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Is there a connection between oral health and systemic diseases in dogs and cats?

Finnes det en sammenheng mellom tannhelse og systemisk sykdom hos hund og katt?

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Preface

We are two veterinary students from the Norwegian University of Life Sciences with an interest for small animals. Outside of the university we have noticed an increased focus on oral health in small animal practice. Since we both are planning to work with small animals, such as dogs and cats, we found oral health to be an interesting subject for our thesis. In our thesis, we have looked for associations between oral health and systemic diseases in available published articles, and whether we could find similarities, or learn from advancements, in human medicine.

Oral health is an important subject in veterinary medicine. We do not get to see much clinical dental work at our practice and that was one of the main reasons we wanted to delve deeper into the subject with our/this thesis. With an increase of small dog breeds the last couple of years we have also seen a lot of animals with bad oral health being admitted to the clinic, and we believe that this calls for owners needing an increased quality of information and guidance on this subject. Periodontal disease is a cause for much pain and discomfort, and we believe that preventative and regular treatment, regardless of whether it can produce systemic effects or not, is important.

With this thesis we want to increase our knowledge on oral health and its associations to other systemic diseases. We hope that this can lead to a larger focus on maintaining good oral health, and act as motivation for preventative and regular treatment.

Summary

Robust evidence on the various relationships between oral health and systemic diseases have been established in human medicine. Some of these connections have been suggested in dogs and cats as well. We have reviewed studies that show connections between periodontal disease (PD) and clinical disease and/or morphological changes in heart, liver and kidneys. Documentation also show correlations between PD and systemic inflammatory responses, liver disease, kidney disease – such as chronic kidney disease (CKD), nephritis, pyelonephritis and glomerulonephritis – and diabetes mellitus in dogs. Few studies are available on cats, but studies that indicate a correlation between PD and increase in systemic inflammatory markers, CKD and diabetes mellitus have been reviewed. Treatment of PD can prevent or reduce the prevalence of systemic diseases in humans, and this also seems to be the case to some extent in dogs. Data indicate that several systemic diseases also have a negative effect on oral health. Further studies on all associations are warranted, as this will strengthen present hypotheses and be important in future veterinary medicine. Hopefully, with all these associations, and possible associations, we will emphasize the importance of PD.

Title: Is there a connection between oral health and systemic diseases in dogs and cats?

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Definitions and abbreviations

AGEs		Advanced glycation end products
ALT		Alanine aminotransferase
AVDC		American Veterinary Dental College
AST		Aspartate aminotransferase
ALP/AP		Alkaline phosphatase
Actin α-SMA		Actin α-smooth muscle actin
BE		Bacterial endocarditis
BUN		Blood Urea Nitrogen
CD		Cardiac disease
CVD		Cardiovascular disease
CKD		Chronic kidney disease
COPD		Chronic obstructive pulmonary disease
CD14		Cluster of differentiation 14
CBC		Complete blood count
CPSS		Congenital portosystemic shunts
CRP		C-reactive protein
DM		Diabetes mellitus
DCM		Dilated cardiomyopathy

DKA		Diabetic ketoacidosis
GGT		Gamma-Glutamyl transferase
GI		Gingivitis index
GCF		Gingival crevicular fluid
HR		Hazard Ratio
HCT		Haematocrit
Hb		Haemoglobin
HCM		Hypertrophic cardiomyopathy
IgG		Immunoglobulin G
IBD		Inflammatory bowel disease
IDDM		Insulin-dependent diabetes mellitus
IL-1		Interleukin-1
IL-6		Interleukin-6
LPS		Lipopolysaccharide
MVI		Mitral valve insufficiency
NO		Nitric oxide
HbNO		Nitrosyl haemoglobin
NAFLD		Non-alcoholic fatty liver disease
NIDDM		Non-insulin-dependent diabetes mellitus
OR		Odds Ratio

PDI		Periodontal destruction index
PD		Periodontal disease
PDB		Periodontal disease burden
PDS		Periodontal disease score
PAF		Platelet activating factor
PI		Plaque index
PCR		Polymerase chain reaction
PGE2		Prostaglandin E_2
PFGE		Pulsed-Field Gel Electrophoresis
RNS		Reactive nitrogen species
ROM		Reactive oxygen metabolites
ROS		Reactive oxygen species
SB		Serum biochemistry
TMPS		Total mouth periodontal score
TNF-α		Tumour necrosis factor α
UPC		Urine protein-to-urine creatinine ratio
USG		Urine specific gravity
WBC		White blood cell
NT		3-nitrotyrosine

Introduction

This is a literature review to investigate if an association between oral health and systemic diseases in dogs and cats exists. Such associations have been verified in numerous human studies, but few studies document this association in dogs, and even fewer in cats. Therefore, many questions remain unanswered regarding periodontal disease (PD) and systemic consequences in pets. Currently no clear understanding of cause and effect relationship regarding PD and systemic diseases have been established, and most of the hypotheses are based on results from human studies. The published research provide mounting evidence that PD has adverse consequences on systemic health (1). Do we have enough reasons to believe we can extrapolate human studies and their results to our pets? Is there a connection between oral health and systemic diseases in dogs and cats?

PD is one of the most prevalent infectious disorders in people aged 13 and beyond. The occurrence of PD in humans in both developed and developing countries is substantial, affecting approximately 20-50 % of the global population. As such a large percentage of the global population is affected it can be considered a public health concern (2). Moderate periodontitis affects 40-60 % of adults, whilst severe periodontitis, and possible loss of teeth, affects 10-15 % of adults in the larger part of human populations researched. PD is as mentioned a strikingly prevalent chronic disease, which will greatly impact affected people's lives, possibly in more ways than previously believed (3).

Overall, PD is normally categorized in two stages: gingivitis and periodontitis. Gingivitis is the earliest, reversible stage where the inflammation is restricted to the gingiva. Microorganisms in the dental plaque is responsible for the gingival inflammation. Gingivitis can be prevented and treated by dental prophylaxis and routine dental care at home (1, 4). The first clinical signs of PD, also known as gingivitis, is hyperaemia, oedema, ulceration or

spontaneous gingival bleeding (5). Periodontitis will be the result of untreated gingivitis which has developed into an infection of the non-gingival components of the periodontium. This is the irreversible disease stage (5). Periodontitis will lead to progressive destruction, which can result in attachment loss (4, 6-8). This stage can be observed as retraction of the gingiva and/or formation of periodontal pockets. The bone loss is irreversible, but it is possible to inhibit further progression and damage. It is more difficult to maintain and protect periodontally diseased teeth (4). Periodontal bone loss can be present both with and without active inflammation. Even though the PD process is histologically similar in dogs and humans, differences in canine and human dental plaque formation and composition have been described (1). Dental disease encompasses any disorder affecting the oral cavity, for example inflammation, calculus, gingivitis, periodontitis etc. (9)

In dogs and cats, PD is considered the number one most common health concern in veterinary medicine today (10). PD was among the top ten diagnosis in toy/small, medium and large breed dogs in 2013. 91 % of dogs and 85 % of cats over the age of three years were diagnosed with some form of dental disease (9). One report indicates that in 2006 until 2016 there has been a 23.3 % increase in prevalence of dental disease in dogs, a substantial increase which continues to rise steadily every year. Over the same time period the increase in dental disease in cats has been 23.2 %. In dogs, the risk of dental disease is higher in small breeds and increases with age in all breeds (9). With PD being as prevalent as it is, possible effects on systemic maladies and vice versa is exceptionally interesting and important.

Despite PD's prevalence, the disease is considered to be underdiagnosed. Lack of outward clinical signs and many pet's resistance to allow oral examination contributes to this. An increased focus on dental health in small animal medicine have emerged throughout the last

decades. More research, resources and advanced odontology courses are easily available. Improved dental equipment, safer multimodal anaesthesia and better trained veterinary nurses and veterinarians are additionally crucial factors in this development. Dental therapy in dogs and cats constitute a considerable amount of the daily patient base in a small animal clinic and is considered one of the largest contributions of their overall income. Small animal clinics will also often have more advanced dental instruments and dental x-ray and even separated rooms for dental work. Going back some years, this would not be present in the traditional smaller clinics. Today we even have specialized dental clinics for small animals, which makes referral of difficult cases possible. Another essential factor for dental diseases becoming a greater problem is the increased popularity of small and toy breed dogs, which have more dental disorders compared to larger breeds. The increased popularity in breeds bred to the extreme exterior, like brachycephalic and toy breeds, also results in more dogs with malocclusion and/or dental disease. Going back one or two decades, larger dog breeds like German Shepherds and Labrador retrievers were among the most popular breeds, thus generating lower demand for dental treatment. Working and hunting dogs are still prominent in more rural areas, but increased urbanizing have led to increased demand for trendy smaller sized breeds. With this gradual popularity shift from working dogs to pure companion dogs, people seem more willing to spend bigger costs on a pet that is considered a family member.

Although human studies have come far regarding evidence on PD's association to systemic effects, further investigation is required. Further studies are most definitely required on dogs and cats. We have explored the published studies that may confirm/ -discredit a such correlation in dogs and cats. Additionally, it is important to highlight that potentially fatal diseases may be prevented by minimal invasive oral prophylaxis and treatment. Better

awareness on this topic will certainly improve the general health and welfare in dogs and cats, and this was therefore considered the main aim of this study.

Materials and methods

In this review we investigated scientific articles in order to find the latest information on periodontal disease and its associations with systemic diseases. Inclusion and exclusion criteria were used in order to maintain focus and quality of the articles used, as well as to contain the number of articles to the more recent publications.

Among our inclusion criteria, we chose to focus on studies that were peer reviewed. The articles were required to be associated with periodontal disease or oral health and one or more of the following; systemic disease, systemic inflammation, hepatic disease, renal disease, respiratory disease, diabetes mellitus (DM), organ pathology, or markers reflecting inflammation/systemic disease process. Preferred studies would be those with the hypothesis being an association between periodontal disease and either of the above-mentioned diseases/inflammatory markers. The study samples were also required to be of a representable size, at least 20 dogs/cats.

As more research on systemic consequences from periodontal disease exist in human medicine, we chose mostly to use larger and more recent studies or meta-studies on this topic. We did however choose to use smaller studies in human medicine as well.

In our exclusion criteria we chose to not use any studies prior to 1994. We did not use studies that did not attempt to find a correlation between periodontal disease/oral health and systemic disease, and we did not use studies not relatable to modern practice.

Some articles were included despite not adhering to the above inclusion and exclusion

criteria. These were statistical and informational in nature and were considered necessary to elaborate various aspects in our thesis.

The time period we used to search for relevant articles started in the end of January 2020 and ended in May 2020. Articles were found through help from our thesis supervisor, but mostly through various search databases and from reference lists in articles already reviewed. Oria, the library search service, and PubMed were extensively used for an overview of potential articles and evaluated according to the inclusion and exclusion criteria. Google Scholar were used for finding articles from reference lists in articles already reviewed.

