Association Between Atherosclerosis and Glomerulopathy in Dogs

Rebecka S. Hess, DVM, DACVIM[1]
Philip H. Kass, DVM, PhD, DACVPM[2]
Thomas J. Van Winkle, VMD, DACVP[3]

[1]*Departments of Clinical Studies*
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

[2]*Department of Population Health and Reproduction*
School of Veterinary Medicine
University of California
Davis, California

[3]*Department of Pathobiology*
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

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ABSTRACT

The objective of this study was to determine if dogs with atherosclerosis are more likely to have concurrent glomerulopathy than dogs that do not have atherosclerosis. A retrospective mortality prevalence case-control study was performed. Thirty seven dogs with histopathological evidence of atherosclerosis, and 279 control dogs with results of a complete necropsy and no histopathological evidence of atherosclerosis were frequency matched on age and year of necropsy. The 279 control dogs included 142 dogs with a final necropsy diagnosis of neoplasia, 71 dogs that were randomly chosen from the hospital population, and 66 dogs that had a diagnosis of diabetes mellitus, hypothyroidism, or hyperadrenocorticism. Dogs with atherosclerosis had significantly more glomerulopathy than dogs in the neoplasia control group ($P < 0.0001$), dogs in the random diagnosis control group ($P = 0.0078$), and dogs in the endocrine control group ($P = 0.0019$). Dogs with atherosclerosis also had significantly higher serum cholesterol concentration than dogs in the neoplasia control group ($P < 0.0001$), dogs in the random diagnosis control group ($P < 0.0001$), and dogs in the endocrine control group ($P = 0.0086$). Results show that glomerulopathy is more prevalent in dogs with atherosclerosis compared to dogs without atherosclerosis. This finding may prompt clinical investigations directed at recognizing vascular disease in dogs with glomerulopathy.

INTRODUCTION

Canine atherosclerosis is a rare vascular disease which has been reported in association with naturally-occurring diabetes mellitus and hypothyroidism.[1] Spontaneous atherosclerosis has also been reported in dogs that do not have evidence of these endocrinopathies, indicating that other factors may be involved in the pathogenesis of canine atherosclerosis.[1]

Renal glomerular disease increases the risk for atherosclerosis in human beings.[2-4] Glomerular disease is characterized by many factors that increase the risk for atherosclerosis including hypercholesterolemia,

hyperlipidemia, hypertension, increased platelet aggregation, and hypercoagulability.[2,3,5] These potentially atherogenic characteristics have also been described in dogs with naturally-occurring glomerular disease.[6]

It was hypothesized that dogs with atherosclerosis are more likely to have concurrent glomerulopathy than dogs that do not have atherosclerosis. The purpose of this study was to investigate whether glomerulopathy is observed more commonly in dogs with spontaneous atherosclerosis compared to dogs that do not have atherosclerosis.

MATERIALS AND METHODS

A computer search of 7,950 dogs that had necropsies performed at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) between January 1986 and October 2003 identified 63 dogs with a histopathological diagnosis of atherosclerosis. Histopathology slides were reviewed by one board-certified pathologist (TVW) to ensure that all dogs included in the case group had atherosclerosis. Medical records were reviewed by one board-certified internist (RSH).

Inclusion criteria for the case group were results of a complete necropsy and a histopathological diagnosis of atherosclerosis. Dogs were considered to have atherosclerosis if they met the criteria described in the histopathology section.

Twenty six dogs identified as having atherosclerosis on the computer search were excluded from the study for the following reasons: misdiagnosis or a missing record (6 dogs), fibrosis of the blood vessel wall with no evidence of foamy macrophages or cholesterol clefts (9 dogs), mineralization of the blood vessel wall with no evidence of foamy macrophages or cholesterol clefts (4 dogs), lack of atherosclerotic lesions on histopathology slides that were available for review (3 dogs), and the presence of atherosclerosis in only one small vessel (4 dogs).

