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The systemic implications of canine periodontal disease: A review

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List of Abbreviations

AVDC – American Veterinary Dental College

BE – Bacterial endocarditis

BUN – Blood urea nitrogen

CBC – Complete blood count

CEJ – Cementoenamel junction

CKD – Chronic kidney disease

CRF – Chronic renal failure

CRP – C-reactive protein

GI – Gingivitis index

HM – Heart murmur

IRIS - International Renal Interest Society

MR – Mitral regurgitation

NO – Nitric oxide

PAL – periodontal attachment loss

PCR – Polymerase chain reaction

PD – Periodontal disease

PD1 – Stage 1 periodontal disease

PD2 – Stage 2 periodontal disease

PD3 – Stage 3 periodontal disease

PD4 – Stage 4 periodontal disease

PDB – Periodontal disease burden

PPD – Periodontal probing depth

PDS – Periodontal disease score

PFGE - Pulsed-Field Gel Electrophoresis

PI – Plaque index

PMN – Polymorphonuclear cell

SB – Serum biochemistry

TMPS – Total mouth periodontal score

UPC – Urine protein to urine creatinine ratio

US - Ultrasound

Introduction

Periodontal disease is one of the most common infections in dogs and humans (Harvey, 1998; Niemiec, 2008; Riggio, 2011; Fernandes et al., 2012; Hoffmann and Gaengler, 1996; Stella et al., 2018). In 1899, Eugene Talbot described PD in dogs as "interstitial gingivitis or so-called pyorrhoea alveolaris". His observations were based on post-mortem examinations. According to him, "25% of dogs between the ages of one and four were found to have interstitial gingivitis, and 75% of dogs between four and eight years old were found to have interstitial gingivitis with recession of the gums and "pyorrhoea alveolaris".

The term "periodontal disease" is generally applied to inflammatory lesions induced by the presence of dental plaque that affects the periodontium, that is, the tooth's attachment tissue (Debowes et al., 1996; Hennet, 1992; Penman & Harvey, 1992). One can then define periodontal disease as gingival infection, often followed by the destruction of periodontal tissues, caused by bacteria that build up dental plaque on the teeth surface (Niemiec, 2008; Pavlica et al., 2008).

Nowadays, there is a growing concern with dentistry in veterinary, as animal owners increasingly seek to preserve their pet's oral health. Oral care, associated with other factors such as a deeper knowledge of animal nutrition and more sophisticated diagnostic tools compared to the previous decades, contributes to prolonging all animals' average life expectancy (Crossley, 2005; Pavlica et al., 2008).

In contrast to dentists and oral hygienists in human medicine, who undergo extensive University courses to specialize in this area and dedicate a considerable amount of time learning about periodontology and proper oral prophylaxis, the veterinarians' experience is more limited. Many factors contribute to this situation, such as lack of professional training, lack of adequate instruments, and ignorance of the anatomy of different animals' teeth (Crossley, 2005).

Based on many studies in both human and animal medicine, veterinarians advise owners to take constant daily care of their pets' oral cavity. This recommendation rests on the fact that PD when left untreated, causes several local consequences. Additionally, there is a theory that, much like what happens in humans, periodontal disease can be the primary cause of several systemic conditions (Gioso, 2003; Gorrel, 2010).

Aims of the Study

The purpose of this literature review was to perform an unbiased study of the published books and articles on the topics of canine dentistry, periodontal disease, the theory of PD as a precursor to systemic diseases, and the origin and relevance of this theory.

Firstly, to carry out this study, it was necessary to understand the disease itself, its importance in a local context, how to diagnose it, and what can be done to treat and prevent periodontal disease. For that, books and articles that report this disorder in the context of veterinary medicine, emphasizing the dog, were used.

Secondly, we searched mainly articles and a few books, mainly in the field of human medicine and dentistry, for tracking down the origins of the theory that postulates a relationship between oral diseases and illnesses of other organ systems.

Finally and most importantly, a specific set of articles within veterinary medicine and their analogs in human medicine were examined for evidence of a correlation and a causation relation between periodontal disease and diseases of the cardiovascular system, renal system, and hepatic system, among other disorders. These studies were published between the years 1996 and 2019, and the most relevant information concerning them is listed in appendix 1.

After carefully examining all the resources available, the goal is to decide if the information provided by them is enough to posit that periodontal disease can affect other parts of the body and expose the possible mechanism through which this happens.

Materials and Methods

The information used in this thesis was obtained through medical books and published scientific articles. The only search engine used for the purpose of gathering relevant information on the topic was "Google Scholar".

The keywords used to collect articles were “Periodontal disease”, “dog”, “veterinary medicine”, “systemic disease”, “hepatic”, “renal”, “cardiovascular”, “disease”, “oral”, “tooth”, “teeth”, “oral sepsis”, “inflammation”, “focal infection”, among others, in different combinations.

Books and articles in English and Portuguese were mostly used. Additionally, books and articles in Spanish and German were consulted in a lesser extent.

Relevance and prevalence of periodontal disease

Periodontal disease is the most widespread malady in pet animal's medicine. In certain populations, between 44% and 100% of the dogs have been diagnosed with having it (Harvey, 1998; Niemiec, 2008; Riggio, 2011; Fernandes et al., 2012; Hoffmann and Gaengler, 1996; Stella et al., 2018). The disease incidence is higher in advanced aged patients than young animals, and it causes significant oral pain and suffering (Hoffmann and Gaengler, 1996; Harvey et al., 1994; Riggio, 2008; Stella et al.,2018). Several variables have been observed to contribute to animal susceptibility, development, and clinical manifestation of the disease (Pavlica, 2008; Albuquerque et al., 2012). Other than age, several other variants can influence a patient's susceptibility to PD, as well as the disease's course and severity. These components are the animal's immunological status, coexisting conditions, environmental factors, behavioral patterns, diet, the owner's compliance with oral cleaning techniques, etc. Certain breeds, especially toy and small dogs, are overrepresented in periodontal disease (Albuquerque et al., 2012; Dan et al., 2014; Harvey et al., 1994; Harvey et al., 1998; Pavlica et al., 2008).

Pathogenesis of periodontal disease

This progressive, multifactorial condition initiates when specific invasive oral pathogens colonize dental plaque biofilms on the tooth root surface, and it involves two phases, gingivitis and periodontitis. Gingivitis is the reversible, initial stage of the disease, an inflammatory insult to the gingiva caused by certain types of bacteria. This initial stage can be reversed with thorough dental prophylaxis and diligent home care, mainly through brushing the pet's teeth daily (Niemiec, 2012; Gorrel, 2010). Periodontitis, on the other hand, corresponds to an inflammatory response to plaque and is limited to periodontium (Gorrel, 2010). Periodontal means "around or near the tooth." (Harvey, 1998). Hence, as the name suggests, it encompasses the structures adjacent to the teeth: the gingiva, the periodontal ligament, the cementum, and the alveolar bone (Gorrel, 2013).