Examples of keywords used for searches:

Periodontal disease/oral health	and	Systemic disease in dogs Systemic disease in cats Systemic disease in human medicine Systemic disease in veterinary medicine Cardiovascular disease Renal disease Hepatic disease Diabetes Mellitus Respiratory disease	in	Veterinary medicine Dogs Cats Human medicine

Table 1. Brief description of the studies conducted on dogs and cats fulfilling the defined inclusion and exclusion criteria (see above, including Definitions and Abbrevations for acronyms).

Reference	Study design	Study population	Periodontal diagnosis	Parameters assessed	Associations
DeBowes et al. (1996)	Cross-sectional study.	45 dogs across breeds, aged 5 months to 14 years. Post-mortem sample collection	PD graded post-mortem; criteria per tooth: plaque index, calculus index, morbidity, furcation exposure, true pocket depth, pseudopocket 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.	PDS-myocardial degeneration (p=0.027) PDS-kidney-glomerulus (p<0.0001) PDS-kidney-interstitium (p=0.042) PDS-liver parenchyma (p=0.035)
Lederer et al. (2003)	Retrospective cohort study.	33 cats with DM and 33 age and gender matched non-diabetic cats	Medical records and owner's anamnesis. No information provided on PD diagnosis criteria.	DM: Weight, appetite, diet, activity level, chronic or medical records, corticosteroid treatment. Statistical analysis: t-test, Wilcoxon sum rank test, Fisher's exact test; statistically significant when P<0.05 and P<0.001.	DM-PD (p=0.05) DM-chronic or medical problems (p=0.001)
Pavlica et al. (2008)	Cross-sectional study.	44 dogs, toy- and miniature Poodles, aged 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	Organ health: Histopathology of kidney, liver, common carotid artery, heart, coronary artery. Ordinal logistic regression	Histopathological changes: PDB-left AV valve (p=0.005) PDB-liver (p=0.03) PDB-kidney (p=0.04)

			assessed were degree of inflamed tissue.	analysis; statistical significance when P<0.05 by Wald chi-square.	
Peddle et al. (2009)	Retrospective case-control study.	156 dogs, undefined cross-section of age and breeds, 76 diagnosed with BE, and 80 healthy controls	Medical history. Inclusion criteria regarding PD were set.	Bacterial endocarditis (BE): Positive diagnosis based on necropsy findings, or positive blood culture results + clinical signs and positive echocardiography. Multiple logistic regression; statistical significance when P<0.05.	Case dogs>Control dogs: New HM/changed intensity of existing HM (p<0.001). Undergone nonoral surgical procedure w/anaesthesia last 3 months (p=0.012)
Glickman et al. (2009)	Retrospective cohort observational study.	59,296 dogs with previously diagnosed PD, where roughly 1/3 each had either stage 1, 2 or 3. 59,296 age matched, healthy controls.	PD diagnosed at the time at Banfield Pet Hospital clinics based on written records and pictures to help grading 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.	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.	38 healthy dogs with clinical signs of PD, aged >1 year, various body weights, breeds and gender.	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	Significant correlations: Attachment loss and reduced platelet number (r=0.54; p<0.001). Attachment loss and reduced creatinine

				correlation; statistical significance when P≤0.05.	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.	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 (p_{trend}<0.0001) PD3/4-IRIS2 (HR: 3.35) PD3/4-IRIS3 (HR: 2.39) PD3/4- IRIS4 (HR: 2.93)
Cave et al. (2012)	Prospective study.	48 healthy inbred cats. 18 cats in control group (no dental treatment), 30 cats in treatment group. 90 days study period.	Scoring of PD from study by Ingham et al. (12). Index for calculus and gingivitis, periodontitis assessed from oral examination.	Collection of blood, urine and saliva before, 16, 45 and 90 days after dental treatment. SB, haematology, urinalysis, serum IgG, salivary IgA. Linear mixed model methodology; statistically significant when p<0.05.	Effect on treatment over time: PD-Globulins (p<0.0001) PD-IgG (p=0.0133) PD-AST (p=0.0497)
Nemec et al. (2012)	Prospective cohort study.	32 healthy dogs divided 3 groups; group 1 (no PD, n=8), group 2 (≤25 % PD, n=14), group 3 (>25 % PD, n=10).	Grading of PD based on AVDC (2009). Group 1 (gingivitis), group 2 and 3 (moderate-advanced periodontitis).	Clinic, HbNO, NOx, NT were evaluated pre and post-PD treatment. Statistical analysis: Mixed linear regression; statistical significance when P<0.05.	No correlation between severity of PD and systemic NO status.
Kouki et al.	Prospective	71 adult healthy dogs,	Gingivitis and	HCT, WBC, PMN from	Significant association:

(2013)	cohort study.	various breeds and gender. At clinic for PD-treatment or planned surgery.	attachment loss using TMPS (11). Gingivitis score 0-3, attachment loss using periodontal probe.	whole blood. CRP concentration, albumin from serum. Statistical analysis: Linear regression; statistical significance when P<0.05.	TMPSG-CRP (p=0.026) TMPSG-WBC (p=0.043) TMPSG-PMN (p=0.016)
O'Neill et al. (2013)	Longitudinal and case-control study.	228 from 107,214 dogs based on CKD inclusion criteria. Various and mixed breeds. 228 randomly picked control dogs.	PD considered a risk factor for CKD. No inclusion criteria for PD given.	CKD diagnosis by primary practitioner (no information). Statistical analysis: Multivariable cox regression; statistically significant when P<0.05.	PD most frequent CKD comorbid, but associations between PD and CKD were not significant (p>0.05).
Greene et al. (2014)	Retrospective cohort study.	1,230 cats with clinical diagnosed CKD, creatinine concentration >1.6 mg/dl, USG <1.035. 1,230 cats, age matched.	PD diagnosed at the time at Banfield Pet Hospital clinics. Criteria for diagnosis not described in study.	CKD diagnosis (creatinine concentration >1.6 mg/dl, USG>1.035). Multivariate logistic regression; statistical significance when P<0.05.	PD-CKD (OR: 1.77; p<0.05)
Nabi et al. (2014)	Cross-sectional study.	46 dogs with CKD (above reference range creatinine, BUN, USG). 40 healthy control dogs. All aged 7-10 years.	Dental recordings using WHO criteria. Pocket formation measured on facial aspects, teeth mobility by digital pressure. Dental indexes: GI, PI, PDI.	General health status, renal functions assessed by haemato-biochemical analysis and US. Statistical analysis: t-test; statistically significant when P<0.05.	Increased severity of PD significantly associated with increased renal failure. CRF-severe PD (p=0.01 when compared to PDI, PI, GI).
Semedo-Lemsaddek et al. (2016)	Cross-sectional study.	32 dogs of unknown breeds, 7 to 17 years. All visually diagnosed with	All dogs in study diagnosed with PD, no information on	Samples from gum, mitral/tricuspid valves. Isolation of *Enteroococcus*	Individual identical PFGE-patterns for enterococci recovered from mouth and

		BE. Post-mortem sample collection	diagnostic criteria.	*spp.* from swabs. Random selection of distinct colonies selected for PCR. Genomic relatedness assessed by SmaI-macrorestriction analysis using PFGE.	from heart in 7 of 32 dogs.
Trevejo et al. (2018)	Retrospective cohort study.	1,230 cats with clinical diagnosis of CKD, creatinine concentration >1.6 mg/dl, USG <1.035. 1,230 cats, age matched.	PD diagnosed at the time at Banfield Pet Hospital clinics, by gross clinical findings ± radiographic evidence. Excluded if not staged (PD1, PD2, PD3/4).	CKD diagnosis (creatinine concentration >1.6 mg/dl, USG<1.035). Cox regression analysis; significance when P<0.5.	PD1-CKD (HR: 1.33; p<0.05) PD2-CKD (HR: 1.34; p<0.05) PD3/4-CKD (HR: 1.50; p<0.05)
Pereira dos Santos et al. (2019)	Retrospective cohort observational study.	136 dogs of both genders consulted between 2011-2016. Divided in two groups; positive PD diagnosis, control group.	PD diagnosed using AVDC (2016).	Renal (US, elevated BUN and Creatinine), hepatic (US, elevated hepatic enzymes), CD (US, echocardiography). Analysed with R statistical software, Microsoft Excel; statistical significance when P≤0.5.	Significant: PD-CD (p=0.026) Non-significant: PD-renal disease (p=0.942) PD-hepatic disease (p=0.316)
Penlington et al. (2019)	Cross-sectional study	30 periodontal cases, dogs of various breeds, aged 2 to 16 years.	PD diagnosed by clinicians using outlined guidelines for grading PD into 3 stages (PD1, PD2, PD3).	General health: Haematology, SB, medical history, pathology reports, dental records, notes from surgery and consultation. Statistical analysis: No information.	Common associations were made between patients. Haemopoietic and cardiovascular system affections were most prevalent in patients.

Results and discussion

Periodontal disease and events leading to potential systemic health effects:

The pathophysiological basis

In human medicine, several of the systemic diseases linked to PD have many of the same risk factors. Therefore, it can be difficult to separate cause and consequence relationships. However, research does indicate significant associations between PD and certain other systemic diseases (13). According to Hegde and Awan (14), the information available does suggest a two-way relationship between PD and systemic health, meaning that PD can affect systemic health, and systemic diseases can cause PD (14). Periodontitis tends to be a recurrent or persistent, often lifelong problem, thereby exposing the host to its systemic effects over a long period (10). It is therefore important to maintain a good dental health, as the possibility of systemic ramifications makes this disease likely to be a risk factor for several other diseases in the body.

About 400 species of bacteria have been found in the sulcus of the gingiva in humans, whereof *Pophyromonas gingivalis (P. gingivalis*) and *Tanerella forsythia (T. forsythia)* are the most prevalent bacteria in periodontitis. *P. gingivalis* is released from the gingival sulcus and into the circulation (3). Bacteraemia with *P. gingivalis* has experimentally shown to enhance atherosclerosis in mice and pigs, and oral pathogens have been identified in distant sites which might suggest their involvement in systemic diseases (10). In a study by Semedo-Lemsaddek et al (2016; see Table 1 and below subsection on cardiac disease for more detail) (15) the authors managed to isolate pathogens that were identical from the gum and from the heart of 32 dogs, potentially giving an increased understanding of the pathogenesis behind BE

and its associations to PD. With their data the authors suggest they have established a strong association between PD and BE in dogs. This study sampled for *Enterococcus spp.* from the gum and mitral/tricuspid valves of dogs that were diagnosed with PD. Results from this study suggests a dissemination of enterococci between the animal's mouth and heart. This has been described earlier in human medicine, which may suggest some similar pathogenesis between humans and dogs regarding PD-driven BE.

Also, numerous human studies have shown that local antimicrobial treatment of PD can help resolve inflammation in distant organs (for more details see organ-specific sections below). Bacteria that accumulate and multiply within a biofilm in the oral cavity are, however, much more resilient (1000-1500 times) to antibiotics than a singular bacterium, and prophylaxis rather than treatment of PD is therefore preferred (16).