The study was designed with 3 different control groups. The first control group (neoplasia control) included 142 dogs that were frequency matched on age and year in which the necropsy was performed. Inclusion criteria for this control group were results of a complete necropsy, no histopathological evidence of atherosclerosis, and a final necropsy diagnosis of neoplasia.

The second control group (random diagnosis control) included 71 dogs with a variety of medical conditions that were frequency matched for age and year in which the necropsy was performed. Inclusion criteria for the second control group were results of a complete necropsy and no histopathological evidence of atherosclerosis. The final necropsy diagnosis did not serve as a basis for inclusion into this control group. However, dogs that had diabetes mellitus, hypothyroidism, or hyperadrenocorticism (HAC) were excluded from this control group and were moved to the third control group of dogs with an endocrinopathy.

The third control group (endocrine control) included 66 dogs that were frequency matched for age and year in which the necropsy was performed. Inclusion in this control group required results of a complete necropsy and no histopathological evidence of atherosclerosis and a diagnosis of diabetes mellitus (documented in 32 dogs), hypothyroidism (documented in 23 dogs), or HAC (documented in 20 dogs). Some dogs had more than one endocrinopathy. Dogs were considered to have one of these endocrinopathies if they met the criteria described in the endocrine testing section.

Ultimately, the case group included 37 dogs with a histopathological diagnosis of atherosclerosis that were admitted to MJR-VHUP between January 1986 and October 2003. Dogs in all 3 control groups were age matched to the case group, had necropsies performed during the same time period as the case group, and had no histopathological evidence of atherosclerosis. Dogs in the first control group had a final necropsy diagnosis of neoplasia (142 dogs), dogs in the second control group had a random final necropsy

diagnosis (excluding dogs with diabetes mellitus, hypothyroidism, or HAC, 71 dogs), and dogs in the third control group had a diagnosis of diabetes mellitus, hypothyroidism, or HAC (66 dogs).

Medical records of dogs included in the study were reviewed, and signalment, clinicopathologic test results (Hematology analyzer, Celldyne 3500, Abbot Laboratories, Abbot Park Ill; Chemistry analyzer, Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY; N-Multistix SG, Bayer, Elkhart, Ind), subjective assessment of lipemia, endocrine test results, histopathology, and necropsy results were recorded. Clinical signs and clinicopathologic findings were recorded from the last time the animal was examined at MJR-VHUP.

Endocrine Testing

Hyperadrenocorticism was diagnosed based on history and clinical signs, and adrenal function testing or histopathology. Standard protocols were used in performing and interpreting the low-dose dexamethasone suppression (LDDS) test.[7] An 8-hour post-dexamethasone plasma cortisol concentration >1.4 μg/dL or a 2-hour post-adrenocorticotropic hormone (ACTH) plasma cortisol concentration ≥22 μg/d were considered consistent with a diagnosis of HAC.[7] Hypothyroidism was diagnosed based on history, clinical signs, and histopathology. Thyroid histopathology confirmed the diagnosis of hypothyroidism in all case and control dogs.[8] Histopathology findings were considered diagnostic of hypothyroidism if severe, bilateral, diffuse thyroid gland atrophy was noted. Dogs treated with thyroid hormone supplementation but without prior endocrine testing or histopathology findings to confirm the diagnosis were not considered hypothyroid. Diabetes mellitus was diagnosed based on history and clinical signs and documentation of persistent hyperglycemia and glucosuria.

Histopathology

All necropsies were performed at MJR-VHUP, and all biopsy and pathology reports were reviewed by a board-certified pathologist at the time the necropsy was performed. Histopathology findings were reviewed a second time by one board certified pathologist (TVW) if any abnormalities were noted in regard to renal histopathology at the time of initial examination. This was done to ensure that identical criteria were employed in describing glomerulopathy in all dogs included in the study. At the time of histopathological examination, the pathologist (TVW) did not know to which study group any given histopathology slide was classified.