The primary cause of gingivitis and periodontitis is the accumulation of bacterial plaque on the surface of the teeth where there is no natural cleaning promoted through abrasion with food, friction with the tongue and lips, in addition to the salivary

flow itself (Emily and Penman, 1994; Gorrel, 2010; Quirynen et al., 2006). Oral calculus is merely a secondary etiological factor (Gorrel, 2010).

Plaque is a smooth and adherent biofilm consisting of oral bacteria and their sub-products and oral debris immersed in a matrix containing salivary glycoproteins and extracellular polysaccharides. Plaque formation happens relatively fast, taking four to six hours to occur, and aerobic, gram-positive bacteria lead it, usually of the genera *Actinomyces spp*. and *Streptococcus spp*. (Harvey and Emily, 1993) present in the oral microbiota, which has great adherence power mainly because they have membranes rich in glycocalyx, making it possible to adhere to smooth surfaces. This process begins with forming a pellicle, a thin, saliva-derived layer containing several proteins, enzymes, and other molecules that can act as attachment sites for bacteria. It initiates in the supragingival region, but it can extend beneath the free gingival margin and into the gingival groove, the region located between the gingiva and the teeth or alveolar bone. This process begins immediately after oral prophylaxis. When bacteria attach to this pellicle, it becomes what is known as plaque (Quirynen et al., 2006; Gorrel, 2010; Niemiec, 2012). In dogs with dental plaque deposited on the tooth surfaces, the resulting plaque derived substances enter into the gingival tissue by diffusion and induce a slight inflammatory response which is responsible for the formation of the gingival sulcus (Hennet, 1992).

Gingivitis is the reversible, first stage of the disease. It consists of an inflammatory insult to the gingiva caused by an increase in the total number of predominantly non-motile, gram-positive, aerobe bacteria, which bind directly to the pellicle. These early colonizers are generally minimally pathogenic. However, they promote the growth of the secondary and more periodontopathogenic colonizers, such as *Porphyromonas gingivalis* and *Bacteroides forsythus* (Van Dyke and Serhan, 2003).

One to two days after the beginning of the plaque formation process, these non-pathogenic bacteria organize themselves into colonies, and from then on, an increase in overall numbers of bacteria is observed, especially of motile gram-negative, anaerobic, and mobile filament rods (Niemiec, 2012; Quirynem et al., 2006; Wiggs and Lobprise, 1997). These microorganisms adhere to the biofilm that now covers the dental surfaces and migrate into the gingival sulcus. This initial stage can be reversed with thorough

dental prophylaxis and diligent home care, mainly through brushing the pet's teeth daily (Niemiec, 2012; Gorrel, 2010).

Although dental plaque has an essential and primary role in PD development, it is the persistent bacterial aggression that causes significant damage to the periodontium tissue (Pavlica et al., 2008). As the bacteria's virulence increases, so does the effect of bacterial by-products, which elicit inflammation, including chemo toxins, mitogens, antigens, and enzymes such as hyaluronidase, chondroitin sulfate, and proteolytic enzymes. These effects cause additional inflammation, eventual loss of the periodontal ligament, bone loss, and finally, tooth loss. (Wiggs and Lobprise, 1997). Generally, anaerobic organisms are the cause of pathological changes (Harvey and Emily, 1993). When they start using the mineral salts present in the animal's saliva, dental deposits form, which cannot be removed only through oral hygiene through brushing. In the later phases of PD, inflammation and the destruction of the structures constituting the periodontium may be seen (Nelson, Couto, 2013).

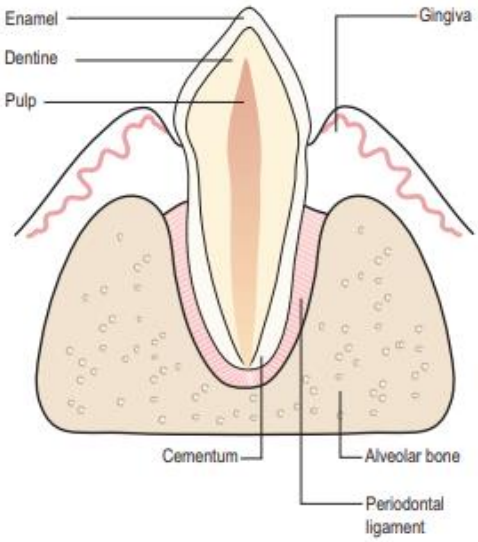

Figure 1: Basic anatomy of the tooth and periodontium (Gorrel, 2013).

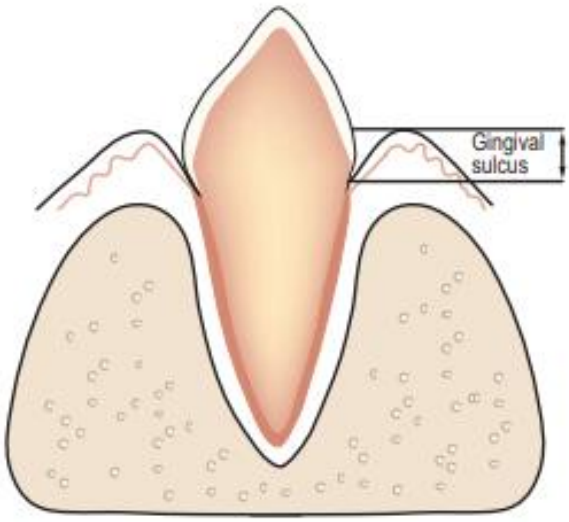

Figure 2: Demonstration of the gingival sulcus, which corresponds to the measure from the free gingival margin until the gingival sulcus base (Gorrel, 2013).

Clinical signs and staging

Veterinarians must be able to diagnose and stage all cases of periodontal disease. To enable that, it is of utmost importance that they are first able to recognize clinically healthy gingiva, without dental plaque or calculus, exhibiting lively pink color, regular texture, thin and knife-like edges, and a sulcus depth of 0 to 3 mm (Gorrel, 2010; Albuquerque et al., 2012, Carreira et al., 2015). The most common local clinical signs expressed by patients suffering from PD are halitosis (oral malodor), sialorrhea, tooth mobility, varying degrees of gingivitis, gingival retraction, root and furcation exposure, mild to moderate gingival hemorrhage, presence of periodontal pockets, nasal discharge, and oronasal fistulas. However, there are also slightly more unusual signs, such as dysphagia, anorexia, severe bleeding from the gingival sulcus, pathological fractures, contact ulcers, intranasal tooth migration, extensive bone loss, and osteomyelitis (Goldstein, 1990; Gioso, 2003; Soukup, 2010). Similarly, oral cancer may also be linked to PD (Niemiec, 2008).