The cell wall of a gram-negative bacteria contains lipopolysaccharide (LPS; endotoxin). When the cell wall of the bacteria is compromised LPS will be released, and in the event of PD it will be released into the gingival crevicular fluid (GCF). The presence of LPS will stimulate monocytes, lymphocytes, macrophages, fibroblasts and epithelial cells to release cytokines (IL-1, IL-6, PGE2 and TNFα) and other inflammatory mediators. Because of its role in development, growth, proliferation and differentiation of immune cells, cytokines are essential in the inflammatory process. They also have a paracrine, autocrine and endocrine function, meaning that cytokines can alter adjacent cell behaviour, their progenitor cell, and they can affect distant tissues, respectively. In the GCF, LPS are able to penetrate the epithelium of the gingiva, thereby triggering release of inflammatory cytokines and B-cell response (antibody response with plasma cells).

Due to the large amount of mainly Gram-negative bacteria in periodontal lesions, the pocket lesions from PD will cause persistent systemic impact, with bacterial products and locally produced inflammatory mediators (17). LPS entering the circulation will bind itself to LPS-binding proteins, creating a complex. The complex can then bind to cells in the mononuclear phagocytic group displaying surface receptors (CD14), enhancing them to release cytokines. This LPS-complex is more biologically active, and a small amount of LPS-complex can elicit a larger release of cytokines. Activated macrophages will produce and release cytokines and other inflammatory mediators, such as proteins (tumour necrosis factor α [TNFα]) and metabolites (prostaglandin E_2 [PGE2], thromboxane A2 and platelet activating factor [PAF]), enzymes and reactive oxygen intermediates. Cytokines entering the circulation may cause or enhance several of the coagulation and vascular complications correlated to atherosclerosis and coronary heart disease. As long as the bacterial plaque impacts the host, the effect from these possibly toxic cytokines and mediators will endure (18).

A study by Han et al. (2016) in humans describes how the cell wall-component of bacteria in dental plaque can mobilize and activate polymorphonucleocytes, leading to an increased production of reactive oxygen species (ROS). Together with reactive nitrogen species (RNS), ROS are important liver toxicity mechanisms, causing oxidative stress and a subsequent depletion of membrane integrity, gene mutations and alterations in protein structures (3).

An article by Rawlinson et al. (2011; see Table 1 for study details) looked at the relationship between PD and systemic health indices in 38 dogs, and the goal of the study was to find out whether systemic health indices would be affected by the severity of the PD, and whether treatment of PD would affect said health indices. Dogs selected for the study were of various

breeds, body weights, gender, and were >1 year of age. Several factors were used as exclusion criteria for the study, including prior history of major systemic disease, as well as oral diseases not related to periodontal disease, systolic blood pressure >160 mmHg, medical or surgical treatment within the last 120 days prior to the study, and positive result for microbial culture of a urine sample. A clinical examination with serum biochemistry (SB), total blood counts and urine analysis (through ultrasound-guided cystocentesis) were conducted on all the dogs. C-reactive protein (CRP) were measured from serum, and microalbuminuria from the collected urine. Treatment of PD was done after first sampling, and the dogs were then assessed 4 weeks after the treatment for comparison. Dental health was evaluated, and PD scored using total mouth periodontal score (TMPS) system (11). One veterinary dental hygienist was tasked with scoring all the dogs in the study, unaware of the results from physical examination or previous medical history.

Bonferroni corrections were used in this study in order to adjust for family-wise error rate. Before PD treatment, a moderate correlation between platelet count and attachment loss were observed ($r=0.54$, $p<0.001$), but no other inflammatory values were significantly correlated with attachment loss or gingivitis. After treatment a decrease in the within-dog CRP value was reported, with a median decrease from 4.1 µg/mL to 2.98 µg/mL, again with detection of significant rank correlations with attachment loss ($r=0.40$; $p=0.01$). The article indicated strong associations between PD and systemic inflammation markers, but as the authors note, no causal relationship was indicated (5).

In a study by Kouki et al. (2013; see Table 1 for study details) 71 clinically healthy dogs were assessed by comparing their TMPS to systemic inflammatory values like CRP, albumin and haematocrit (HCT), as well as their white blood cell (WBC) and polymorphonucleated (PMN) cell counts. In order to be considered clinically healthy the dogs in the study were required to

be categorized according to criteria set by the American Society of Anaesthesiologists (ASA). Biochemical values like creatinine, alkaline phosphatase (ALP), alanine aminotransferase (ALT), glucose, total protein, sodium, potassium and BUN were also required to be within their respective physiological ranges. However, for 34 of the dogs serum biochemistry (SB), CBC and infectious serological testing were not conducted, and those dogs were admitted to the study based on routine physical examinations. Linear regression were used and statistically significant associations were observed between TMPS-G (gingival bleeding index) and CRP concentration ($p=0.026$), as well as WBC ($p=0.043$) and PMN ($p=0.016$) counts, indicating that an active inflammation in the periodontium (as the gingival bleeding would suggest) could be associated with increased systemic inflammatory markers in the body (19).

Two studies, DeBowes et al. (1996) and Pavlica et al. (2008) (see Table 1 and below for study details), compared the extent of PD to histological findings in various organs of dogs post-mortem. In both studies associations between the severity of PD and histopathological changes in multiple organs were made and significant associations between PD and histopathological changes in the heart, kidney and liver were observed (10, 20). It should be noted that in the study by Pavlica et al. both increasing periodontal disease burden (PDB) and attachment loss was associated with increased age and increased weight. Using logistic regression model on histopathologic changes in the heart, kidney and liver, only PDB (out of age, gender, weight, attachment loss and PDB) were shown to be a predictor of odds ratio (OR) with statistical significance. In the study by DeBowes et al., histopathological changes due to age were accounted for, according to the authors. Pavlica et al. proposed that the dogs participating likely had been exposed to the effects of PD over years, and that bacteraemia likely would have occurred over time from minor trauma sites of periodontal inflammation.

Inflammatory cytokines (IL-1, IL-6, PGE2 and TNF-α) would likely also have been spread to distant organs via the blood stream. Direct immune response to bacteria and endotoxemia from bacterial products could also give toxic and immune mediated diseases in these organs (10). The studies suggest that all these factors could have led to infection and inflammation in distant organs.

Glickman et al. (2009; see Table 1 and below for study details) published a retrospective study, observing significant associations between the severity of PD and general markers of inflammation ($p<0.05$). This included elevated WBC count and an increase in the percentage of monocytes in blood samples (21).

Compared to the large amount of research in human medicine and to a lesser extent dogs, much remains to be learned about the importance of PD on systemic diseases in cats. In a study by Cave et al. (2012; see Table 1 for study details) it was suggested that the severity of periodontitis in cats was associated with an increase in IgG and total globulin. The study looked at the systemic implications that PD might have in cats, and after dental prophylaxis the above-mentioned values had a significant reduction, implying an association between the severity of PD and systemic markers. As with dogs and humans, high grade periodontitis will lead to inflammation in the oral cavity of the cat, and it is believed that with a significant local inflammatory response, systemic responses as described above would likely be observed in cats as well (22).

Thus, many studies investigate the associations between PD and systemic diseases. Veterinary and human literature suggest that PD might be associated with transient, perhaps in some cases sustained, bacteraemia and subsequent systemic release of endotoxins and inflammatory mediators into the blood stream, which can then infect and/or produce direct toxic or immune-

mediated changes in distant organs. We have seen in this chapter how LPS and the host immune system can lead to a strong local and potential systemic impact.

Association between periodontal disease and cardiovascular disease

In humans, CVD is a collection of diseases causing high mortality rates and is a major cause of death in most countries of Europe in both women and men, amounting up to 3.9 million victims each year (23). PD have been associated to CVD in several human studies, and it has been specifically linked to ischaemia, atherosclerosis, peripheral arterial disease, bacterial endocarditis (BE), and acute myocardial infarction (13). After adjusting for other possible risk factors, such as diabetes, age and smoking (among others), patients with high grade chronic PD still have an increased risk of developing CVD (24).

Several veterinary studies have also studied the associations between PD and CVD, such as endocardiosis (10, 20), cardiomyopathy (21), and BE (15). Most veterinary studies investigating the associations between PD and CVD have been carried out on dogs, while published articles on cats are lacking. As in humans, the prevalence of PD has been shown to be high also for dogs and cats. With PD being a possible risk factor for the development of diseases like BE, a deadly disease affecting the heart valves of the endocardium (25), it is important to study the systemic effects of PD.

BE is considered a disease with a high mortality rate, but with a low reported prevalence (0.09-6.6 %) (25). A definite diagnosis of the disease is difficult to make, as it requires positive echocardial findings, fever, heart murmur, bacteraemia and positive blood culture (25). Leukocytosis and anaemia are commonly seen in patients with endocarditis as clinopathological abnormalities (25, 26), as seen in dogs diagnosed with BE in a study from

2009 (Peddle et al.; see Table 1 and below for study details). The disease almost exclusively affect medium to large breed dogs (dogs >15 kg), while small-breed dogs are rarely affected (25). Pathogenesis of BE is complex and existing theories are for the most part extrapolated from human studies. The bacteria will attach to heart valves with previous damage. Deposition of platelet-fibrin in these areas provides a nonbacterial thrombotic vegetation for bacterial colonization and subsequent adherence (27), but the bacteria needs to express surface components related to adherence in order for this to happen (15, 28). As mentioned earlier, bacteria (mainly Gram-negative) from PD may enter circulation through inflammatory processes produced by bacterial products and locally produced inflammatory mediators, and in theory colonize and adhere to previously damaged heart valves.

DeBowes et al. (1996; see Table 1 and above for study details) investigated the relationship between PD and histological lesions in various tissues of 45 mixed breed dogs post-mortem. In 11 of the dogs, gross changes consistent with endocardiosis on their mitral valve leaflets were detected. This association was not significant, but a statistically significant relationship ($p=0.027$) was found between the severity of PD and myocardial degeneration (20). Pavlica et al. (2008; see Table 1 and above for study details) also studied the relationship between PD and histological lesions. Post-mortem sampling of tissues from various organs of the 44 dogs were conducted and the organs were compared to the periodontal disease burden (PDB) of the animals. In 37 of the 44 dogs, histological changes in the atrioventricular (AV) valves were detected. These could be divided into different groupings. 17 of the dogs had milder changes and the 20 remaining dogs showed more significant changes, with a more severe myxomatous and fibrotic valvular thickening. The latter dogs also had mild inflammation and/or mild calcifications affecting the left AV valve. Changes in the first 17 dogs were more concentrated on the right AV valve. A correlation could be made between the PDB and the

pathology score on the left AV valves. Ordinal logistic regression model showed no statistically significant association between PDB and pathology on right AV-valve ($p=0.81$). It did, however, give indications that the degree of left AV valve was associated with increased PDB ($p=0.005$). Chronic degeneration of the AV valves was the most common pathology, and most of the dogs with CVD were shown to be older than 10 years of age and were more likely to have had PD for several years (10). It should be noted that toy and miniature poodles are among breeds commonly affected by degenerative AV-valve disease (29). With an estimated 70 % in dogs, chronic degenerative AV-valve disease is considered the most common cause of heart failure, but it is unlikely that this heart disease is a predisposing factor for the development of BE (25). The left AV-valve is more commonly affected than the right, but involvement of degenerative lesions in the right AV-valve can also be seen (29). This disease progresses slowly, over months to years, and will lead to a gradually increased leakage from the affected valves. Clinical signs from degenerative AV-valve disease usually will not show for years, and heart failure does not develop for some dogs. For dogs with clinical signs of degenerative valve disease prognosis varies, with congestive heart failure being the most common cardiac cause of death (29).