All tissues were fixed in 10% neutral buffered formalin at the time of necropsy. Tissues were embedded in paraffin, cut at 4-5 microns, and stained with hematoxylin and eosin. Dogs were considered to have atherosclerosis if gross pathology changes were consistent with atherosclerosis and foamy macrophages or cholesterol clefts were observed in the intima of blood vessel walls. All available kidney sections were examined for each animal. Dogs were considered to have glomerulopathy if the majority of the glomeruli were involved (usually the change affected all glomeruli) and there was either thickening of the mesangium and capillary loops or an increase in cells in the glomerulus or both. Severe cases had adhesions of the glomerular tuft to Bowman's capsule.

Statistical Analysis

Proportionate changes in the prevalence of glomerulopathy in dogs with or without atherosclerosis were calculated using prevalence odds ratios (POR) and 95% confidence intervals (95% CI). Multiple logistic regression analysis was used to examine the combined effects of prevalence determinants while controlling for age and year of necropsy. When model convergence was problematic due to small numbers of individuals in the respective exposure-age-year strata, exact logistic regression was employed. Group comparisons for continuous dependent data were evaluated using the 2-sample Student's t-test and the Mann-

Whitney test. *P*-values < 0.05 were considered statistically significant (LogXact, CYTEL Software Corporation, copyright 2005, Cambridge, Mass).

Dogs were classified into one of a small finite number of breed categories due to sparse representation of less common breeds. These categories included Doberman Pinscher, Labrador Retriever, Miniature Schnauzer, Rottweiler, Shetland Sheepdog, and other breeds.

RESULTS

Eleven of 37 dogs (30%) with atherosclerosis had glomerulopathy, 6 of 142 dogs (4%) in the neoplasia control group had glomerulopathy, 9 of 71 (13%) dogs in the random diagnosis control group had glomerulopathy, and 6 of 65 (9%) dogs in the endocrine control group had glomerulopathy.

Dogs with atherosclerosis had significantly more glomerulopathy than dogs in the neoplasia control group (P < 0.0001, POR = 20.5, 95% CI = 4.6-127.8), dogs in the random diagnosis control group (P = 0.0078, POR = 4.8, 95% CI = 1.5-15.2), and dogs in the endocrine control group (P = 0.0019, POR = 6.8, 95% CI = 2.0-22.8).

The median age of dogs with atherosclerosis was 8 years (range 0.75-18 years) and was not significantly different than the age of dogs in the neoplasia control group, random diagnosis control group, or endocrine control group. There was no significant difference between the sex distribution of dogs with atherosclerosis (13 [35%] neutered female dogs, 12 [32%] intact male dogs, 11 [30%] neutered male dogs, and 1 [3%] intact female dog) compared to the sex distribution of dogs in the neoplasia control group, random diagnosis control group, or endocrine control group.

Sixteen breeds of dogs were included in the group of dogs with atherosclerosis. Mixed breed dogs (12 dogs) were observed most commonly in the group of dogs with atherosclerosis, followed by Labrador Retrievers (4 dogs), Rottweilers (4 dogs), Doberman Pinschers (3 dogs), and other less represented pure breed dogs. One Miniature Schnauzer and 2 Shetland Sheepdogs were also present in the group of dogs with atherosclerosis. Labrador Retrievers, Doberman Pinschers, Miniature Schnauzers, and Shetland Sheepdogs were not significantly over-represented in the group of dogs with atherosclerosis compared with all 3 control groups combined together. However, Rottweilers were over-represented in the group of dogs with atherosclerosis when compared to breeds of dogs other than those listed above in all 3 control groups combined together (*P* = 0.037, POR = 4.1, 95% CI = 1.1-15.8)

Twenty nine of 37 dogs (78%) with atherosclerosis had diabetes mellitus, hypothyroidism, or HAC and 8 of 37 dogs (22%) with atherosclerosis did not have these endocrinopathies. Four of the 8 dogs that had atherosclerosis and no detected endocrinopathy had glomerulopathy and 4 did not have glomerulopathy. Two of 8 dogs with atherosclerosis and no evidence of an examined endocrinopathy had increased serum cholesterol concentration (greater than 359 mg/dL). One of these 2 dogs had glomerulopathy and the other did not have glomerulopathy.