A complete oral evaluation is required for identifying periodontal disease signs, combined with supplementary diagnostic techniques, such as oral X-ray images and periodontal probing (Gorrel, 2010; Albuquerque et al., 2012; Carreira et al., 2015).

As previously mentioned, periodontal disease comprehends two distinct phases, gingivitis and periodontitis. The first noticeable clinical sign of gingivitis is mucosal erythema, proceeded by edema, gingival bleeding, gingival retraction, gingival hyperplasia or swelling, and halitosis. These changes can often be reverted (Gioso, 2003; Niemiec, 2008; Gorrel, 2010; Albuquerque et al., 2012). Conversely, periodontitis is marked by irreversible changes, such as periodontal attachment loss (PAL) and the onset of periodontal pockets as a result of apical migration of the junctional epithelium, gingival recession, reabsorption of alveolar bone, grade of tooth mobility, and furcation involvement (Bellows, 2010; Gorrel, 2010; Niemiec, 2010; Carreira et al., 2015). Each tooth should always be examined independently, along with its supportive structures.

Periodontal probing depth

The periodontal pockets can be investigated by periodontal probing depth (PPD) measurement, in which a periodontal probe is used to examine the tooth sulcus circumferentially (Tutt, 2006). The depth from the free gingival margin to the base of the sulcus is measured in millimeters at several locations around the tooth's whole circumference (Gorrel, 2013).

Gingival recession

Gingival recession is also measured using a periodontal probe. It is the distance (in mm) from the cementoenamel junction (CEJ) to the free gingival margin. At sites with gingival recession, the PPD may be within normal values despite the loss of alveolar bone due to periodontitis.

Periodontal attachment loss

The periodontal attachment loss records the distance from the CEJ (or from a fixed point on the tooth) to the base or apical extension of the pathologic pocket. It is a more accurate assessment of tissue loss in periodontitis than periodontal probing depth alone. PAL is either directly measured with a periodontal probe or calculated (Gorrel, 2010; Gorrel, 2013).

Furcation involvement

Furcation involvement refers to when the bone between the roots of multi-rooted teeth is destroyed by periodontitis. The furcation sites of multi-rooted teeth should be examined with either a periodontal probe or a dental explorer by placing it under the teeth' crown (Gorrel, 2013; Niemiec, 2008). It presents in three stages, as demonstrated in table 1.

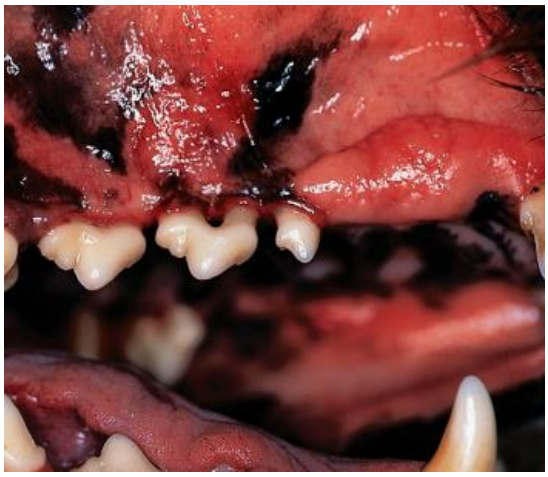

Figure 3: Furcation involvement in a multi-rooted tooth. From Gorrel, 2013.

Staging of furcation involvement	
Normal	There is no furcation involvement.
Stage 1	Early furcation involvement: the furcation can be felt with the probe/explorer, but horizontal tissue destruction is less than one-third of the furcation's horizontal width.
Stage 2	Partial furcation involvement: it is viable to explore the furcation, but the probe/explorer cannot be passed through it; horizontal tissue destruction is more than one-third of the horizontal width of the furcation.
Stage 3	Complete furcation involvement: the probe/explorer can be passed through the furcation from buccal to palatal/lingual.

Table 1: Staging of furcation involvement. Adapted from Gorrel, 2013.

Tooth mobility

The extent of tooth mobility must be assessed using a fitting instrument. The blunt end of the handle of a dental mirror or probe can be used to appraise tooth mobility by gently applying pressure to the tooth in a few areas to determine movement. It should not be assessed using fingers directly since the yield of the soft tissues of the fingers will mask the extent of tooth mobility (Gorrel, 2013; Tutt, 2008). The staging of mobility is demonstrated in table 2.

Staging of tooth mobility	
Normal	There is no mobility.
Grade 1	A horizontal movement of ≤1 mm is present.
Grade 2	A horizontal movement of >1 mm. Note that multi-rooted teeth are scored more severely, and horizontal mobility above 1 mm is generally considered a Grade 3 even in the absence of vertical movement.
Grade 3	Vertical as well as horizontal movement is possible.

Table 2: Staging of tooth mobility. Adapted from Gorrel, 2013.

Staging Periodontal Disease:

Based on its clinical signs and lesions' severity, PD can be ultimately classified into three or four stages, depending on the author. The most commonly used system according to the consulted literature for the purpose of this literature review proposes four subdivisions: PD 1 (gingivitis), PD 2 (early periodontitis), PD 3 (moderate periodontitis), and PD 4 (advanced periodontitis) (Harvey and Emily, 1993; Niemiec, 2008; Bellows, 2010), as represented in table 3.

Periodontal disease classification

Stage	Description
Normal (PD0)	Clinically normal oral cavity; no gingival inflammation or periodontitis clinically evident. No radiographic signs are visible.
Stage 1 (PD1)	Gingivitis only, without attachment loss. The alveolar margin's height and architecture are normal, as seen by normal periodontal probing and no bone loss on X-ray images.
Stage 2 (PD2)	Early periodontitis; less than 25% of attachment loss, or at most, there is a stage 1 furcation involvement in multi-rooted teeth. There are early radiographic signs of periodontitis, and probing with up to 4 mm deep pockets can be appreciated. The loss of periodontal attachment is less than 25% from the CEJ relative to the root's length.
Stage 3 (PD3)	Moderate periodontitis; 25-50% of attachment loss as measured either by probing of the clinical attachment level or radiographic determination of the distance of the alveolar margin from the CEJ relative to the length of the root or there is a stage 2 furcation involvement in multi-rooted teeth. Additionally, PPD between 4 and 6 mm can be observed.
Stage 4 (PD4)	Advanced periodontitis; more than 50% of attachment loss as measured either by probing the clinical attachment level or radiographic determination of the distance of the alveolar margin from the CEJ relative to the root's length or there is a stage 3 furcation involvement in multi-rooted teeth. In this stage, the PPD can be deeper than 6 mm.

Table 3: Periodontal disease classification. Adapted from Harvey and Emily, 1993; Niemiec, 2008; Bellows, 2010.

