

Insulin Resistance Due to Periodontal Disease in an Old Diabetic Female Poodle

Alan Gomes Poppl^{1*}, Fernanda Muller², Luciana Queiroga³ and Félix Hilário Díaz González⁴

¹Adjunct Professor, Department of Animal Medicine, Veterinary Clinical Hospital, Federal University of Rio Grande do Sul (UFRGS). Av. Bento Gonçalves 9090, Agronomy, Porto Alegre, Rio Grande do Sul, Brazil

²Dentist. Rua Germano Petersen Junior, 627/401, Help, Porto Alegre, Rio Grande do Sul, Brazil

³Anesthesiologist, Department of Animal Medicine, Veterinary Clinical Hospital, Federal University of Rio Grande do Sul (UFRGS). Av. Bento Gonçalves 9090, Agronomy, Porto Alegre, Rio Grande do Sul, Brazil

⁴Titular Professor, Department of Animal Clinical Pathology, School of Veterinary Medicine, Federal University of Rio Grande do Sul (UFRGS). Av. Bento Gonçalves 9090, Agronomy, Porto Alegre, Rio Grande do Sul, Brazil

Summary

The purpose of this work was to report a clinical case of a spayed, 13-year-old diabetic poodle on insulin therapy with insulin resistance and poor diabetes control secondary to severe periodontitis. Prior to establishing the periodontal surgical approach, the insulin dose needed to be increased to stabilize the patient. Periodontal treatment included the extraction of 19 teeth. After periodontitis treatment, the insulin dose could be reduced to the previous effective dose. To our knowledge, this is the first case report of insulin resistance due to periodontal disease in dogs.

***Corresponding Author:** Alan Gomes Poppl, Adjunct Professor, Department of Animal Medicine, Veterinary Clinical Hospital, Federal University of Rio Grande do Sul (UFRGS). Av. Bento Gonçalves 9090, Agronomy, Porto Alegre, Rio Grande do Sul, Brazil; Tel: +55 51 96684995; Fax: +55 51 33086112; E-mail: alan.poppl@ufrgs.br

in human patients, once diabetic state predisposes to periodontal disease by means of different mechanisms, and periodontal disease may trigger insulin resistance [2]. However, there is a paucity of studies correlating diabetes and periodontal disease in dogs. The purpose of this work is to report one case of a diabetic female poodle on insulin therapy for more than one year with insulin resistance secondary to severe periodontitis.

Case Report

A spayed, 13-year-old dog weighing 6 kg was under adequate glycemic control by use of a commercially available high-fiber diet and human NPH insulin (3U) twice daily. Its latest fructosamine and albumin concentrations were 318 $\mu\text{mol/L}$ and 3.15 g/L, respectively. Although the owner was advised to look for a veterinary dental service to treat his dog's prominent calculus formation, gingivitis and halitosis, he refused to do so because of the risk of a general anesthesia. The owner monitored glycosuria at home every single day by the use of reagent strips, and traces of glucose, or negative results, were often found. Suddenly, four months after the last follow-up visit to the endocrinologist, the owner reported an increase in glycosuria to +++ / +++++. The development of polyuria and polydipsia on the past days was another worry. The owner also

Introduction

Periodontitis is the most common pathological condition in dogs; [1] in addition, the interplay between diabetes and periodontitis has been widely recognized as a two-way process

reported that there was no change in the patient's routine. The animal showed severe halitosis and was in distress at the manipulation of the oral cavity. The oral examination revealed severe periodontal reaction with severe gingival hyperemia and edema, with gingival retraction in the region of upper right and left canines, premolars and molars, calculus accumulation grade II to III between the canines, premolars and molars of both upper dental arches, purulent exudate, with obvious gingival recession, as well as grade II mobility in teeth 105, 106, 108, 109, 110 201, 202, 205, 206, 207, 208, 302, 303, 305, 306, 309, 310, 405 and 410 and loss of teeth 107, 307 and 308, characterizing active periodontal disease (Figure 1).



Figure 1: Patient's oral examination showing intense calculus, significant gingival inflammation, calculus accumulation, and purulent exudates with obvious gingival recession, indicating attachment loss due to periodontal disease.