It should also be noted that in this study, evidence of atherosclerosis was observed in arteries of 6 dogs, but this was insufficient to achieve statistical significance ($p=0.29$ and 0.27, respectively). This is most likely due to few arteries being sampled but could also be explained by the relatively low prevalence of this condition in dogs compared to humans. A later study should take this into consideration (10). The articles from DeBowes et al. (1996) and Pavlica et al. (2008) both identified significant correlations between PD and morphological changes in the heart, but further studies on risk factor, incidence and clinical

relevance should be conducted, for which case-control and cohort studies are better suited study designs.

In a study by Pereira dos Santos et al. (2019; see Table 1for study details), the goal was to assess and evaluate associations between PD and other systemic diseases, including cardiac disease (CD). As criteria for a positive diagnosis of CD, the medical records had to include heart murmur and ultrasonography (i.e. results from echocardiography relating to valvular disease). Medical records from 136 dogs were used in the retrospective study, and a statistically significant association ($p=0.026$) was found between PD and CD. Out of the 136 dogs in the study, 40 animals showed signs of CD, and among those 38 had been diagnosed with PD (30). It should be mentioned that the PD group included a larger percentage of smaller dog breeds (40/69 PD dogs were <10 kg), as well as the dogs in the PD group on average being older (145 months versus 70 months in the control group). The risk of developing dental disease is, as mentioned, higher in small breeds and will increase with age in all breeds. With the dogs in the PD group being on average <10 kg and >12 years of age they are likely to both have a higher incidence of PD and endocardiosis, as the authors of this study also mention (30). In later studies this should be considered, with a more even distribution regarding age and weight between the case- and control groups.

The role of PD in the development of endocarditis were investigated in dogs by Peddle et al. (2009; see Table 1 for study details) (31). The purpose of the study was to look for and identify risk factors with possible associations to the development of BE. PD and previous dental or oral procedure during the 3 months prior BE diagnosis were investigated for possible associations with BE, but no evidence of any association was present. The process of undergoing a nonoral surgical procedure prior to BE diagnosis were significantly more likely

to have happened (p=0.012) for case dogs compared to control dogs. Case dogs in this study were linked to the detection of a new heart murmur or the detection of a change in the intensity of an existing heart murmur. Using logistic regression analysis on these variables, dogs from the case group were found to be significantly more likely than dogs from the control group to have developed a new heart murmur or had a change in the intensity of an existing heart murmur (p<0.001). in majority of dogs with BE (89-96 %), a murmur could be auscultated (25), and this was not unexpected. Results from complete blood counts (CBC) were available for both case- and control dogs. A significant decrease in median red blood cell (RBC) count (p=0.034), haemoglobin (Hb) concentration (p=0.028) and HCT, with p=0.045), as well as a significant increase in WBC count (p=0.001) and neutrophil counts (p=0.001) were observed in case dogs compared to control dogs (31). In the study by Peddle et al. no evidence suggest a significant relationship between PD and BE. Results relating to heart murmur and change in CBC values are factors already related to BE.

Glickman et al. (2009; see Table 1 and above for study details) proposed a stronger association between PD and CVD, with a strong emphasis on BE. This retrospective study used the electronic health records from Banfield Pet Hospital and produced a study group with approximately 120 000 dogs. Dogs with various severity (1-3) of PD and dogs without a history of PD were then compared with the risk of cardiovascular related events: endocarditis and cardiomyopathy, as well as markers of inflammation. In their study they found significant associations between various grades of PD and an increasing risk of cardiovascular related events. They did not find associations between the grade of PD and non-cardiovascular related events, such as hip dysplasia, cruciate ligament rupture, behavioural problems, DM, hypothyroidism, mast cell tumour, hemangiosarcoma, urinary incontinence or borreliosis.

Glickman concluded that their findings would suggest an association between the PD and endocarditis (21).

The results from the previous article including 120 000 dogs would suggest a strong connection between the periodontal disease score and the risk of developing endocarditis, but it has however been questioned by specialists in cardiology (32). In a letter to the editor, published in Journal of the American Veterinary Medical Association (AVMA), Peddle and Sleeper questioned the methods, data, and conclusion communicated in Glickman's article. Their concern was mainly about the lack of standardized method of diagnosing CD in the dogs used for the study. In the article from Peddle et al. (2009) it is noted how they used strict criteria for the diagnosis of BE, which included evidence from necropsy or positive blood culture results together with compatible clinical and echocardiographic findings. Because of the criteria, some dogs may have been excluded from the study, but the authors themselves were certain of the diagnosis of the dogs remaining (31). Glickman et al. used primary-care veterinarians for the diagnosis of various cardiovascular diseases in their study from 2009, and while they said that dogs whose diagnoses were uncertain were referred to specialists, this did not always happen. A lack of established diagnostic criteria prior to cardiovascular events therefore led to an emphasis on the judgement of the treating veterinarian for diagnosis. Their critique was also about the accuracy of the diagnoses of CVD in other dogs participating in the study, and Peddle and Sleeper questioned the accuracy of the data used as it did not seem to correlate with already established knowledge of CD in dogs (32).
While Glickman et al. (2009) agreed that their study had its limitations they also argued that significant associations with stage 3 PD in their study were evident, and several variables related to CVD as well. They also proposed that the inconsistencies in CD diagnoses may stem from these being made by primary-care practices in their study, while Peddle et al. based

theirs' on diagnoses made by specialists (32). The large study sample still presents a lot of information to consider for prospective studies in the future.

With BE caused by PD it should be expected that the same bacteria can be isolated from both periodontal lesions and from the vegetative lesions in the heart. In dogs the most commonly identified causative agents include gram-positive bacteria like coagulase positive *Staphylococcus* spp., *Streptococcus* spp., *Corynebacterium* spp., and *Erysipelothrix rhusiopathiae*, and gram-negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa* (27). A study from 2016 (Semedo-Lemsaddek et al.; see Table 1 and above for study details) managed to isolate and match bacteria from both the gum and the heart of 32 dogs post-mortem, by using pulsed-field gel electrophoresis (PFGE) patterns. The dogs in the study were visually diagnosed with BE, and while the authors noted that they all were diagnosed with PD they did not elaborate on what criteria they used for this. The authors were confident that they had avoided contamination, both environmental and post-mortem, during necropsy or through dissemination from intestinal microbiota. When subjected to analyses for genetic relatedness, they saw that 7 of the 32 sampled PFGE-patterns from the animals had an identical match between the enterococci from the mouth and the heart. The isolates also presented identical antimicrobial resistance and virus profiles, such as ebpABC and efaA, which are virulence factors previously related with enterococcal endocarditis. All the isolates also presented with the ability to produce biofilm. The bacteria found in plaque of PD patients is mostly gram-negative and are mentioned above. However the *Enterococcus spp.* is a group of gram-positive bacteria, indicating that uncommon infectious bacteria in the oral cavity should not be underestimated as a cause of disease, like BE (15). Even though the authors were certain contamination can happen regardless, and the results from this study should be evaluated along with other studies regarding PD and BE.

Many studies have been carried out on the associations between PD and CVD in human medicine, and recently an increase in articles on this subject in veterinary medicine as well. DeBowes et al. (20) and Pavlica et al. (10) have shown associations between PD and morphological changes in the heart. Pereira dos Santos et al. (30) found associations between PD and clinical values relating to CD, and a possible relationship between PD and BE has been investigated by Peddle et al. (31), Glickman et al. (21) and Semedo-Lemsaddek et al. (15). No relationship was found in the study by Peddle et al., and the results from Glickman et al. is questioned. Few studies on cat regarding this association is available to our knowledge. In the future, cats should also be investigated more in such studies, as it has been established that PD and CVD are a common problem in cats as well as dogs. Currently a lack of randomized control studies is evident, and such studies would be necessary in order to establish causation between PD and CVD.

Association between periodontal disease and liver disease

PD, which as previously stated is the number one most common chronic infectious disorder in dogs and humans, has been associated with hepatic disease (10). Rising evidence in human medicine indicates that PD may be involved in the progression of hepatic diseases, like non-alcoholic fatty liver disease (NAFLD), cirrhosis and hepatocellular carcinoma, and that it could also be altering liver transplantation (3). Inflammation of the liver parenchyma and portal fibrosis can be increased as a result of bacterial invasion of the liver (20). Periodontopathogens (periodontal pathogens) causing hepatic bacterial infiltration have also been associated with overall liver pathology and disease (33-35). Additional evidence shows a robust correlation between the PDB and increased inflammation in hepatic parenchyma (10).

The most prevalent liver diseases in cats are both acute and chronic cholangitis, an inflammation of the biliary tract, and hepatic lipidosis, a hepatopathy with massive lipid accumulation in liver parenchyma. We could not find reliable data with estimation of disease prevalence in cats. Diseases of the biliary tract is often concurrent with pancreatitis and/or inflammatory bowel disease and is then referred to as triaditis. Cats are seldom affected by extreme liver fibrosis or cirrhosis, defined as a slowly progressive, irreversible scarring/fibrosis of the liver parenchyma, both conditions are much more common in dogs. Chronic hepatitis is the most prevalent liver disease, a disease which rather often progresses quietly to cirrhosis and copper storage disease. Canine chronic hepatitis had a registered prevalence of 12 % in a post-mortem study in UK (36, 37). Less prevalent in dogs is acute hepatitis mostly due to toxicity or infections. Cats and dogs may suffer from congenital portosystemic shunts (CPSS) and primary and secondary hepatic neoplasia (37). The prevalence of these diseases is to our knowledge unidentified. To our awareness only a few studies demonstrating correlations between PD and liver disease in dogs is available at the moment, and none in cats, unfortunately.

In the study by DeBowes et al. (1996; see Table 1 and above for study details) (20), 45 mix breed dogs were evaluated for the presence and degree of PD and histological changes in distant organs. A statistically substantial correlation ($p=0.035$) was found between the extent of PD and severity of histopathological changes in the hepatic parenchyma. This study did not try to culture or document oral pathogenic bacteria from the hepatic parenchyma. The hepatic inflammation in these dogs was generally mild, multifocal and of minimal clinical implication (20).