Treating periodontal disease

The owner's motivation and education in oral health are key in treating a patient with periodontal disease. These are key points so that he can understand the evolution of the disease and its seriousness. They must also be trained to perform daily care at home,

establishing daily teeth cleaning regime (Gorrel, 2010). Professional periodontal treatment is also recommended, including supragingival and subgingival cleaning and polishing, root scraping, and extraction of very affected teeth under general anesthesia since the elimination or reduction of subgingival bacteria load and toxic substances are also one of the objectives of treatment (Niemiec, 2010). Performing surgical periodontal treatment without general anesthesia is considered malpractice (Gioso, 2003). If there is a need for an exodontic approach, the periodontal ligament must first be dislodged with an appropriately sized dental lever or Molt periodontal lift, and only then gently pull the tooth, which must already be completely loose, with the help of an extraction forceps. After extraction, the socket should be debrided and, if necessary, the site can be sutured (Holmstrom et al., 2004).

Before beginning the periodontal ligaments' dislocation of multi-rooted teeth, it is necessary to perform the tooth's odontosection, respecting its anatomical features (Holmstrom et al., 2004). After performing this procedure, each root must have its periodontal ligaments dislocated, and, just as in the single-rooted teeth, they must be pulled with the help of an extraction forceps when they are loose. It is imperative to schedule regular veterinary visits to ensure that the recommendations are followed and continue the owner’s motivation (Gorrel, 2013). The administration of antibiotic drugs pre and postoperatively can offer benefits in treating patients with higher degrees of periodontal disease (Niemiec,2010). Additionally, it is important to use analgesic and anti-inflammatory medications from the trans-operative period (one can even start in the pre-operative period if the patient's oral health is very compromised) because once the pain is established, analgesic drugs are very less effective. The pain becomes more difficult to control, inferring greater suffering to the patient (Gorrel, 2004).

Systemic effects of the periodontal disease

Many authors believe that the changes caused by periodontal disease can be an important factor leading to the occurrence of systemic illness. This is attributed to both the migration of microorganisms present in the oral cavity to other organs and systems through the bloodstream and lymphatics (Semedo-Lemsaddek et al., 2016; Guntheroth, 1984; DeBowes et al., 1996), as well as to the presence of bacterial toxins in the oral cavity (DeBowes et al., 1996). If the animal is very weak, this phenomenon, called

anachoresis, can even cause sepsis and lead to death. This way, researchers believe the mouth can act as a source of infection (Penman, 1990; Goldstein, 1990).

Evolution of the theory of PD causing systemic impacts on the body

The theory that oral sickness can impact the human body's distant organ systems has its roots at least 3550 years ago. The first known reference to gingival disease dates from 1550 B.C. in the Egyptian papyrus Ebers. Hippocrates, in 460 B.C., attributed necrosis of the jaw to maladies of the teeth. The Greek physician also insisted on having cured arthritis by extracting a tooth. After him, Aristotle, recognizing the importance of oral infections, wrote about the teeth' diseases in minute detail (Pumpelly, 1929; Bingham III and Moni, 2013). The theory continued to interest scientists throughout the centuries, from Greek to Rome, and even throughout the middle ages (O'Reilly and Claffey, 2000). In the early 1800s, a famous American doctor and signatory to the Declaration of Independence, Benjamin Rush, followed Hippocrates' steps and reported curing a person suffering from rheumatism by extracting the patient's aching tooth (Pumpelly, 1929; O'Reilly and Claffey, 2000).

In 1880, W. D. Miller first introduced the term "oral focal sepsis". He discussed it in his book "*The Micro-Organisms of the Human Mouth: The Local and General Diseases Which Are Caused by Them*", in which he also suggested dental fillings or root canal therapy should be used to treat tooth decay - which he referred to as a bacterial disease (Miller, 1880). Two decades later, in 1900, William Hunter made history when he published his paper "Oral sepsis as a cause of disease", in which he called the mouth the "chief channel of access of all pyogenic infections". This was the first scientific article ever released on this topic (Hunter, 1900).

The physician Frank Billings replaced the term "oral sepsis" with "focal infection" in the following years. The focal infection theory gained strength when Billings and Lewellys F. Barker wrote several case reports attributing illnesses of all organ systems to several pathogens. Furthermore, these authors claimed in these reports to have healed their patients by performing tonsillectomies and dental extractions, which, according to them, removed the foci of infections (Billings, 1909, 1912, 1914; Barker, 1920).

However, the published literature was based solely on observation and a few anecdotal case studies.

Inoculation experiments and animal trials

One of Billing's research associates, Rosenow, utilized special methods for culturing samples from diverse foci of infection. This led to him obtaining several distinct pathogenic bacteria, which were then injected into dogs. By studying these animals, he discovered that the bacterial strains recovered from patients with chronic arthritis, rheumatism, or chronic infectious endocarditis, produced lesions similar to secondary manifestations observed in the same patient who donated the sample. In a post-graduate lecture held at the Royal Dental Hospital of London, in 1930, he proposed that oral microorganisms or their toxins have a tropism to areas composed mainly of mesenchymal tissues, especially joints, muscles, and neuronal sheaths. Rosenow posited that their "unique functions of repair, regeneration, and scavenging of waste products" made them particularly susceptible to bacteria and their toxins. Additionally, he suggested that some pathogenic agents exhibited a predilection for certain target tissues ("elective affinity") and that bacteria were capable of spontaneously turning into another species ("transmutation") (Rosenow, 1930). Eventually, Billings' and Rosenow's work were discredited (Barnfield, 1945).

Other scientists ran inoculation experiments in laboratory animals attempting to create focal infections that would propagate to the rest of the body. Moreover, these experiments provided opportunities to understand the mechanism by which this happens in a controlled environment. Krause and Willis studied the rate of dissemination of selected bacteria in guinea pigs. They found that if these microorganisms are injected into an already sensitized animal, they are confined to the site of injection and display little propensity to disseminate from the initial spot (Krause and Willis, 1924; Willis, 1925). In 1925, the researcher Weston A. Price also divulged the results of his experiments in animals. He induced systemic illness by implanting infected teeth under the skin of a group of rabbits. He also resorted to early laboratory examination methods to verify his subjects' clinical state and the hematologic changes caused by his experiments (Price, 1924, 1925). Years later, Cecil and Angevine (1938) wrote a literature review on 200

cases of rheumatoid arthritis that reported no benefit from tonsillectomy or dental extractions, but conversely showed exacerbation of arthritis in some cases. In the same paper, they demonstrated the results of their experiment with laboratory animals. The team injected bacteria suspensions in several rabbits' body structures to observe if this could empirically cause arthritis. The researchers were successful, developing the disorder in 11 out of 100 subjects. This study proved that the gums are a particularly favorable site for the absorption of bacteria. However, the team also concluded that, even though it was proven that chronic localized infection plays an important role as far as rheumatoid arthritis is concerned, the time had arrived for a total revaluation of the focal infection theory (Cecil and Angevine, 1938).