A blood workup was done and the main findings were marked neutrophilia ($15,975/\text{mm}^3$) with activated monocytes, glycemia of 419 mg/dL after two hours and of 326 mg/dL after 10 hours of insulin application, as well as a fructosamine concentration of 379 $\mu\text{mol/L}$, and serum ALT of 403 U/L. Other parameters were within the reference range (ALP, creatinine, albumin). Table 1 shows the patient's hematological and biochemical parameters three months before loss of diabetes

control, at the time when active periodontal disease was diagnosed and three weeks, and six months after periodontal treatment. The abdominal ultrasound showed no abnormalities regarding urinary tract and size of adrenal glands. Notwithstanding, a urinary culture and a low-dose dexamethasone suppression test were performed, indicating absence of bacterial growth after 72h of incubation and a serum cortisol level of 0.32 $\mu\text{g/dL}$ 8h after the intravenous administration of 0.01 mg/kg of dexamethasone (normal < 1.0 $\mu\text{g/dL}$, consistent with Cushing's disease > 1.4 $\mu\text{g/dL}$). The insulin dose was then increased to 4U twice daily and a diagnosis of active periodontal disease was made.

Immediate treatment was initiated with metronidazole and spiramycin at the dose of 75,000 IU/kg of spiramycin and 25 mg/kg of metronidazole once daily for 14 days, in addition to oral hygiene with chlorhexidine 0.12% once daily, applied every day with gauze for an indefinite time period. Based on the specific clinical signs of the oral cavity, the periodontal treatment consisted of extraction of the affected teeth.

After three days on routine antibiotic therapy, the patient was submitted to oral prophylaxis in the morning, with observation of fasting after that. Before taking the patient to the clinic, the owner was told to give her dog half of the insulin dose (2U), without feeding her.

Midazolam at the dose of 3mg/kg and methadone hydrochloride at the dose of 0.2 mg/kg, were given intramuscularly as preanesthetic medications. Anesthetic induction was performed by intravenous administration of propofol at the dose of 5mg/kg, whereas anesthetic maintenance was obtained by isoflurane, applied by a universal vaporizer. Throughout the procedure, the patient received lactated Ringer's solution at the dose of 10ml/kg/h. Lidocaine hydrochloride (2 mg/kg) was used for local block of the right and left infraorbital nerves and right and left mandibular nerves. Before and during the procedure and in the immediate post-anesthetic period, glucose was checked every 20-30 minutes using a portable glucose meter. To maintain glucose levels between 150 and 250 mg/dL, a bolus dose of glucose 25% was given whenever necessary.

Table 1: Patient's hematological and biochemical parameters three months before loss of diabetes control, at the time when active periodontal disease was diagnosed and three weeks and six months after periodontal treatment and the extraction of 19 teeth.

Parameter	Three mo before	Periodontal diagnosis	Three wk after prophylaxis	Six mo after prophylaxis	Reference Values
Erythrocytes ($\times 10^6/\text{mm}^3$)	5.65	5.9	6.39	6.72	5.5-8.5
Ht (%)	42	42	45	49	37-55
Hb (g%)	14.5	15	14.8	16.4	12-18
Leukocyte ($\times 10^3/\text{mm}^3$)	8.2	21.3	14.2	12	6-17
Seg neutrophil ($\times 10^3/\text{mm}^3$)	5.6	15.9	8.6	8.7	3-11.5
Eosinophil ($\times 10^3/\text{mm}^3$)	0.08	0	0.85	0.36	0-0.3
Lymphocytes ($\times 10^3/\text{mm}^3$)	2.13	4.05	3.41	2.28	1-4.8
Monocytes ($\times 10^3/\text{mm}^3$)	0.32	1.28*	1.29	0.6	0.15-1.35
Glucose (mg/dL)	166 6 h AII	419 2 h AII	120 8 h AII	136 7 h AII	80-200 At# AII
Fructosamine ($\mu\text{mol/L}$)	318	379	319	299	170-338
Albumin (g/L)	35	40	-	27.9	26-33
ALT (U/L)	43	493	308	125	<102
ALP (U/L)	115	< 20	114	177	<152
Creatinine (mg/dL)	0.6	0.49	-	1.02	0.5-1.5
Glycosuria (reported in crosses)	traces	3+/4+	1+	traces	negative

mo = month. wk = week. h = hour. AII = After Insulin Injection. * Activated monocytes. At# = anytime (for diabetic patients – reference values for non diabetic 60-118 mg/dL).