Seven of 11 dogs with atherosclerosis and glomerulopathy had an endocrinopathy; 5 dogs had hypothyroidism, 1 dog had diabetes mellitus, and 1 dog had HAC. Four of 11 dogs with atherosclerosis and glomerulopathy did not have one of the investigated endocrinopathies.

Ascites was noted in 1 of 11 dogs that had atherosclerosis and glomerulopathy. Edema or pleural effusion was not noted in any of these 11 dogs.

Median serum cholesterol concentration in the group of dogs with atherosclerosis (461 mg/dL, range 95-1,577 mg/dL; reference range, 128-359 mg/dL) was significantly higher than median serum cholesterol concentration in each of the 3 control groups (197 mg/dL, range 57-456 mg/dL, *P* < 0.0001, POR = 7.5, 95% CI = 3.3-17.3 in the neoplasia control group; 193 mg/dL,

range 74-389 mg/dL, $P < 0.0001$, POR = 3.5, 95% CI = 1.9-6.4 in the random diagnosis control group; and 286 mg/dL, range 48-2,010 mg/dL, $P = 0.0086$, POR = 1.3, 95% CI = 1.1-1.5 in the endocrine control group). Odds ratios pertain to a 100 mg/dL change in cholesterol concentrations.

Eight of 11 dogs with atherosclerosis and glomerulopathy had elevated serum cholesterol concentration (>359 mg/dL), and 3 dogs had normal serum cholesterol concentration (128-359 mg/dL). Two of the 3 dogs with atherosclerosis, glomerulopathy, and normal serum cholesterol concentration did not have evidence of diabetes mellitus, hypothyroidism, or HAC and the third dog with normal serum cholesterol concentration had HAC.

Serum was assessed subjectively for lipemia in all dogs included in the study. Lipemia was noted in 13/37 dogs (35%) in the case group, 10/142 dogs (7%) in the neoplasia control group, 2/71 dogs (3%) in the random diagnosis control group, and 17/66 dogs (26%) in the endocrine control group. Hypercholesterolemia was documented in 11/13 case dogs that had lipemia and in 9/17 endocrine control dogs that had lipemia. However, serum cholesterol concentration was normal in all 12 dogs that had lipemia in the neoplasia control group (10 dogs) or random diagnosis control group (2 dogs).

Lipemia was noted in 3 of 11 dogs with atherosclerosis and glomerulopathy. One dog with lipemia had diabetes mellitus, another dog with lipemia had HAC, and the third dog with lipemia did not have one of the investigated endocrinopathies. Two of the 3 dogs with lipemia also had hypercholesterolemia, and 1 of the 3 dogs with lipemia (the dog with HAC) had normal serum cholesterol concentration. The dog with atherosclerosis, glomerulopathy, lipemia, hypercholesterolemia, and no detected endocrinopathy was a Yorkshire Terrier.

Creatinine was abnormally increased (>1.8 mg/dL) in 5 of 11 dogs with atherosclerosis and glomerulopathy. Blood urea nitrogen (BUN) was also abnormally elevated (>30 mg/dL) in these same 5 dogs. Median creatinine and BUN concentrations in the 5 dogs with azotemia were 8.5 mg/dL and 157 mg/dL, respectively (range 2.4-16.6 mg/dL and 90-196 mg/dL, respectively).