The majority of periodontopathogenic bacteria are, as previously stated, gram-negative bacteria. Gram-negative bacteria will release endotoxins (LPS) that mediate the local excretion of inflammatory cytokines and trigger the immune response in the host (18). Intrahepatic cholestasis in dogs can be caused by extrahepatic bacterial infections such as PD, which are associated with mild, transient endotoxemia (10). In a study from 2008 (Pavlica et al.; see Table 1 and above for study details) (10) almost 50 % of the dogs, being mature miniature and toy poodles, necropsied had hepatic pathology of which moderate focal or diffuse inflammation, with or without multifocal fibrosis, were the most prevalent findings. Of all the organ pathologies reported in this study, it was only the severity of hepatic morphological changes that were markedly different between genders. The male study population of dogs had a moderate or focal or diffuse inflammation and/or mild focal or multifocal fibrosis (score 2), whilst the female dogs with liver pathology had only mild focal and diffuse inflammation of the liver parenchyma or the portal system (score 1). Thus, female dogs had milder forms of hepatic pathology. The authors hypothesized that the gender deviations might be a result of diverse oral impulses, like higher drift for fighting, playing and biting in male dogs, and immune suppression (hormone induced) as a result of progesterone secretion in female dogs. Frequent findings in this study was combined mild mononuclear infiltrates of the portal tracts, foci of hepatocytes within neutrophils and macrophages, and mild hepatocellular vacuolar change. These morphological changes suggest recent or ongoing stimuli of the immune system, and can be a result of diverse extrahepatic maladies, like for instance chronic infection located in the mouth. Considering that these dogs only had gross evidence of inflammation in the oral cavity, it’s reasonable to assume that the hepatic changes were not caused entirely by local hepatic aetiology, but that the periodontal inflammation was the initiator and place of origin. It was not possible to completely rule out low-grade inflammatory bowel disease (IBD) as another potential factor in this study. The association

between PDB and hepatic pathology can be a true indicator of the effect LPS (from gram-negative periodontopathogenic bacteria), bacteria and inflammatory cytokines, that have been absorbed from the oral cavity, have on inducing local hepatic inflammation and eventually hepatic damage. This observational and retrospective study identified compelling associations between chronic PD and the degree of pathological changes in several internal organs in small breed dogs (10).

NAFLD, which is defined by presence of fat in the liver – hepatic steatosis, is the most frequently occurring form of chronic liver disease in developed countries. NAFLD has a prevalence of 20-30 % in the general population and a prevalence as high as 57-74 % amongst obese people. Almost 25 % of the global population of adults has excessive lipid accumulation in the liver. Diagnostic approach for NAFLD is often biochemistry with increased serum levels of ALT and Gamma-Glutamyl transferase (GGT). Studies have shown correlation between periodontitis and increased levels of ALT in serum. In a cross-sectional study involving a large human sample size, the findings were that ALT and GGT levels were higher in people with periodontal pocket formation (≥4 mm) than in people with good oral health. Some specific liver function parameters, such as aspartate aminotransferase (AST) and ALT in NAFLD affected people, have been improved after periodontal treatment. Treatment include oral hygiene procedures, including scaling, root planning procedures and application of minocycline hydrochloride (tetracycline) (3). Studies indicate a relationship between prevalence of PD and higher liver specific enzymes such as AST, ALT- and GGT levels in serum. These enzyme-levels have decreased after dental therapy (3). Liver cirrhosis (LC) is an extensive, life-threatening disorder amongst humans globally. Hepatic damage due to a variety of different aetiologies may lead to damage of the hepatocytes, hepatic inflammation and fibrogenesis, which may result in LC. LC can additionally lead to the

occurrence of hepatocellular carcinoma (HCC). The eradication of normal liver parenchyma and architecture will prevent the normal hepatic functions, such as detoxification, synthesis and metabolic functions, which will ultimately lead to portal hypertension and hepatic failure. Since LC is classified as an end-stage disease, the affected patient will die unless receiving a liver transplantation. Studies have revealed that people with non-alcoholic LC had more severe periodontal attachment loss compared to healthy individuals. Cirrhosis patients have been shown to have worse periodontal health compared to healthy control groups. Studies have additionally shown that patients having LC for over three years had more extensive attachment loss, plaque and calculus formation. The LC effect on PD is suggested to be due to decreased blood supply to the mucogingival junction and elevated levels of ALP. The effect LC have on PD is not entirely researched, and more studies on this topic is required (3).

Hepatocellular carcinoma (HCC) is worldwide the sixth most frequent form of cancer, more prevalent in men than in women, and generally more prevalent in developing countries. The increasing trend seen is correlated to infections with hepatitis B and C viruses (HBC and HCV). In Europe, North America and Japan, HCV infection and alcohol abuse are the major risk factors. HCC is characterised as a multistage disease, its incidence is related to dietary, environmental and lifestyle factors. This cancer type normally develops in an already pathological organ, especially when chronic hepatopathy, cirrhosis or hereditary disorders affect the liver. In a Japanese study, they found association between the stage of HCC and periodontitis. HCC patients with chronic periodontitis had a more severe stage of HCC and higher total bilirubin levels, compared to the patients without PD. The best current treatment for suitable LC and HCC patients is liver transplantation. Prior to liver transplantation the patients must go through a dental examination, as periodontitis-induced immunosuppression might cause postoperative infections or sepsis. The mortality rate in patients undergoing liver

transplantation have shown to diminish with dental treatment pre- and postoperatively. Patients on the waiting list for transplantation are sadly often neglecting their own oral health. This circumstance is thought to be not only limited to the patients; doctors also seem to be failing to recognize the potential hepatic destruction PD might cause. Correlation between stage of HCC and periodontitis have been documented, more severe periodontitis is linked to more severe HCC. Han et al. (2016) demonstrated that oral prophylaxis and therapy decreased mortality in individuals undergoing liver transplantation (3).

The liver acts as the body's first defence mechanism against bacterial infections. People with cirrhosis are 4-5 times more likely to get bacterial infections than the general population. Bacteria have undoubtedly negative effects on the liver. *P. gingivalis* and *T. forsythia* are as stated previously the most prevalent bacteria in periodontitis. Both animal experiments and human trials have demonstrated existence of *P. gingivalis* in liver parenchyma. Oral infections with *P. gingivalis* in animals have shown aggravating of pathological progression of non-alcoholic steatohepatitis (NASH), from steatohepatitis to fibrotic steatohepatitis. These observations demonstrate that presence of *P. gingivalis* inflammation could be an independent driver for progression of NAFLD and could also assist to the development of other liver diseases (3).

Inflammatory mediators generated by periodontopathogens might result in recruitment of activated neutrophils, which causes hepatocyte and endothelial cell damage by releasing oxidants and proteases (3). The circulatory load of LPS can stimulate the hepatocytes to enhance their synthesis of acute phase proteins, both directly and indirectly. Kupffer cells are the primary cells in hepatic inflammation that responds to LPS and thereafter produce cytokines, chemokines and ROS. One animal experiment with overweight mice revealed that

LPS generates modifications in Kupffer cells' functionality and increases the liver parenchymal sensitivity to TNFα (3).

Different studies have documented the effects PD have on ROS in the circulation and oxidative stress. Human trials have also reported that treatment of PD enhance the levels of circulatory prooxidants/antioxidants in patients with chronic periodontitis (38). Documentation have also shown that periodontal treatment has been effective in decreasing Reactive oxygen metabolites (ROMs) in plasma. Based on numerous studies and their findings, it is believed that periodontitis-induced ROS might be participating in hepatic injuries (39-42).

Several studies have shown that bacteria from the stomach might enhance progression of liver disease. It is believed that some of these bacteria are derived from the oral cavity. The periodontopathogenic bacteria that enters the stomach will change the microbiotic flora and enhance to stomach-liver axis malfunction (3). The correlation between orally originating bacteria in the stomach and its effect on hepatic disease necessitate added research.

We have reviewed evidence of correlations between periodontitis and NAFLD, LC, HCC and liver transplantation in humans. In dogs we believe that bacterial hepatic inflammation may increase inflammation of hepatic parenchyma and portal fibrosis, and evidence exists that oral pathogens may be linked to general hepatic injury and disease. Mounting evidence from canine studies shows connection between the degree of PD and extent of hepatic inflammation. As we have far less knowledge about these possible associations in dogs and cats, more studies are warranted on these topics. In the meantime, we should be using evidence gained from human and canine studies to increase focus on dental health,

prophylactic therapy and as a part of the overall treatment for dogs and cats affected with some form of liver disease.

Association between periodontal disease and renal disease

It is believed that chronic kidney disease (CKD) is the most prevalent kidney disease in dogs and cats. The prevalence estimate varies extensively depending on the source population, the overall prevalence of CKD has been estimated to be 0.5-1.0 % in dogs, and 1.0-3.0 % in cats. This prevalence increases significantly with age, above all in older cats, with a reported prevalence of 80 % in the geriatric cat population (43, 44). A study has reported kidney disease in as much as 28 % of all cats over 12 years of age. CKD in dogs is documented to be more prevalent in small breeds and in dogs with PD (45). Feline and canine CKD will often result in severe secondary oral manifestations. Bad, uremic breath and oral ulcers is not uncommon findings in cats with CKD. Dogs with CKD may develop oral ulcers, halitosis, glossitis and stomatitis as a result of gastritis, vomiting or due to the effects uremic toxins have on oral mucosa (46).

CKD is also a highly prevalent human disease that has been linked to CVD, premature mortality, reduced welfare and considerable health-care expenses. Data from the National Health and Nutrition Survey report that 16.8 % of people ≥ 20 years in USA had CKD. This is an increase of 15.9 % from 1988-1994. If CKD is left untreated, it may progress to end-stage renal disease, which requires day-to-day dialysis or kidney transplantation to prevent a fatal outcome. During the last 25 years a constant increase in the prevalence of people with end-stage renal disease has been the reality (47, 48). Numerous studies have assessed the association between PD and CKD in humans. In dogs, associations have been found between PD and morphological changes in the renal glomeruli and interstitium (49).

It is known that CKD and CVD share several risk factors, so it is reasonable to presume that PD wields related effects within the renal vasculature (50). The suggested pathogenesis on how PD is involved in the development of kidney disease is by causing systemic inflammation. A more indirect way may be via cardiovascular effects. Periodontopathogenic bacteria have the capability of adhesion, invasion and proliferation in the coronary endothelium, which leads to atheroma formation and impairment of the vasculature's mechanisms for relaxation (50). Human studies have shown evidence, as mentioned earlier, implying that periodontitis results in a subclinical systemic inflammation which stimulate atherosclerosis and thereby localized arterial narrowing and reduced cardiac output. These effects will result in secondary hypoxemia of the kidneys, progressive injury to the kidneys and in the end CKD (48).

Studies have also demonstrated that oral infection that generate bacteraemia or sepsis might lead to interstitial nephritis and pyelonephritis in dogs (10). Kidney disease, especially glomerulonephritis, seems to be a potential sequel of chronic low-grade bacteraemia as caused by PD in dogs (20).