The animal was placed in lateral decubitus and the surgical procedure began with the hygiene of the oral cavity using gauze soaked in chlorhexidine 0.12% rubbing it on the vestibular face of all teeth of the left half of the upper and lower arch. With a graded probe, all the teeth of the upper and lower half of the arch were examined. The probe went deep into the gingival groove of all teeth on all faces (Figure 2), except for the canines. With a forceps, the coarsest dental calculus was removed, and it was possible to observe the exposure of furcation grade III in teeth 106,109,110, 206, 207, 208, 306, 309 and 310 (Figure 3).



Figure 2: Periodontal probing showing an evident deep periodontal pocket.

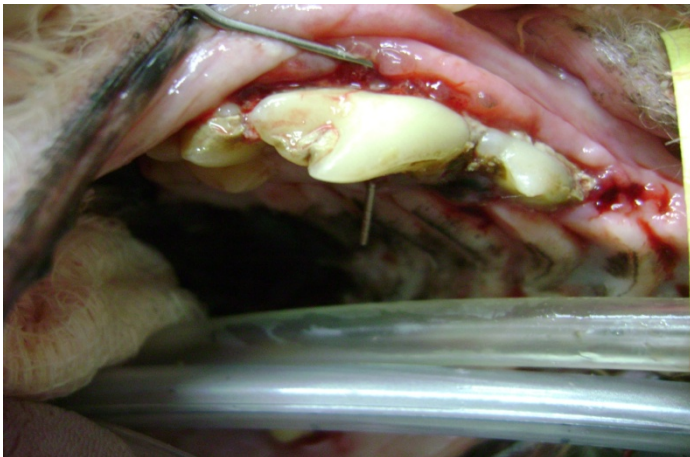


Figure 3: Furcation involvement grade III evidenced after calculus removal.

Owing to the mobility of these teeth, we decided to pull them out using an extraction technique for single-rooted teeth. By placing a periosteal elevator between the tooth and the alveolar crest, delicate rotation movements were performed for 10 seconds in order to break off the remaining fibers of the periodontal ligament of the root of each tooth and, after that, using a forceps, the teeth were pulled out from their sockets. Each socket was curetted and irrigated with sterile saline. Teeth 108, 208 and 309 were extracted according to the multi rooted tooth extraction technique. Due to the exposure of the furcation of these teeth and to mobility, they had to be broken into chunks with an inverted cone bur attached to the high-speed handpiece. The bur was drilled into the furcation and then crown-wise, turning multi rooted teeth into single-rooted ones. Thereafter, the periosteal elevator was inserted between the tooth and the dental crest and, with delicate rotation movements for 10 seconds, the remaining periodontal ligament underwent luxation, and the roots were pulled out from the sockets using a forceps. The sockets were curetted and irrigated with sterile saline. The gingival mucosa of all extracted teeth was sutured with a polyglactin 910 absorbable mesh of size 4-0, using a simple interrupted pattern.

The remaining teeth of the right upper and lower half of the arch were extracted by the same afore-mentioned methods, totaling 19 teeth (Figure 4). A dental ultrasound was used in canines and teeth, 104, 204, 304 and 404 for removal of

superficial dental calculi. The same was done for teeth 103, 101, 102, 203, 301, 401, 402, 403, 406, 407, 408 and 409. Probing of these teeth revealed no abnormalities. The remaining teeth were polished with a rubber cup attached to the straight low-speed handpiece, using pumice stone and fluorine as prophylactic agent.



Figure 4: Nineteen harshly periodontally affected teeth extracted at the end of the oral prophylaxis, in random order and named according to the Triadan system. Upper line: teeth 208,108,309. Middle line: teeth 106, 207, 206, 110, 310, 306, 210. Lower line: teeth 202, 305, 303, 105, 410, 302, 301, 405, 205.

In the immediate post-anesthesia period, the patient received meloxicam, 0.1 mg/kg, IV. In the same evening, the patient was back to its regular insulin scheme and eating habits; however, the commercial dry food was replaced with diabetic canned dog food temporarily during the first postoperative days.

