause of periodontal breakdown [84–86].

Another experimental model discovered a more natural occurring peri-implantitis progression after being induced by ligatures. Shibli et al. [54] placed ligatures around 36 dental implants during 2 months removing them after this period and let the natural peri-implantitis progress for an extra 12 months. A total of 17 implants were lost due to “significant peri-implant bone loss”. Other studies also make reference to implant loss during experimental peri-implantitis [22, 38, 55]. Zitzmann et al. [38] described a two-step ligature-induced peri-implantitis model. Previous models had only an initial period of active breakdown of the peri-implant tissues with ligatures. However, this new model started with a similar induction period but was followed by a period of “spontaneous” progression. Following ligature removal, plaque accumulation was allowed to continue for another 12 months (“spontaneous” breakdown). Unlike the initial ligature peri-implantitis experimental models, this had a natural disease progression. This natural progression more closely resembles a human peri-implantitis. With small differences in design, this model was later used in other studies [34, 43, 44]. Berglundh et al. [34] induced peri-implantitis in moderately rough and polished implant surface over a 4-month period with the use of ligatures (the so called “active” experimental peri-implantitis). During this “active” period, bone loss occurred in both surfaces: moderately rough and polished. Then, ligatures were removed and plaque was allowed to accumulate on both surfaces for another 5 months. This was a “spontaneous” period bone loss. In this study, the bone loss that occurred during the ligature period (“active”) was similar between both surfaces while following ligature removal (“spontaneous”) it was higher on a moderately rough comparative to polished surface. However, it is known that bacteria adhesion is higher on a moderately rough surface than on a polished one. This was confirmed in this study by the fact that areas occupied by plaque were larger on the moderately rough than polished surface [34]. So, we may assume that if, during the ligature-induced period, bone loss was only related with bacteria adhesion, this loss would be higher on a moderately rough surface, which has not happened, probably because the traumatic action of the ligatures was comparable on both implant surfaces. This parameter, and not the implant surface characteristics, could have been responsible for bone loss and overlap the natural contribution of the loss.
A great heterogeneity exists among the studies reporting on the induction of peri-implantitis in canine experimental models. The notions of “naturally occurring peri-implantitis” and “ligature-induced peri-implantitis” should be clearly defined and experimentally compared.

The ideal canine peri-implantitis induction model would be a naturally occurring peri-implantitis induction without the action of any ligature. Some efforts should be made to thoroughly follow “naturally occurring peri-implantitis” in dogs, from mucositis to peri-implantitis.

CONCLUSION

A great heterogeneity exists among the studies reporting on the induction of peri-implantitis in canine experimental models. The notions of “naturally occurring peri-implantitis” and “ligature-induced peri-implantitis” should be clearly defined and experimentally compared.

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