Deposition of renal *in situ* immune complexes proceed to glomerulonephritis. Bacteraemia caused by oral pathogens is composed of bacterial species which seem to facilitate good adhesion mechanisms to endothelium, and renal filtration of these bacteria will increase the risk of the renal capillary walls being damaged. Immune complexes in the kidneys (or elsewhere in the body) originate from bacteria, free LPS and other antigens reacting with certain immunoglobulins. Immune complex-accumulation in the glomeruli occurs under filtration of plasma. The immune complexes enhance the production of bioactive mediators such as cytokines, growth factor, eicosanoids and nitric oxide. Secreted leukotrienes will

bring neutrophils to the site and stimulate adhesion of leukocytes, and thereby generate inflammation. Leukotrienes will additionally promote increased production of mesangial cells (specialised cells in the kidney that make up the mesangium of the glomerulus) and the production of the intracellular microfilament actin α-SMA and extracellular matrix proteins. Other elements that are reasonable to believe affect the development of renal pathology include PAF and nitric oxide (NO). PAF can be produced by macrophages, neutrophils, platelets and glomerular endothelial and mesangial cells. Nitric oxide is also produced by neutrophils, platelets, macrophages and endothelial cells inside inflamed glomeruli (10). Data from studies document a relationship between PD and more acute kidney diseases such as interstitial nephritis, pyelonephritis and glomerulonephritis in dogs. Oral pathogenic bacteria have the ability to adhere to endothelium in the glomeruli and enhance more pro-inflammatory mediators promoting localized inflammation.

PD and kidney disease are associated with inflammatory markers such as CRP and chronic low-grade inflammation since PD might lead to an endothelial dysfunction which is essential in the pathogenesis of edentulous patients. Systemic inflammations destructive effects on renal function might occur during active periodontal inflammation, and in addition aggregate over the time of the individual's lifetime (50).

The study by DeBowes et al. (1996; see Table 1 and above for study details) (20) documented a correlation between PD and histopathological alternations in renal interstitium and glomeruli of dogs. The histopathological changes in glomeruli were mild and had variable thickening of the mesangium, changes consistent with immune-complex mediated destruction. In the renal cortex, medulla and pelvis, increased amounts of lymphocytes and plasma cells were present. These findings were histological changes with renal failure as a

possible consequence (20). Evidence from a study (Pavlica et al.; see Table 1 and above for study details), where 44 miniature and toy poodles, considered periodontitis and possibly CKD predisposed breeds, documenting periodontal assessment, standard necropsy and organ histology, revealed an association between PDB and the degree of organ pathology. These findings suggest a link between PDB, that is a result of plaque-bacteria associated PD, and the degree of pathology in distant organs, and that PD can elicit or enhance systemic pathology. Pathohistological changes in the kidneys were demonstrated. 50 % of the poodles in this study had renal pathology, with the most prevalent findings being tubular degeneration with cystic and/or inflammatory changes. The interstitial and glomerular changes seen in these dogs (mild, variable mesangial thickening, lymphocytic and plasmacytic interstitial infiltration) is indicative of immune complex- mediated damage. CKD might be the outcome. The strong association between suggested PDB and kidney pathology makes it likely that PD contributed to these renal changes, probably through chronic, persistent or repetitive and cumulative impact. In this study, the presence of PD in the poodle population correlated with earlier findings and indicated exposure of PD's systemic effects over several years (10). The study implies that periodontitis may participate in the progression of systemic pathological changes and documents a correlation between extent of PD and kidney pathology. It should be taken into consideration that with poodles already being susceptible to both PD and CKD, it is likely that a lot of poodles might have both diseases independently.

In periodontitis affected dogs, simultaneous renal disease is believed to be a consequence of the low-grade bacteraemia. However, the clinical manifestation of the bacteraemia is inadequately associated with the causative pathogen or the bacteraemia may not be provoking clinical signs in the animal. In a cross-sectional study from 2014 (Nabi et al.; see Table 1 for study details), evidence of a significant relationship between extent of PD and markers of

renal failure in dogs with renal failure were documented. Considerable recession of the gingiva was observed in the maxillary teeth of dogs with CKD and not in the group of healthy control dogs. In the group of CKD dogs, non-uniform mobility of the mandibular incisors was observed as well. All index scores regarding PD, showed higher values in dogs with renal disease compared to the healthy dogs. The findings were consistent with the positive association between PD and CKD in human studies (49). In a retrospective cohort study from 2014 (Greene et al.; see Table 1 for study details), where risk factors for CKD in cats were evaluated, they concluded with the following list; poor body condition score, polyuria, polydipsia, anorexia, lethargy, vomiting, halitosis, prior PD, cystitis, dehydration or previous anaesthesia (51). PD is considered a potential risk factor for CKD in cats as well, but more research is needed on this topic. To our knowledge, not much literature is available on different systemic correlation between cats and PD. A correlation between the extent of PD and CKD in dogs have been described and PD is suggested to be a risk factor for progression of CKD. A similar correlation is likely in cats.

Since electronic health records are being kept on dogs and cats in substantial parts of the world, improved and larger epidemiological studies on PD's systemic effects are now possible. In a retrospective longitudinal study by Glickman et al. (2011; see Table 1 for study details) (48) that followed two cohorts, one group of dogs with PD and one healthy group, compelling data on a positive correlation between the grade of PD and the incidence of azotemic CKD over a longer period was reported. Creatinine concentrations and serum BUN were measured in all dogs, and the criteria for being diagnosed with azotemic CKD were a serum creatinine concentration > 1.4 mg/dl and a diagnosis of chronic renal failure. The dogs within the azotemic CKD-group were further subdivided into three groups based on disease severity. The risk of a diagnosis of azotemic CKD in this study population of dogs increased accordingly with increasing degree of PD, regardless of the amount of increase in the

creatinine concentration and BUN. In other words, increasing degree of PD was correlated with increasing BUN and creatinine concentrations. Other findings in this study were that by going through PD treatment, the risk of dogs getting azotemic CKD decreased by 23 % (48).

An earlier longitudinal study has confirmed compelling association between extent of PD and non-specific biomarkers of inflammation, such as WBC count and percentage of monocytes in peripheral blood. Systemic inflammation can, as mentioned previously, result in endothelial dysfunction and renal failure (49). Studies have documented that extent of PD is correlated to amount of increase in BUN and creatinine concentrations, and that by undergoing dental therapy, the risk of developing azotemic CKD decreased dramatically. The findings suggested severe periodontitis as a risk factor for CKD.

Rawlinson et al. (2011; see Table 1 and above for study details) examined a group of 38 dogs before and 4 weeks after treatment of PD, where the dogs underwent full clinical examinations together with SB, total blood counts and urine analysis. Creatinine concentration from before PD treatment were compared with the both the severity of gingivitis and attachment loss. After Bonferroni correction a moderately negative correlation between creatinine concentration and attachment loss were observed ($r=-0.49$, $p=0.001$), with creatinine ranging from 0.6 to 1.9 mg/dL. BUN was significantly increased ($p<0.001$) after treatment, which could be theorized to be affected by protein consumption, as no decrease in renal function were seen based on the urine specific gravity (USG), and anaesthesia was ruled out as a possible cause. The authors theorized that the dogs had less discomfort after treatment and consequently ate more, resulting in increased consumption of protein (5). Only BUN had a significant change in values from before to after treatment of PD when Bonferroni correction were applied.

Mounting evidence are documenting a relationship between PD and CKD in humans, and several canine studies are backing these findings. PD has been linked to histopathological renal changes and degree of severity of PD seems to be linked to degree of renal pathology. Additional evidence documents a relationship between PD and kidney diseases such as interstitial nephritis, pyelonephritis and glomerulonephritis in dogs. Oral pathogenic bacteria are able to adhere to endothelium in the glomeruli and enhance more pro-inflammatory mediators promoting localized inflammation in the kidneys. PD is also considered a potential risk factor for CKD in cats, but further research is needed on this topic. To our knowledge, as stated earlier, not much literature is available on different systemic correlation between cats and PD. Since PD is suggested to be a risk factor for development of CKD, treating dental diseases may substantially decrease the risk of azotemic CKD in dogs. An important fact to consider is that CKD affected dogs and cats are prone to worsened oral health such as oral lesions and stomatitis. Considering how big an impact kidney disease has on (especially) older dogs and cats, simple prophylactic dental cleaning should be a requirement in every pet's life. Further well-controlled long-term studies are needed to confirm the etiological association between PD and kidney disease.

Association between periodontal disease and diabetes mellitus

Diabetes mellitus is a relatively common chronic disease amongst dogs and cats, with a reported hospital prevalence rate of 0.4-1.2 %. DM in dogs resembles type 1 diabetes in humans (insulin- dependent DM), while DM in cats resemble type 2 diabetes in humans with 80 % of cats having this non-insulin-dependent form (52). Diabetes in dogs has from 2006-2016 increased by 80 %, while the prevalence of diabetes in cats has increased 18 % over the same time period. Feline diabetes is more prevalent than canine diabetes (9). DM is defined as

absolute or relative insulin shortage that leads to hyperglycaemia and glucosuria. The incidence of DM in dogs and cats is increasing, presumably due to increasing prevalence of obesity. DM in dogs are normally diagnosed in middle aged or older dogs and is commonly called insulin-dependent DM (IDDM). IDDM is thought to be induced by autoimmune-mediated destruction of insulin-producing beta cells in the pancreas. Diabetic dogs might develop diabetic ketoacidosis (DKA) and administration of insulin is essential. Stimulation from insulin and glucagon on beta cells in these dogs will not lead to increased insulin secretion since the beta cells are either too injured, unresponsive or absent. The cause of DM in dogs is evidently multifactorial (53). Non-insulin-dependent DM (NIDDM) (type 2) in cats consists of a combination of impaired insulin action in liver, muscle and adipose tissue, considered insulin resistance, and failure of the β-cell. The aetiology for development of NIDDM in cats is also multifactorial, with obese older cats and cats with amyloidosis having increased risk of this disease. The recommended treatment for diabetic dogs and cats is administering insulin twice a day, morning and night (52).

Human diabetic patients have more than double the amount in health care expenses compared to what non-diabetic people spend. It is presumed that diabetes and complications thereof make up approximately 5-10 % of the entire health care budget in several countries (17). WHO (World Health Organization) have previously estimated that by the year 2030 the number of people with diabetes will be as high as 366 million, presumably driven by higher prevalence of people with type 2 diabetes, with the prevalence of type 1 diabetes continuing to be rather constant. This massive increase is believed by WHO to be happening due to population growth, unhealthy diets, aging, obesity and people living more comfortable, inactive lifestyles. Such a massive increase in diabetic patients will burden the health care systems economy and people’s welfare drastically (54).

A prospective cohort study of > 600 individuals documented that patients with type 2 diabetes with concurrent severe PD have a 3.2 higher risk of mortality than patients with no or mild form of PD (2). Human studies also indicate that inadequate glycaemic control, as is the case in diabetic patients, leads to worsened periodontal health (17). On the other hand, treatment of PD have documented improved glycaemic control in patients with type 2 diabetes (2). DM has been reported to be one of the systemic risk factors for development of PD and DM's effects can be a contributing factor in further progression of PD. Damage of the periodontal ligament and subsequent disattachment and tooth loss are seen in association with diabetes in humans. Saliva and the GCF contain elevated concentrations of inflammatory mediators in periodontitis-affected diabetic patients, compared to non-diabetic patients with PD. The European Federation of Periodontology and the American Academy of Periodontology held a collective workshop in 2013 and drafted a report identifying a dose-response relationship between the degree of PD and the extent of adverse diabetic complications. Additionally, periodontal therapy has been reported to be as favourable as administering antidiabetic drugs to patients with DM (2).