Ten days after surgery, while maintaining antibiotic therapy and daily 0.2% chlorhexidine cleaning, the owner reported a hypoglycemic episode with muscular jerks. The insulin dose was reduced to 3U and the dog achieved normoglycemia, as detected by the traces of glucose in the urine reported every day since then, as well as by the biochemical tests (Table 1). There were no healing problems at this visit

(Figure 5) and after six months, an extraoral laterolateral radiograph indicated that the remaining teeth were intact, except for the lower right first molar, which showed periapical bone lysis around the mesial root and bone loss on the palatine and vestibular faces in the furcation (Figure 6).



Figure 5: Adequate gingival healing after 10 days of oral prophylaxis.

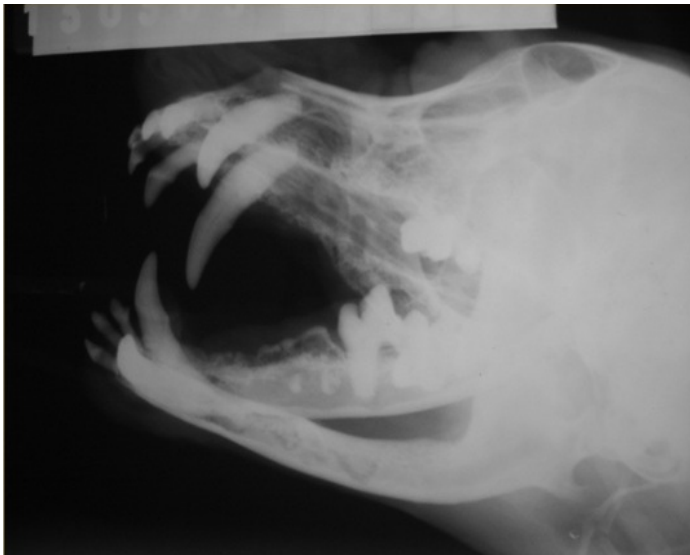


Figure 6: Control radiograph six months after the procedure showing signs of root resorption and furcal exposure in the lower third molar and possible bone resorption in the lower dental arches.

Discussion

Although it is a common issue in endocrinological and dental services in human medicine [2-6], little is known about the interactions of oral diseases such as periodontitis with insulin resistance and diabetes mellitus in pets. One case of diabetes mellitus deregulation secondary to multiple dental infections has been recorded [7], and periodontal disease has been implicated as a risk factor for diabetes development in Australian cats [8]. On the other hand, it was demonstrated decades ago that inflammatory reactions, as well as leukocyte migration, are reduced in diabetic dogs during bacterial plaque formation [9]. This is in agreement with observations in the medical and dental literature that characterize periodontitis and diabetes as a two-sided coin [2, 3].

Many diabetic pets suffer from some degree of periodontal disease, one of the most regular pathological conditions in veterinary practice [1]. The majority of evidence demonstrates an increase in the prevalence and severity of periodontal disease in people with diabetes mellitus [3, 5]. Several studies in humans show that the risk and rate of gingivitis, periodontitis and alveolar bone loss progression is two to four-folds higher in diabetic patients, even after adjusting for confounding variables such as age, sex and oral hygiene measures [2]. However, it seems that there is a dose-response relationship between periodontal disease risk and glycemic control, so patients with well-controlled diabetes may not be at an increased risk for developing periodontal diseases [6], as well as it is likely that there is individual patient variability in the degree to which glycemic control influences periodontal status [2], related not only to different levels of metabolic control, but also to different gene pools that appear to have a strong relationship with rapid periodontal breakdown [3, 5, 6].

Although periodontal diseases are infectious pathologies, occasional differences in microbial flora among patients with and without diabetes were shown to be of minor importance [2], even with the higher concentrations of glucose, calcium and urea in the saliva and crevicular fluid of patients with diabetes, which create a unique environment with possibility of shifts in the bacterial flora [6]. Instead, the host-response abnormalities

observed in diabetic patients seem to be the major difference [2]. For example, the adherence, chemotaxis and phagocytosis functions of neutrophils, monocytes and macrophages are often impaired in people with diabetes, and the inhibition of their function may reduce bacterial destruction in the periodontal pocket [6]. This reduced polymorphonuclear function observed in diabetes is also well recognized in veterinary practice [10] and may have had some involvement in the progression of periodontal disease in this case.