The focal infection theory weakened, but it was not forgotten; Scholars from different continents were still investigating it, directly or not. Several doctors linked periodontal disease cases and teeth extractions with the development of infective endocarditis, mostly through observation and retroactive studies (Rushton, 1930; Pogrel, 1975; Anolik et al., 1981; Bayliss et al. 1983). In 1967, in the Osaka University Dental School, Okada and others were still trying to understand the pathogenesis of focal infection. The group repeatedly administered antigen through the dental pulp canals of laboratory rabbits, causing both a local and systemic immune response. These rabbits also showed systemic morphological changes of allergic origin (Okada et al., 1967).

In 1987, Daniel Overholsen and others finally created a research model that allowed them to study the relationship between tooth extractions and the subsequent emergence of infectious endocarditis. They used three groups of rats (groups one and two presented with different degrees of induced periodontal disease, and the third without induced periodontitis) in which sterile aortic valve vegetations were produced. Groups one and three underwent teeth extractions. All animals were euthanized 72 hours later. The researchers used clinical examination, bacterial culture of the aortic vegetations, and histologic techniques to evaluate the periodontal status and endocarditis incidence. The model proved that it was possible to produce endocarditis in rats with catheter-induced aortic vegetations following extractions of the teeth affected by periodontal disease. The results showed this experimental model could be used to study the correlation between dental manipulation and the posterior development of endocarditis and the systematic

testing of antibiotic treatments currently recommended for humans (Overholsen et al. 1987).

Current status of the theory in the human medicine community

During the 20th century's final decades, the emergence of new techniques for bacterial identification and classification provided researchers with more refined tools to bolster the search for understanding oral microorganisms' role as etiologic agents to other conditions. In 1984 Guntheroth found that during mastication, microorganisms gain access to the bloodstream through the lymphatic system at an approximate accumulative rate 1,000 times higher than that from a single exodontic procedure. He postulated that "scrupulous oral and dental hygiene is undoubtedly superior in preventing IE than any chemoprophylaxis regimen" (Guntheroth, 1984).

By 1996, the discipline of "periodontal medicine" would officially originate as scientists, doctors, and dentists accepted that oral disease could significantly affect the body, triggering disease in these organ systems. However, the theory that periodontitis can have significant implications on a patient's general health status kept attracting opposition from a small group of researchers, even when most of the scientific community has already adopted it as an accepted truth (Arbes, 1999; Bingham III and Moni, 2013; Kumar, 2017; O'Reilly and Claffey, 2000; Pallasch, 2003; Van der Meer, 2002; Williams, 2008).

Oral sepsis and in the veterinary medicine

The systemic implications of periodontal diseases have been extensively reported in human literature, as the topic has been researched extensively for over a century. While this discussion started more recently in veterinary medicine than in the human medical field, there is mounting evidence in the veterinary medicine of systemic ramifications of periodontal disease (Davé & Van Dyke, 2008; DeBowes et al., 1996; Glickman et al., 2009; Glickman et al., 2011; Lemmons, 2009; Nabi, 2014; Niemiec, 2008; Pavlica et al., 2008; Penlington and Faixová, 2019; Shirai et al., 2015; Semedo – Lemsaddek et al., 2016; Tou et al., 2005; Whyte et al., 2014). The systemic implications of PD result from its pathogenesis. As previously mentioned, plaque is a microbial

biofilm with complex bacterial interactions, in which the metabolic products of bacteria create lesions directly in the periodontal tissues, activating the animal's immune system and inflammatory response. Bacteremia and the consequent inflammatory response are primarily responsible for the systemic implications of periodontal disease (Semedo – Lemsaddek et al., 2016). Systemic diseases possibly related to PD include renal, hepatic, cardiac, thromboembolic diseases, and atherosclerosis (Niemiec, 2008; Pavlica et al., 2008).

It has been stated that the inflammation of the periodontium, which stimulates the immune system's action against invading bacteria, also allows these same bacteria to spread in the host organism, promoting the development of systemic diseases. The high prevalence of PD in dogs and the possibility of developing associated systemic diseases demonstrate this theme's importance (Pavlica et al., 2008). Kouki et al. (2013) found a statistically significant relationship between C-reactive protein (an inflammatory marker of hepatic origin) levels and the severity of the periodontal disease, suggesting that the intensity of gingival inflammation in periodontitis is proportional to the intensity of the systemic inflammatory response triggered by the host (Kouki et al., 2013).

Effects of periodontal disease on the cardiovascular system

Even before the abundance of systematic studies was available on the topic, some authors had already stated that periodontal disease is a factor predisposing dogs to infectious endocarditis (Miller and Sisson, 1990). Davé and Van Dyke (2008) suggested that, if a periodontal-cardiovascular relationship really exists, it is most likely based on the incremental contribution of chronic periodontal inflammation to systemic inflammation rather than the direct colonization of atherosclerotic plaques with periodontal pathogens (Davé and Van Dyke, 2008). On the other hand, Niemiec believes infective endocarditis may result from bacteremia and adhesion of bacteria to the endocardium and may progress to thromboembolic diseases (Niemiec, 2008).

The severity of the PD is described as directly impacting the probability of endocarditis development (Abbott, 2016; Miller et al., 2004). Nakano and others reported that genomic DNA specific for Porphyromonas gingivalis was found in approximately 10% of heart valves and 20-30% of atheromatous plaque samples from humans. These results suggest that specific oral bacterial species are related to bacteremia and strengthen

the theory of a correlation between periodontal disease and cardiovascular diseases (Nakano et al., 2009). In the veterinary medicine, Shirai et al. (2015) found that *Porphyromonas gulae* fimA genotype C, which is shown to have a higher virulence for periodontal disease, was the dominant in the oral cavity of 48% of dogs with mitral regurgitation (Shirai et al., 2015).

In the following year, Semedo-Lemsaddek et al. established the association between periodontal disease and bacterial migration to the heart in the dog. In this study, the occurrence of bacteria spreading from the animals' oral cavity and establishment in the heart was proven through the molecular typing of the isolates from the two organs collected from various animals. Identical enterococcal species were isolated from the heart and oral mucosa of 7 out of 32 studied dogs (Semedo-Lemsaddek et al., 2016).

More recently, a study of 19 dogs suffering from PD3 and PD4 established a relationship between advanced pathological changes in these animals' left hearts' anterior wall. The pathologic changes were more severe in patients with PD4, suggesting an association between chronic inflammatory lesions within periodontal tissues and cardiac tissues (Polkowska et al., 2018).