In a narrative review of English-language literature from 1960-2000, Taylor (2001) reported that 44 of 48 observational studies postulated data that DM negatively affected periodontal health in humans (17). Offenbacher et al (1996), and Grossi and Genco (1998) published studies suggesting that increased vascularity in inflamed periodontium caused the inflamed tissue to be a source of an endocrine-like supply of TNF-α and other pro-inflammatory mediators. TNF-α, IL-6 and IL-1 are all essential mediators produced in periodontitis, and they have an impact on glucose and lipid metabolism, especially after acute infection or trauma. TNF-α has been documented to intervene in lipid metabolism and can function as an

insulin antagonist. Both IL-1 and IL-6 have been reported to compete with effects of insulin. Worsened glycaemic control is acknowledged to have a crucial role in progression of chronic diabetic complications. Studies have established that sustaining good glycaemic control could reduce the risk and decrease the progression of microvascular complications in patients with type 1 and type 2 DM. A cohort study mentioned earlier (17) reported that patients with severe degree of PD had a 3.2 timer higher risk of mortality due to cardio-renal disorders, for instance ischemic heart disease concurrent with diabetic nephropathy, than individuals with no, mild or moderate PD (17). Inflamed periodontium may act as a reservoir for pro-inflammatory mediators which can intervene in lipid metabolism and function as an insulin antagonist in humans. Expanding evidence are proposing that PD negatively affect glycaemic control and increases the risk and extent of diabetic complications.

Many diabetic dogs and cats have a higher prevalence of PD and the extent of PD is correlated to quality of the pets glycaemic control (55). PD is the most common co-morbidity in dogs and cats with DM (56). To our knowledge, few studies are to be found on the association between PD and DM in dogs and cats today. A case report from 2009 revealed insulin resistance as a result of PD in an old (13 years old) female poodle with diabetes. The poodle was diagnosed with DM and mild PD over a year prior to deterioration of the condition and clinical admission. She was controlled glycaemic-wise by eating a high fibre diet and given human NPH insulin morning and night. The owner controlled urinary glucose levels daily, and normally observed no or just traces of glucose. The owner then reported a sudden onset of glucosuria, polyuria and polydipsia, with a duration lasting the last three days. The veterinarian examined the poodle and revealed severe periodontal reaction with severe gingival hyperaemia, dental plaque and furcation of teeth. Other laboratory findings were marked neutrophilia, glycemia and high fructosamine concentrations. The insulin dosage

was increased. After three days of antibiotic therapy, the dog received periodontal treatment, and eighteen teeth were extracted. Ten days post antibiotic and periodontal treatment, and daily cleaning with 0.2 % chlorhexidine, the poodle had an episode with hypoglycaemia and muscular tremors. Insulin dosage was reduced to original dosage, and subsequently the dog remained in a normoglycemic state and no more glucosuria was detected. This case reported an association between insulin resistance enhanced by severe PD and how much better the glycaemic control got after periodontal therapy (57). This one case report documents correlations between PD and DM in one dog, but the response to treatment is indicative of how big of an impact PD might have on glycaemic control in dogs.

Present findings suggest that the association between PD and DM is correlated to constant hyperglycaemia in diabetic humans. This hyperglycaemic state leads to an amplified immune-mediated inflammatory response toward the oral pathogens and thereby an intensified impairment of the periodontal tissue. The regulation of metabolism is inadequately managed in diabetic individuals, and constant hyperglycaemia leads to non-enzymatic glycation and oxidation of proteins and lipids with subsequent production of Advanced glycation end products (AGEs). These AGEs concentrate in tissue and plasma. Persistent hyperglycaemia and production of these AGEs are believed to be a crucial causal factor or a part of the development of diabetic complications. In the gingiva of diabetic patients with periodontitis studies have documented AGEs and concurrent markers for elevated oxidative stress. Researchers hypothesize that increased oxidative stress in the gingiva could enhance the rate and severity of periodontal tissue loss in individuals with diabetes (17). Persistent hyperglycaemia is believed to increase the host immune response and magnify the periodontal tissue destruction. Hyperglycaemia may also lead to production of AGEs, which are involved

in the pathogenesis of diabetic complications. We have found no such studies in dogs and cats.

DM has been described to negatively affect bone repair in humans by reducing expression of genes that activate differentiation of osteoblast cells, and by decreasing growth factor and production of extracellular matrix, possibly increased by AGEs. AGEs might also activate apoptosis of cells responsible for production of extracellular matrix and by so interrupt wound healing. Reduced extracellular matrix will reduce the number of fibroblastic and osteoblastic cells that are essential for repair of alveolar bone, also important for periodontal tissue. In addition to increased apoptosis, AGEs might diminish tissue healing in the oral cavity by lowering production of collagen and enhance inflammation (17). Studies have documented a negative effect DM has on bone repair and wound healing (oral lesions included), partly due to the formation of AGEs.

Multiple studies have established an association between diabetes and PD in humans, fewer in dogs, and very few in cats. Therefore, less is known about the systemic effects of PD in cats, and more studies are needed. One study researched the association between PD and systemic effects in cats. IgG levels and total globulins were correlated to PD in some cats, and a remarkable decrease in these levels and other markers for systemic inflammation were shown after periodontal treatment (22). It is suggested that glycaemic control in diabetic cats will improve after periodontal treatment and that this might reduce the need for insulin therapy. A small study of Burmese cats described that cats with PD in need of treatment were at increased risk for developing DM (58). Only a few minor feline studies have to our knowledge researched this topic, a topic that warrants further investigation (59). Dental

disease in cats has systemic effects and these effects can be improved with periodontal therapy.

Dogs and cats with diabetes are prone to infections of various types, since hyperglycaemia can weaken their immune system. Furthermore, some diabetic complications, like neuropathy and reduced circulation in the extremities, will increase the susceptibility to infection. On the other hand, an ongoing chronic infection from PD (for instance) may alter the body's ability to retain normoglycemia. As a response to infection some endogenous hormones will cause insulin resistance and hyperglycaemia. Periodontal treatment and anaesthesia in diabetic patients might require higher insulin doses to keep the patient normoglycemic during treatment. It is essential to not do any harm whilst giving periodontal treatment to diabetic patients. Any kind of oral intervention will affect the animal's appetite in some degree, and anorexia in diabetic patients treated with insulin is a bigger concern than in the normal non-diabetic patient. Excessive insulin administration in a patient with hypo-/anorexia could result in hypoglycaemia, while insufficient insulin administration could end in ketoacidosis, neither of which is beneficial and should be prevented (56).

Several studies have confirmed a robust correlation between DM and increased PD, and likewise between PD and an escalation in insulin resistance (60-65). This association seems reasonable, as any acute infection (viral or bacterial) will increase insulin resistance and impair glycaemic control, and this will happen even in healthy patients without diabetes (66, 67). These facts mean that PD contribute to not only poorer glycaemic control, but perhaps more significantly to the increased criticalness of diabetic complications, such as microvascular disease and wound healing, as well as with renal and CD (68-73). PD has been labelled as the sixth diabetic complication, with the other complications being; diabetic

cardiocerebrovascular disease, diabetic eye disease, diabetic nephropathy, diabetic neuropathy and diabetic sexual dysfunction (3).

The correlation between PD and diabetes in humans is bi-directional. Robust evidence endorses diabetes having negative effect on periodontal health, and periodontal infection having negative effect on glycaemic control and prevalence of diabetic complications. Overall, new large and comprehensive studies are required to confirm that treatment of PD can better glycaemic control and even lead to reduction of diabetic complications (17). Emerging evidence from human studies strengthen the evidence of PD and diabetes having a synergetic relationship. We need more research regarding this bidirectional relationship in dogs and cats. However, with what we know from human studies, we should put in more effort to encourage owners to come in for dental check-ups and treatment, regardless of their pets health, and emphasize how good periodontal health could prevent development of systemic diseases like diabetes. It is also important to highlight the importance of good oral hygiene to owners with diabetic dogs and cats, as this probably could provide better glycaemic control as shown in human studies.

Association between periodontal disease and respiratory disease

In 1990 respiratory disease and chronic obstructive pulmonary disease (COPD) were ranked as the third and sixth most common mortality cause in humans globally, representing 4.3 and 2.2 million deaths, respectively (74). COPD is chronic obstruction of lung airflow and is characterized by inflammation and narrowing of the lower airways and injury to the alveoli. This disease is by year 2030 believed to be one of the major causes of mortality globally. The reported COPD-prevalence in one study were 9.23 % in men and 6.16 % in women. Smoking cigarettes is by far the biggest risk factor for COPD, but evidence show that 20 % of COPD-affected patients have indeed never inhaled smoke (75). The oral cavity and dental plaque are

considered to be a constant local reservoir for bacteria included in infections in the respiratory system. The Gram-negative anaerobic bacteria, which make up for the major bacterial constituent in dental plaque, might contribute to the development or complications of these disorders (3).

COPD more commonly called chronic bronchitis, in dogs is a long-term, irreversible and slowly progressive inflammatory disease. The most common symptoms are persistent coughing ≥ 2 months, and this can progress to exercise intolerance and dyspnoea (76). Chronic bronchitis is the most prevalent chronic respiratory disorder in dogs (77). No definitive aetiology of COPD in dogs has yet been established but is has been suggested that chronic respiratory inflammation might be caused by inhalation of airway irritants, such as cigarette smoke from owners, air pollutants or allergens, from dental disorders or from intermittent respiratory infections. Dental disease will heighten the likelihood of periodontopathogens exacerbating secondary infections in the lung parenchyma (76). Chronic bronchitis is also a term used in cats with consistent coughing for over 2 months, although the term Feline asthma is probably more frequently used (78). Feline asthma is a chronic lower airway inflammation of great importance, and to differentiate feline asthma from the other chronic lower airway diseases, such as chronic or infectious bronchitis, parasitic infections), can be challenging due to similar clinicopathological signs. Feline asthma is believed to be of allergic aetiology (74). The consequence of the respiratory system disorders is hypoxemia, and the cat can develop reduced exercise intolerance, persistent coughing and respiratory distress. Middle aged to geriatric cats are more often affected, and Siamese cats seems predisposed to chronic bronchitis (78). COPD and chronic bronchitis are relatively common disorders in humans, dogs and cats. We have currently no reliable data regarding the

incidence and prevalence of canine chronic bronchitis, feline asthma and/or bronchitis, but we do know the importance of these respiratory diseases in dogs and cats.