However, these cells can also exhibit an upregulated immunoinflammatory response to periodontal pathogens, with elevated production of proinflammatory cytokines such as interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF- α), which may increase host tissue destruction [2]. This upregulated response is mediated by interactions between Advanced Glycation End products (AGEs) and their receptors in inflammatory cells [6]. The accumulation of AGEs in diabetic patients is associated with many chronic complications of diabetes and can cause endothelial dysfunction, capillary growth and vessel proliferation in periodontal tissues of diabetic people [2]. Notwithstanding, this higher production of proinflammatory cytokines have also been correlated with imbalances in lipid metabolism that are common features of diabetic state, such as hypertriglyceridemia and high levels of free fatty acids and LDL cholesterol [11, 12]. Fructosamine concentration, is a measure of glycated proteins in the plasma, especially albumin, and thus reflects how glycemia behaved during the past 2-3 weeks [13]. The elevation of fructosamine concentration in this patient, associated with periodontal disease progression, does not only point out an insulin resistance status, but is also in agreement with observations of positive correlation between serum fructosamine, degree of gingival bleeding and severity of gingival inflammation observed in human diabetic subjects [14, 15].

Furthermore, there is an elevated production of Matrix Metallo Proteinases (MMP) in people with diabetes, and these MMP can quickly degrade the collagen produced by the fibroblasts during wound healing, impairing periodontal wound healing in patients with persistent hyperglycemia. Moreover,

fibroblasts do not function properly in high-glucose environments [2]. In addition, degenerative vascular changes observed in other tissues in diabetic people also occur in gingival tissues, reducing the capacity of delivery of nutrients, the leukocyte access and the elimination of metabolic products, thus worsening wound healing in long-term diabetic patients [6].

Regarding collagen metabolism, evidence shows that the diabetic state can increase the degradation of any newly synthesized collagen in various connective tissues throughout the body, including gingival tissue, where high levels of AGEs can induce glycosylation of the existing collagen at wound margins and consequent delayed remodeling due to excessive oxidative stress as a potential mechanism [6, 16].

Notwithstanding, evidence shows that periodontal diseases can contribute to poorer glycemic control in people with diabetes due to higher IL-1 and TNF- α levels in crevicular fluids and serum of people with periodontitis. Once periodontal disease has a major chronic inflammatory component, plasma elevation of those cytokines can generate insulin resistance and make it difficult for diabetic patients to control their glycemic level [17, 18], exactly as we documented in this case. The mechanisms whereby these main proinflammatory interleukins (IL-1, TNF- α) released in the serum of patients with periodontal diseases cause insulin resistance are diverse. Basically, those cytokines impair intracellular signaling of insulin in target cells such as adipose and muscle tissue, inducing a lower expression of IRS-1 (Insulin Receptor Substrate - 1, the most important second messenger of insulin receptor) and also inducing phosphorylation in serine residues of the IRS-1 instead of phosphorylation in tyrosine residues [19, 20].

In fact, we investigated any other cause of insulin resistance in this case; especially occult urinary tract infections and hyperadrenocorticism, two conditions that are often diagnosed in old diabetic female poodles [10, 21]. However, negative urine culture and low dexamethasone dose suppression test together with ultrasound evaluation of urinary tract and adrenal gland morphology rule out these diseases. Occasional mistakes in insulin storage, handling or dosage were also taken

into account, but the owner has a large experience with the treatment and no failures were identified [10]. Based on the latest blood work and clinical history [10, 22, 23], the dog was under perfect diabetes control by means of two injections of NPH insulin (0.5U/kg), associated with two meals of an adequate commercial food every 12 hours, before the development of polyuria, polydipsia and increased glycosuria, indicating that there was something wrong going on [24]. Meanwhile, CBC showed a marked inflammatory reaction with important neutrophilia and active monocytes, and after evaluation of the case, the only obvious inflammatory reaction was located in the mouth (Figure 1). Interestingly enough, while bacterial infections are often associated with insulin resistance, periodontitis, one of the most prevalent bacterial conditions in veterinary practice, has not been associated with it [1, 10, 21, 25].

Moreover, it has been shown that, in some cases, a minimal treatment of gingivitis and periodontitis in diabetic patients is sufficient to provide a better glycemic control in humans [26], despite no agreement among all papers looking for this association, probably due to differences in methodology and clinical criteria adopted in different studies [4]. In the present report, we observed quick restoration of the previous insulin sensitivity status few days after resolution of the infectious condition, and generally, this better glycemic control secondary to periodontal treatment came along with the reduction in IL-1 and TNF- α level [2, 4].