A large observational (retrospective cohort) epidemiological study conducted by Glickman and others (2009) reviewed the electronic medical records of 59,296 pet dogs with periodontal disease and 59,296 dogs without periodontal disease of a large private veterinary practice in the United States. These patients' information was analyzed for up to five years to observe the incidence of cardiovascular diseases. The researcher detected significant associations between the severity of periodontal disease and the subsequent risk of cardiovascular conditions, such as endocarditis and cardiomyopathy. Nonetheless, an association between the stage of periodontitis and common infectious and non-infectious diseases of other organ systems was not seen (Glickman et al., 2009). However, these results were questioned by Peddle and Sleeper (2009), who found the findings inconsistent with data from their previously published paper (Paddle et al. 2009; Peddle and Sleeper, 2009). After Glickman's report, other researchers followed his lead and kept investigating the possible impact of PD on the cardiovascular system (Shirai et al., 2015).

Tou et al. (2005) published the first case study of mitral valve endocarditis occurring immediately after dental prophylaxis in a dog with prior myxomatous mitral

valve degeneration. Even though the research team could not prove a direct causal relationship between the dental procedure and infectious endocarditis, the lack of clinical illness before and the rapid onset of clinical signs shortly after the dental prophylaxis strongly suggest acquired IE secondary to the procedure (Tou et al., 2005).

In 2019, Penlington and Faixová found the prevalence of certain diseases was much higher in periodontal patients compared to dogs without periodontitis. These patients were over 17 times more prone to show mitral valve disease, they were 6 times more likely to present heart disease in general and the prevalence of heart murmurs was over 4 times higher in this population compared to dogs without PD. The authors also established a relationship between the severity of PD and the worsening of the animal's overall health (Penlington and Faixová, 2019).

Even with some controversial studies on the topic, some veterinary cardiologists recommend that when patients with cardiac injuries undergo procedures that predispose to infectious endocardiosis, such as dental prophylaxis, tooth extraction, and other surgical or diagnostic procedures are candidates to receive prophylactic antibiotic therapy (Jericó et al., 2015).

Effects of periodontal disease on the kidneys

Several studies have specifically investigated the relationship between PD and chronic renal failure in humans (Fisher and Taylor, 2009; Dasanayake, 2009). However, although periodontitis is listed as a risk factor for chronic kidney disease, certain patients exhibiting laboratory changes consistent with renal damage do not show any clinical symptoms (Schmalz et al., 2016; Sharma et al., 2016).

In veterinary medicine, there is evidence linking PD to morphological changes in renal glomeruli and interstitium of dogs (DeBowes et al. 1996; Pavlica et al., 2008; Nabi et al., 2014; Polkowska et al., 2018). These lesions are suggestive of immune complex-mediated damage and can result in chronic renal failure. Periodontal disease increases both local and systemic inflammation and associated markers (Nabi et al., 2014). This disease may contribute to renal damage through a chronic, persistent, or repetitive insult to the kidney (Pavlica et al., 2008). Glickman et al. (2011) described significant positive associations between the severity of periodontal disease and the

incidence of azotemia, that is, abnormally high levels of nitrogen-containing compounds in the blood, associated with chronic kidney disease over time in dogs. Their study found that periodontal disease treatment is associated with a 23% reduction in the risk of chronic kidney disease and azotemia (Glickman et al., 2011).

The activation of platelet production factors and nitric oxide production by several cells may also be involved in developing kidney disease secondary to PD (Pavlica et al., 2008). However, when present and because they have an affinity for the renal endothelium, bacteria can promote changes in the kidney's filtering capacity. According to Pavlica et al. (2008), the bacteremia and toxemia associated with PD can lead to pyelonephritis and interstitial nephritis. The bacteria also react with immunoglobulins, forming immune complexes that deposit in the glomeruli and stimulate pro-inflammatory mediators' production, causing glomerulonephritis (Pavlica et al., 2008; Glickman et al., 2011).

It is important to note that, even though the aforementioned studies demonstrated evidence of periodontal disease acting as a precursor to renal injury, there are published papers indicating the opposite (Barcellos, 2017; Pereira dos Santos, 2018; O'Neil et al., 2013). In a study by Barcellos (2017), no relationship was detected between periodontal disease and renal injury parameters. Furthermore, in her study, there was no significant difference between dogs' laboratory results with different stages of PD, even after undergoing dental prophylaxis (Barcellos, 2017). Similarly, Pereira dos Santos et al. (2019) found no significant association between PD and renal diseases in a group of 136 dogs. A study by O'Neil et al. also found that, even though PD is the most frequent co-morbidity in dogs with chronic kidney disease, there was no significant association between the two conditions (O'Neil et al., 2013).

Effects of periodontal disease on the liver

Periodontal disease is listed as one of several extrahepatic bacterial infections causing bacteremia, which is a leading factor for intrahepatic pathological changes such as cholestasis, inflammation of the liver parenchyma, and portal vein fibrosis, as well as laboratory changes such as increase liver enzymes (DeBowes, et al., 1996; Pavlica et al., 2008; Peddle et al., 2009, Penlington and Faixová, 2019). The body's inflammatory response in PD may contribute to the occurrence of lipidemia (Niemiec, 2008). Cross-sectional studies have described a correlation between the stage of periodontal disease

and the degree of inflammatory lesion detected in dogs' liver parenchyma (DeBowes et al., 1996; Pavlica et al., 2008). Furthermore, high liver enzymes were one of the most commonly detected alterations in dogs with periodontal disease in a study of 30 dogs by Penlington and Faixová (2019). However, to the present moment, there is still not enough evidence proving that PD can lead to hepatic disease in dogs. On the other hand, Pereira dos Santos et al. (2019) could not find a significant association between PD and hepatic disease.

The available literature regarding the burden of PD on the liver is mainly based on anecdotal evidence, with diverging results across different studies. Moreover, the mechanism through which PD could affect the liver has not been elucidated yet. Further experiments are necessary to confirm a correlation between periodontitis and hepatic diseases.

Discussion

Periodontal disease is a multifactorial disorder. It is the most commonly diagnosed disease in pet dogs. Therefore, it is of extreme importance that clinicians are aware of it and can recognize its local and systemic effects and the physiopathological processes through which PD can affect the rest of the body.

The local effects of periodontitis have been known for decades, but a more recent line of study investigates the possibility of oral bacteremia affecting other organ systems. If this theory is true, it must be proved and shared widely among veterinarians once it could significantly help treat animal patients, increasing their life expectancy, and improving their general health.

After a systematic review of the literature, there is compelling evidence suggesting a correlation between PD and cardiovascular diseases, which should be investigated with additional studies, preferably.

Concerning the other organ systems, there were diverging results across the investigated literature. I would suggest that further experiments are necessary before postulating about the correlation of canine periodontal disease and kidney and hepatic diseases due to overwhelming conflicting scientific evidence.

Nonetheless, periodontal disease has been proven to cause severe enough local effects on patients suffering from it, which makes it worth studying, diagnosing, and treating it.

Abstract

The systemic implications of oral diseases have been studied in humans throughout the ages by observing clinical cases and collecting anecdotal evidence. With the advances in the medical sciences in the last century, it was possible to conduct investigations that are more sophisticated; the modern observation of cases was assisted by physical evaluation and laboratory tests as well as the association of animal testing. These technological improvements in the field of human medicine extended to veterinary medicine.