Several studies have indicated a probable correlation between chronic obstructive respiratory disease and PD in humans (79). Scannapieco et al. did an extensive epidemiological study investigating the correlation between diseases in the oral cavity and PD, by reviewing data from a NHANES 1 study (National Health and Nutrition Examination survey). The authors' conclusions from this study were that people with chronic respiratory disease had remarkably worse hygiene index score regarding oral health than people without respiratory disease. When they corrected for confounding factors like age, gender, ethnicity and smoker/non-smoker, the individuals with lowest oral hygiene index score were 4.5 times more exposed to having chronic respiratory disease compared to healthy individuals. Although providing data suggesting a correlation between general oral status and chronic respiratory disease, the study did not find a convincing specific relationship between gingivitis or the periodontal index score and chronic respiratory disease (80). A different study using data from a nationwide survey of almost 6000 people reported a markedly higher incidence of periodontitis in people with COPD than in healthy individuals. One additional large cohort study, where more than 22 000 COPD-affected patients were compared to non-COPD-individuals, revealed that individuals with COPD had a higher risk for evolving PD in comparison to the general population (2). Further studies have documented that based on current evidence, PD is a substantial and independent risk factor of COPD. Whether this is a causal association or not deems further investigation (81). These studies seem to indicate an interdependency; that individuals with COPD had significantly worse oral hygiene and higher incidence of periodontitis than healthy individuals, and individuals with bad oral hygiene and PD were at increased risk of having COPD.

Reported data have indicated that dental prophylaxis, by mechanical removal and/or topical chemical disinfection or antimicrobials, would enhance oral hygiene and thereby reducing the prevalence of hospitalized-occurring pneumonia by 40 % on average (79). Bacterial pneumonia is a common respiratory infection in humans and the most frequently occurring route of infection is by aspiration of fluids containing oral pathogenic microorganisms from the oropharynx. With immunosuppressed individuals being particularly susceptible to disease development (82). Research has shown that patients at a dental department reduced the number of oral microorganisms by regular tooth brushing and gargling with iodine and thereby prevented pneumonia caused by periodontopathogens. Antiseptics with povidone-iodine appear to prevent infections caught in hospital and opportunistic infections (83). The effects of using povidone-iodine as gargle have also been documented by Nagatake et al. (84), where patients experienced a remarkable reduction in acute aggravation of chronic respiratory infections compared to previous periods of not using povidone-iodine. The percentage of people getting infections with *Staphylococcus aureus*, (MRSA (*Methicillin-resistant Staphylococcus aureus*) included) *Pseudomonas aeruginosa* and H. influenza was reduced by 50 %. The authors hypothesized that the bacteria colonizing the oral cavity were destroyed by the treatment and therefore could not lead to a respiratory infection. More studies are warranted on this topic (84).

Dental plaque can also be referred to as a biofilm and consists of extreme numbers of possible periodontopathogenic bacteria, which could through entering saliva and aspiration, enter the lower respiratory tract and cause infections. Cytokines and enzymes derived from the bacteria in the periodontal lesions by dental plaque can enhance local inflammatory processes and facilitate colonization of pathogenic bacteria/virus/fungi and an actual pulmonary

inflammation. Other suggested theories of the pathogenesis of pulmonary infections are inhalation of airborne pathogens or migration of local infections (for instance in the oral cavity) via transient bacteraemia. Healthy individuals will normally have a good immune response preventing such pulmonary infections, but this is not the case for immunosuppressed elderly, patients with decreased salivary flow, insufficient cough reflex, disorders affecting the swallowing reflex or those not capable of maintaining appropriate oral hygiene or health. Periodontitis and poor oral hygiene which facilitates colonization of periodontopathogenic bacteria in plaque might promote pneumonia (85). People with an underlying respiratory disease like COPD might encounter some difficulties in achieving and maintaining good oral hygiene and health, and this might be the reason why studies have shown that COPD-patients have increased risk of developing PD (86).

Various human studies have published correlations between gingival diseases to the rising prevalence of respiratory disease like COPD and pneumonia. Infections in the oral cavity are also considered to worsen chronic respiratory diseases and proper oral prophylaxis and therapy will reduce complications. To our knowledge no such data on dogs or cats is available, but we have reason to believe that these human studies can be extrapolated to our pets, at least to some extent. Further human and animal studies are required to acquire better insight in the correlation between disease in the oral cavity and the lungs. Dentist, doctors, nurses and veterinarians should underline how relevant optimizing oral prophylaxis, hygiene and treatment is to individuals with respiratory diseases due to the mounting evidence of a correlation between PD and respiratory disorders in humans.

Conclusion

The prevalence of PD and its common associations with systemic disease, some potentially life-threatening, suggest that PD should be considered a general health concern, not only in human medicine but also in companion animal medicine. A bidirectional relationship has also been documented in some situations. It is important to keep in mind that if one condition is present, the hazard of comorbidities being present or under development will be high, especially if the conditions have been allowed to progress over time and in severity. However, by managing one condition, it's likely to benefit for the other conditions as well (50). And for the most efficient treatment, the root cause should be investigated. Therefore it is important to continue research on cause and consequence relationships.

Strong associations have been documented between PD and systemic inflammation in dogs. Both veterinary and human literature suggest that PD might be associated with transient bacteraemia and chronic, systemic release of endotoxins and inflammatory mediators into the blood stream, which can infect and/or exert direct toxic or immune-mediated changes in distant organs. Evidence exists indicating that the degree of PD is linked to degree of distant organ pathology. Canine studies have documented evidence of correlations between PD and morphological changes in the heart and atherosclerosis. PD have also been suggested to be associated with BE, but few canine studies support this association. In dogs we have evidence that oral pathogens have been linked to general hepatic damage and disease. Bacterial hepatic inflammation can increase inflammation of hepatic parenchyma and induce portal fibroses. More canine studies show association between degree of PD and degree of hepatic inflammation. Considerable evidence documents a relationship between PD and CKD in humans, and a few canine studies support this relationship. PD has been linked to histopathological renal changes and severity of PD seems to be linked to extent of renal

pathology. Associations between PD and interstitial nephritis, pyelonephritis and glomerulonephritis in dogs have also been reported and PD is considered a potential risk factor for feline CKD. A bi-directional correlation between PD and diabetes mellitus is established, with diabetes having negative effects on periodontal health, and periodontal disease having negative effect on glycaemic control and prevalence and extent of diabetic complications. Numerous human studies have published correlations between gingival diseases to the increasing prevalence of respiratory diseases like COPD and pneumonia. We have reason to believe that the same correlations might exist in dogs and cats. Infections in the oral cavity is suggested to worsen chronic respiratory diseases and proper oral prophylaxis and therapy will reduce complications, although studies are needed to verify and understand the clinical relevance for dogs and cats.

The present hypothesis is that human periodontitis and its systemic effects considerably burden systemic health, welfare and economy. Amongst the different mechanisms (bacteria, pro-inflammatory mediators and oxidative stress), different bacteria species are present in the dental plaque, in different amounts and some are more prevalent in severe PD, and these could be linked to other pathological mechanisms. Even though PD is highly prevalent and could easily be prevented/treated/improved, it seems, compared to the other life-threatening diseases, quite harmless. And patients, pet owners and even doctors and veterinarians will often neglect the significant impact PD might have on systemic health. We hope increased knowledge about these associations will lead to improved over all health care and journal systems that will ensure better collaborations between veterinary technicians and veterinarians. As well as increased focus on oral health in patients (3). We believe that veterinarians should give dental health greater focus, both in first line practice and in referral hospitals. Although veterinary study results are backing a causal association between PD and

organ pathology in dogs, numerous hypothetical confounding factors that could affect both exist. Independent variations in factors like aging, dietary imbalances, and abnormally low or high body weight, which can also negatively impact innate immune mechanisms and organ health. These factors should be accounted for in new studies, using animals with same age, breed, diet and body conditions as control groups (10).

We should take knowledge from successful human studies and design similar studies for future work in dogs and cats. Further well-controlled long-term studies are needed to understand and confirm the association between oral health and systemic diseases. Ideally, we would like to see more randomized control studies, investigating for several factors and for common diseases as mentioned in this review. Clinical trials will be the preferred choice of study design, as confounding factors could be controlled, but these studies are extremely challenging to conduct in real life. Since several of the diseases mentioned in this review have multifactorial aetiologies, and with PD being as prevalent as it is, these studies would be almost impossible to design. However, these studies would be able to generate relevant hypotheses that could be used to design further, more specific studies. More long-term cohort studies are also warranted. Veterinarians in Norway keep animal health records in electronic data systems that could be used as databases for new, larger and more comprehensive studies. With new and bigger veterinary health franchises/chains establishing common electronic record systems in shared databases, a larger study sample will be more available in other countries as well. Standardization of the diagnosis across dental diseases should be trialed and validated prior to doing so, as examination practices of the oral cavity among veterinarians may vary. As bigger databases with differentiated diagnoses are established, larger cross-sectional studies will be more feasible, advancing our knowledge on the associations between PD and systemic diseases in pets. Evidence that verify direct connections between PD and the

systemic diseases in dogs and cats mentioned in this review are lacking, but some studies describe possible associations in some cases.

Oral, dental and maxillofacial diseases are without doubt the most frequently occurring problem in dogs and cats. Due to these conditions, the animals will be in serious discomfort, and may have localized and possibly systemic infection. Our knowledge regarding un- and underdiagnosed dental diseases is therefore of great concern for animal welfare. The dentistry courses in small animal practice in veterinary school is barely present. Increased focus on odontology in the curriculum should be a priority. Luckily, an increased focus on oral health in small animals have arisen, and this field is in continuous growth (1). By reflecting over what we do know from human studies, we should look for more associations in dogs and cats, and extra dental care should be provided in the sick patients. Adequate guidance for pet owners regarding satisfactory dental health, cleaning, routine dental cleaning at a clinic and regular follow ups are extremely important. With small bred dogs' popularity constantly increasing, special attention should be given to owners with these dogs, and dogs and cats with increased risk of dental disease. It is of great importance that veterinarians educate the owners from early kitten or puppy stage about maintaining good oral health and the benefits this has in preventing several serious systemic complications.

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Sammendrag

En rekke humane studier har etablert ulike sammenhenger mellom tannhelse og systemiske sykdommer. Noen av disse assosiasjonene har også blitt forsket på hos hunder og katter. Vi har utført en litteraturstudie hvor vi har sett på artikler som undersøker om det finnes en sammenheng mellom tannhelse og ulike systemiske tilstander, både humant og hos hund og katt. Studier på hund har vist korrelasjon mellom tannsykdom og morfologiske forandringer i hjerte, lever og nyrer. Andre studier viser at det også er sammenheng mellom tannhelse og systemiske inflammatoriske effekter som kan utøve sine effekter i viktige organer. Assosiasjoner hos hund har blitt funnet mellom dårlig tannhelse, leversykdom, diabetes, og nyresykdom, som kronisk nyresvikt, nefritt, pyelonefritt og glomerulonefritt. Svært få studier med katt som fokus er publisert. Dog har det blitt funnet korrelasjoner mellom tannsykdom, inflammatoriske responser, kronisk nyresvikt og diabetes. Tannbehandling har vist dokumentert effekt på lindring av flere sykdommer og kan også redusere prevalensen av enkelte. Flere studier tilsier også at systemiske lidelser kan ha negativ innvirkning på tannhelsen. Det er svært viktig med økt fokus på tannhelse og bedre studier på hund og katt i fremtiden, da disse korrelasjonene har stor påvirkningskraft og er viktige for dyrs velferd.

Tittel: Finnes det en sammenheng mellom tannhelse og systemisk sykdom hos hund og katt?

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