To treat this dog, a preoperative antibiotic therapy was proposed to prevent severe bacteremia and occasional systemic infections of periodontal origin during the surgical approach, as commented [27-29]. For the same reason, we decided to start the procedure with oral hygiene using chlorhexidine [30]. The anesthetic management with the use of potent tranquilizers and painkillers, as well as bilateral mandibular nerve block, sought to reduce the release of hyperglycemic hormones secondary to anesthetic and surgical stress [10, 31]. The administration of half of the insulin dose in the morning in which the surgery was performed, keeping the patient under fasting conditions, is in line with the protocol used in large centers for diabetes

treatment and, in this case, glucose levels must be monitored regularly to prevent intra operative hypoglycemia or hyperglycemia. The aim in these cases is to maintain glucose levels between 150-250 mg/dL, and to achieve that, continuous intravenous infusion of 2.5 to 5% glucose, or a bolus dose of 50%, or a regular dose of intramuscular insulin 0.1 mg/kg as needed [10] is given. In the present report, a regular dose of insulin was not necessary as NPH insulin, given as a half dose, maintained good glycemic control in the intra operative period. With respect to the surgical technique used for the extraction of the most severely affected teeth, followed by curettage of the sockets and ultrasonographic maintenance and cleaning of the least affected teeth, the adopted procedures are in agreement with the classic recommendations for the treatment of periodontitis in dogs [27, 28]. Intra operative assessment and probing of periodontal pockets during the procedure unequivocally confirmed the diagnosis of severe periodontitis [1], despite the absence of pre surgical radiographs, which were not authorized by the dog owner. During the three-year follow-up of this case, the owner cleaned her dog's teeth with chlorhexidine 0.12% on a daily basis, being successful at maintaining adequate oral health, even though most pet owners eventually quit doing that some months after the prophylaxis [32].

Although it is not certain whether oral intervention improves glycemic control, it seems to be a reasonable approach in people and pets with diabetes to conduct an aggressive management of oral health and a regular follow-up, given the potential link between periodontal disease and diabetes [3]. Many classical interactions between periodontitis and diabetes could be observed in the present report; however, we cannot provide evidence that periodontal disease has progressed faster secondary to the diabetic state in this case. Nevertheless, it was clear that periodontitis was the cause of insulin resistance in the present case once many studies in humans and other models have pointed out that periodontal disease, as well as any chronic inflammatory process, can be considered strong risk factors for diabetes development and worse glycemic control of diabetic patients [2-6]. In addition, encouraging owners of diabetic dogs

to maintain the adequate oral health of their pets by tooth brushing, chews, and a diet that is not exclusively wet (canned food), can help prevent the progression of gingivitis and periodontitis in many cases [33, 34].

Acknowledgments

The main author (A.G.P.) would like to thank Dr. Cristiano Gomes DVM., MSc., and posthumously thank Prof. Dr. Breno Martins Futuro for their valuable incentive to study the relationships between veterinary endocrinology and dentistry.