Periodontal disease is the most common disease of pet animals. It is a progressive, multifactorial disease that is more severe in small breed animals and geriatric patients. Due to its high prevalence, it is of utmost importance that all the pathogenesis of PD as well as all its consequences are understood by all veterinarians. There has been a consensus for decades that periodontal disease, when left untreated, can lead to dysphagia, anorexia, severe bleeding from the gingival sulcus, pathological fractures, contact ulcers, intranasal tooth migration, extensive bone loss, and osteomyelitis. On the other hand, its systematic impacts, although accepted by part of the veterinary medical community, are still not well established. The goal of this literature review was to analyze the available studies on the topic and ponder about the possible correlation between periodontal disease and systemic illness in dogs to inform veterinarians in what concerns the real relevance of this widespread condition.

While most of the published scientific research showed that PD in dogs leads to cardiovascular disorders, there is less evidence suggesting the same for renal injury, and hepatic disease; not all sources in the literature could observe the same correlations. Furthermore, the exact pathophysiology of the events that led to these observations is still not understood.

Due to the scarcity of studies in this topic, together with the conflicting evidence presented by the available literature, it is impossible to establish a clear relationship between periodontitis and systemic diseases. The prevailing trend in the papers evaluated for this literature review showed that PD may be related to cardiac diseases, but due to the diverging results, further research is necessary.

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Scientific consent

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- *increase awareness of Hungarian veterinary science not only in Hungary, but also internationally;*
- *increase citation numbers of publications authored by Hungarian veterinarians, thus improve the impact factor of Hungarian veterinary journals;*
- *present the knowledge base of the University of Veterinary Medicine Budapest and its partners in a focussed way in order to improve the prestige of the Hungarian veterinary profession, and the competitiveness of the organizations in question;*
- *facilitate professional relations and collaboration;*
- *support open access.*

Appendices

Reference (Author, year)	Study design	Studied population	PD diagnosis	Parameters evaluated and technique used	Systemic correlations
DeBowes et al., 1996	Cross-sectional study	Sample size: **45 dogs** of different breeds with PD. Age: 5 months to 14 years. Post-mortem sample collection	PD staging post-mortem; PDS per tooth was the sum of plaque index, calculus index, tooth mobility, furcation exposure, true pocket depth, pseudo-pocket depth and gingival recession.	Organ health: Histopathology of lungs, heart, kidney, liver, spleen, tracheobronchial and submandibular lymph nodes, and tonsils. Multiple regression analysis; Statistical significance when P<0.05.	**No significant association:** PDS-mitral valve endocardiosis **Significant association:** PDS-myocardial degeneration (p = 0.027) PDS-kidney glomerular degeneration (p = 0.0001) PSD-kidney intestitium degeneration (p = 0.042) PDS-liver parenchyma degeneration (p = 0.035)
Pavlica et al., 2008	Cross-sectional study.	Sample size: **44 dogs**, toy- and miniature Poodles Age: 6 to 15 years. Post-mortem sample collection	Estimation of PDB by six measurements of probing depth (when >1mm) for each tooth and tooth circumference. Not assessed were degree of inflamed tissue.	Organ health: Histopathology of kidney, liver, common carotid artery, heart, coronary artery. Ordinal logistic regression analysis; statistical significance when P < 0.05 and P < 0.001.	**Significant association:** PDB-left AV valve (p = 0.05) PDB-hepatic alterations (p = 0.03)
Paddle et al., 2009	Retrospective case-control study.	Sample size: **156 dogs** of undefined breeds of which:	Medical history. Inclusion criteria regarding PD were set. Patients were	BE: Positive diagnosis through necropsy findings or positive blood culture results associated with	**No evidence of an association** between bacterial endocarditis in dogs and either dental or oral

		76 dogs diagnosed with BE, Control group: 80 healthy dogs. Age: Undefined cross-section.	examined by a board certified veterinary dentist.	clinical signs and positive echocardiography. Multiple logistic regression; statistical significance when P<0.05.	surgical procedures or oral infection.
Glickman et al., 2009	Retrospective cohort observational study.	Sample size: **59,296 dogs** with previously diagnosed PD (PD1, PD2, PD3) Control group: 59,296 age matched healthy dogs.	PD was diagnosed at several different Banfield Pet Hospital clinics by analyzing written and photographic records to categorize PD into 3 stages (PD1, PD2, PD3).	Cardiovascular events: specific diagnoses and suggestive clinical findings. General inflammatory outcome events: WBC count and increased % of monocytes. Cox regression analysis; statistical significance when P<0.05.	**Significant associations:** PD3-endocarditis (HR: 6.36; p < 0.05) PD3-HCM (HR: 3.96; p<0.05) PD3-MVI (HR: 2.74; p<0.05) PD3-DCM (HR: 2.44; p<0.05)
Rawlinson et al., 2011	Prospective cohort study.	Sample size: **38 dogs** with clinical signs of PD, but otherwise healthy. Age: >1 year, various breeds, females and males, body weight variations	Gingivitis and attachment loss using TMPS (11). Gingivitis score 0-3, attachment loss using periodontal probe.	Kidney health: SB, CBC, urinalysis + microbial culture, microalbuminuria, UPC, serum CRP pre and post-PD treatment. Statistical analysis: Rank correlation; statistical significance when P≤0.05.	**No significant associations** between the severity of gingivitis and any hematologic and urine values before treatment Significant associations: Attachment loss and reduced platelet number (r = 0.54; p < 0.001). Attachment loss and reduced creatinine concentration (r = -0.49). Within-dog difference in CRP concentrations before and after treatment (r=0.40)