References

1. Niemic BA. Periodontal disease. *Top Companion Anim Med* 2008; 23: 72-80.
2. Mealey BL. Periodontal disease and diabetes: a two-way street. *J Am Dent Assoc* 2006; 137: 26S-31S.
3. Skamagas M, Breen TL, et al. Update on diabetes mellitus prevention, treatment, and association with oral diseases. *Oral Dis* 2008; 14: 105-114.
4. Taylor GW. The effects of periodontal treatment on diabetes. *J Am Dent Assoc* 2003; 134: 41S-48S.
5. Ship JA. Diabetes and oral health. *J Am Dent Assoc* 2003; 134: 4S-10S.
6. Ryan ME, Carnu O, et al. The influence of diabetes on the periodontal tissues. *J Am Dent Assoc* 2003; 134: 34S-40S.
7. Van Nice E. Management of multiple dental infections in a dog with diabetes mellitus. *J Vet Dent* 2006; 23: 18-25.
8. Lederer R, Rand JS, et al. Chronic or recurring medical problems, dental disease, repeated corticosteroid treatment, and lower physical activity are associated with diabetes mellitus in Burmese cats. *J Vet Inter Med* 2003; 17: 433.
9. Matsson L, Attström R, et al. Inflammatory reactions in the gingival region during the development of bacterial plaque in alloxan-diabetic dogs. *J Period Res* 1980; 15: 516-524.
10. Feldman EC, Nelson RW. Canine diabetes mellitus. In: Feldman EC, Nelson RW, eds. *Canine and Feline Endocrinology and Reproduction 3rd*. Missouri: Saunders, 2004; 486-538.
11. Cutler CW, Shinedling EA, et al. Association between periodontitis and hyperlipidemia: cause or effect? *J Periodontol* 1999; 70: 1429-1434.
12. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: recent concepts involving serum lipids. *J Periodontol* 2000; 71: 1375-1380.
13. Loste A, Marca MC. Fructosamine and glycated hemoglobin in the assessment of glycaemic control in dogs. *Vet Res* 2001; 32: 55-62.
14. Unal T, Firatli E, et al. Fructosamine as a possible monitoring parameter in non-insulin dependent diabetes mellitus patients with periodontal disease. *J Periodontol* 1993; 64: 191-4.
15. Firatli E, Unal T, et al. Serum fructosamine correlates with gingival index in children with insulin-dependent diabetes mellitus (IDDM). *J Clin Periodontol* 1994; 21: 565-8.
16. Schmidt A, Weidman E, et al. Advanced glycation end products (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes. *J Periodontal Res* 1996; 31: 508-515.
17. King GL. The role of inflammatory cytokines in diabetes and its complications. *J Periodontol* 2008; 79: 1527-1534.
18. Iacopino AM. Periodontitis and diabetes interrelationships: role of inflammation. *Ann Periodontol* 2001; 6: 125-137.
19. Grimble RF. Inflammatory status and insulin resistance. *Curr Opin Clin Nutr Metab Care* 2002; 5: 551-559.
20. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. *Mol Med* 2008; 14: 222-231.

21. Hess RS. Insulin resistance in dogs. *Vet Clin Small Anim* 2010; 40: 309-316.
22. Fleeman LM, Rand JS. Management of canine diabetes. *Vet Clin North Am Small Anim Pract* 2001; 31: 855-880.
23. Schulman RL. Insulin and other therapies. *Vet Med* 2003; Apr: 334-347.
24. Behrend EN. Diabetes mellitus: an update on oral hypoglycemic agents and monitoring options. *Vet Med* 2002; Oct: 743-751.
25. Hess RS, Saunders HM, et al. Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993-1998). *J Am Vet Med Assoc* 2000; 217: 1166-1173.
26. Madden TE, Herriges B, et al. Alterations in HbA1c following minimal or enhanced non-surgical, non-antibiotic treatment of gingivitis or mild periodontitis in type 2 diabetic patients: a pilot trial. *J Cont Dent Pract* 2008; 9: 1-13
27. Wigs RB, Lobprise HB. Periodontology. In: *Veterinary Dentistry, Principles and Practice*. Philadelphia: Lippincott-Raven 1997; 186-231
28. Harvey CE, Emily PP. Periodontal Disease. In: *Small Animal Dentistry*. St. Louis: Mosby 1993; 89-144
29. Alexander R. Routine prophylactic antibiotic use in diabetic dental patients. *J Calif Dent Assoc* 1999; 27: 611-618.
30. Bowersock TL, Wu CC, et al. Prevention of bacteremia in dogs undergoing dental scaling by prior administration of oral clindamycin or chlorhexidine oral rinse. *J Vet Dent* 2000; 17: 11-16.
31. McAnulty GR, Robertshaw HJ, et al. Anaesthetic management of patients with diabetes mellitus. *Br J Anaesth* 2000; 85: 80-90.
32. Miller BR. Compliance with oral hygiene recommendations following periodontal treatment in client-owned dogs. *J Vet Dent* 1994; 11: 18-19.
33. Harvey CE, Shofer FS, et al. Correlation of diet, other chewing activities and periodontal disease in North American client-owned dogs. *J Vet Dent* 1996; 13: 101-105.
34. Rawlings JM, Vet CG, et al. Effect on canine oral health of adding chlorhexidine to a dental hygiene chew. *J Vet Dent* 1998; 15: 129-138.