Glickman et al., 2011	Retrospective cohort observational study.	Sample size: **164,706 dogs** with diagnosed PD, where roughly 1/3 each with stage 1, 2 or 3/4. 164,706 dogs age matched healthy controls.	PD diagnosed at the time at Banfield Pet Hospital clinics. Medical history and pictures to grade PD into 3 stages (PD1, PD2, PD3/4).	Azotemic CKD: serum creatinine concentration >1.4 mg/dl, concurrent diagnosis code of "chronic renal failure", BUN from medical records, along with. IRIS staging. Cox regression analysis; significance when P≤0.5	**Significant association:** Increased severity of PD, increased BUN and creatinine (ptrend < 0.0001) PD3/4-IRIS2 (HR: 3.35) PD3/4-IRIS3 (HR: 2.39) PD3/4- IRIS4 (HR: 2.93)
Kouki et al., 2013	Prospective cohort study	Sample size: **71 healthy dogs**, undefined breeds, males and females. Age group: adults. Presented at clinic for PD treatment or other planned surgical procedure.	Estimated TMPS, gingivitis (TMPSG) and periodontal destruction (TMPS-P). Gingivitis score 0-3, attachment loss using periodontal probe.	HCT, WBC, PMN from whole blood. CRP concentration, albumin from serum. Statistical analysis: Linear regression; Statistical significance when P<0.05	**Significant association:** TMPSG-CRP (p = 0.026) TMPSG-WBC (p = 0.043) TMPSG-PMN (p = 0.016) **No significant association:** TMPSP-CRP (p = 0.866) TMPSP-WBC (p = 0.111) TMPSP-PMN (p = 0.268)
O'Neill et al., 2013	Longitudinal and case control study.	Sample size: **228** out of 107,214 **dogs**. Selection was based on CKD inclusion criteria. Various and mixed breeds. Control group: 228 randomly picked dogs.	PD considered a risk factor for CKD. No inclusion criteria for PD given.	CKD diagnosis by primary practitioner (no detailed information was provided). Statistical analysis: Multivariable cox regression; Statistically significant when P<0.05.	PD was the most frequently observed CKD comorbidity. **No significant association** between PD and CKD (p > 0.05).
Nemec et al., 2013	Prospective cohort study.	Sample size: **32 healthy dogs** divided into 3 groups: Group 1 (no PD, n = 8);	Grading of PD based on AVDC (2009). Group 1: gingivitis. Group 2 and 3: moderate to	Clinic examination, HbNO, NOx, NT were evaluated pre- and post-PD treatment. Statistical analysis: Mixed linear regression;	**No significant association** between the severity of the periodontal disease and systemic NO status. Overall increase in systemic NO response 2 weeks after

		Group 2 (≤25 % PD, n = 14); Group 3 (>25 % PD, n = 10).	advanced periodontitis.	Statistical significance when P < 0.05.	periodontal treatment in dogs with advanced PD, but the response is greatly individually-dependent.
Nabi et al., 2014	Cross-sectional study.	Sample size: **46 dogs** with CKD (above reference range creatinine, BUN, USG). Age: 7 to 10 years old. Control: **40 healthy dogs.**	Dental recordings using WHO criteria. Pocket formation measured on facial aspects, teeth mobility by digital pressure. Dental indexes: GI, PI, PDI.	CKD diagnosis: General health status, renal functions assessed by haemato-biochemical analysis and US. Statistical analysis: t-test; Statistically significant when P<0.05.	**Significant association:** Increased severity of PD – increased severity of CKD. CRF-severe PD (p=0.01 when compared to PDI, PI, GI).
Shirai et al., 2015	Cross-sectional study.	Sample size: **25 dogs** diagnosed with MR, 18 males, and 7 females. Age: 10.8 +- 0.3 year old. Control group: **32 dogs** older than 6 years without PD, MR, diabetes mellitus, or other relevant clinical histories.	The oral conditions of the studied population was assessed by dental calculus score, gingival score, and periodontal score. PCR detection of *Porphyromonas gulae* and its dominant genotype (A, B and C).	Diagnose of MR based on physical examination, thoracic X-ray, ECG and echocardiographic findings. Severity of MR Bacterial DNA was extracted from the swab sample and PCR test was performed for identification of *P. gulae* and fimA genotypes (A, B and C).	**Significant association:** The rate for genotype C dominant specimens was 48.0% in the MR group, which was significantly higher than that in the control group (18.8%) (P b0.05).
Semedo-Lemsaddek et al., 2016	Cross-sectional study.	Sample size: **32 dogs** of undefined breeds visually diagnosed with BE. Age: 7 to 17 years.	No information was provided concerning the diagnostic criteria for PD.	Swab samples from the gingival margin, mitral/tricuspid valves. Isolation of *Enterococcus spp*. from swabs.	**Significant association:** Identical enterococci species recovered from the mouth and heart of the same patient in 7 of 32 dogs.

		Post-mortem sample collection.		Different colonies were selected for PCR identification. Genomic relatedness was studied by SmaImacrorestriction analysis using PFGE.	
Polkowska et al., 2018	Cross-sectional study.	Sample size: **19 dogs** (10 males and 9 females) between 6 and 15. years old separated into two groups: PD3: 5 dogs PD4: 14 dogs Post-mortem sample collection	Periodontal health status: followed the Wiggs & Lobrise scoring system. PD staging: Clinical and radiological exam. Parameters evaluated: Connective tissue attachment, PPD.	Swab samples from the gingival margin, heart, and kidney. Samples inoculation in various types of solid media, identified by colony morphology, hemolytic pattern, and Gram staining. Further tests were performed according to each isolate specificities. Samples for histological investigation from left ventricle and kidney. Statistical analysis $\chi 2$ test. Statistical significance $p < 0.05$. STATISTICA 8.0 software was used.	**Significant association:** Number of bacteria isolated from the kidneys was significantly higher in patients with PD4 (65.91%) compared with PD3 (34.09%). $\chi 2 = 4.45$ $p < 0.01$ Microorganisms isolated from the dogs' cardiac tissues occurred much more frequentl in the group with PD4 (70.59%) than in the group with PD3 (29.41%). $\chi 2 = 5.76$ $p < 0.01$ Anatomopathological examination discovered lesions characteristic of endocarditis in the heart, and lesions characteristic of pyelonephritis in the kidneys.
Pereira dos Santos et al., 2019	Retrospective cohort observational study.	Sample size: **136 dogs** that presented for consultation between the years 2011 and 2016 separated into two groups:	PD diagnosed using AVDC (2016)*	Diagnose of renal disease: ultrasonographic examination, elevated BUN and Creatinine; Diagnose of hepatic disease: US, elevated hepatic enzymes;	**Significant association:** PD-CD (p=0.026) **Non-significant association:** PD-renal disease (p=0.942) PD-hepatic disease (p=0.316)

		75 positive PD diagnosis. 61 dogs without PD in the control group.	**The address provided by the author could not be accessed on October 3rd, 2020*	Diagnose of cardiac disease: US and echocardiography. Analyzed with R statistical software, Microsoft Excel; statistical significance when P≤0.5.	
Penlington and Faixová, 2019	Cross-sectional study	Sample size: **30 dogs** with PD of various breeds. Age: 2 to 16 years old.	PD diagnosed by clinicians using outlined guidelines and dental charts for grading PD into 3 stages (PD1, PD2, PD3).	General health assessment to identify comorbidities by analyzing SB, electronic medical history analysis, pathology laboratory reports, dental records, further notes from previous surgeries and consultations. No information was provided regarding statistical analysis.	There were common associations in the periodontal patient samples. The haematopoietic and cardiovascular systems were the most prevalent systems affected. The most common comorbidities were: high liver enzymes, heart murmur, mitral valve disease, monocytosis and lameness. The comorbidity prevalence increased with more severe periodontal disease: 50% of patients with PD1 had comorbidities, 70% of patients with PD2 had comorbidities and 92% of patients with PD3 had comorbidities.

Appendix 1. Brief summary of the most relevant articles researched for this study.