Albumin concentration was measured in 10 of 11 dogs with atherosclerosis and glomerulopathy and was lower than the reference range in 2 dogs (1.9 mg/dL and 2.2 mg/dL, reference range 2.5-3.7 g/dL). One of the dogs with a low albumin concentration (1.9 mg/dL) had a urine-protein-to-creatinine ratio of 26.4. Urine-protein-to-creatinine ratio was not measured in any of the other dogs that had atherosclerosis. Proteinuria (>30 mg/dL) was noted in 7 of 11 dogs with atherosclerosis and glomerulopathy, and urine-specific gravity ranged from 1008-1026 in these dogs. Median albumin concentration in dogs with atherosclerosis (2.9 g/dL, range 1.1-4.0 g/dL, reference range 2.5-3.7 g/dL) was not significantly different than median albumin concentration in any of the 3 control groups (2.9 g/dL, range 1.0-4.6 g/dL in the neoplasia control group; 2.8 g/dL, range 1.3-5.0 g/dL in the random diagnosis control group; 2.6 g/dL, range 1.2-4.4 g/dL in the endocrine control group; reference range 2.5-3.7 g/dL).

DISCUSSION

Dogs with atherosclerosis had significantly more glomerulopathy than dogs in each of the 3 control groups. The association between atherosclerosis and glomerular disease is well established in human beings.[3] Results of this study suggest that an association between naturally occurring atherosclerosis and glomerular disease also exists in dogs.

The association between atherosclerosis and glomerular disease in human beings is multifactorial and not fully understood.[3] Some of the well recognized risk factors for atherosclerosis in humans with glomerulopathy include hypercholesterolemia, hyperlipidemia, hypertension, increased platelet aggregation, and hypercoagulability.[3]

Mechanisms involved in the dyslipidemia of glomerular disease have been studied extensively.[5] The theory of decreased albumin synthesis in patients with glomerular disease[9,10] has not been substantiated,[11-13] and altered renal clearance of albumin has been suggested as a possible cause for the dyslipidemia observed with glomerular disease.[11,12] Studies that demonstrated an inverse relationship between oncotic pressure and albumin synthesis have also not been confirmed in vivo.[5,14] Several alterations in the metabolism of cholesterol have been documented in association with glomerular disease. These metabolic alterations include increased cholesterol synthesis, decreased cholesterol clearance, and decreased recycling of cholesterol.[4,15,16] Recently, dysregulation of cytokine production has also been implicated in the pathogenesis of hyperlipidemia and atherosclerosis.[17]

Results of this study suggest that dogs with atherosclerosis have more glomerulopathy and higher serum cholesterol concentration in comparison to other dogs. Nine of 11 dogs with atherosclerosis and glomerulopathy had hypercholesterolemia (6 dogs), lipemia (1 dog), or both hypercholesterolemia and lipemia (2 dogs). It is possible that among dogs with atherosclerosis, glomerulopathy contributes to an elevation in serum cholesterol concentration. Hypercholesterolemia has been previously described in dogs with naturally occurring glomerular disease,[18-20] but it is also observed in association with canine diabetes mellitus and HAC.[21,22] Several reports have suggested that dogs with diabetes mellitus or HAC may develop glomerular disease.[23-25] It is therefore possible that diabetes mellitus and HAC contribute to development of glomerulopathy in dogs with atherosclerosis. However, dogs with atherosclerosis had significantly more glomerulopathy even when comparing them to the endocrine control group. Similarly, serum cholesterol concentration was significantly higher in dogs with atherosclerosis when they were compared to dogs with an endocrinopathy.

Dogs with spontaneous glomerular disease have been shown to have characteristics, other than hypercholesterolemia, that may increase the risk of atherosclerosis. Specifically, dogs with spontaneous glomerular disease have been shown to have hypertension and decreased antithrombin III concentration.[20] It is possible that these factors also contributed to development of atherosclerosis in dogs included in this study. However, indirect blood pressure measurements were performed in too few of the dogs to allow for meaningful reporting, and antithrombin III concentration was not measured in any of the dogs included in the study.

Atherosclerosis and glomerular disease were diagnosed or excluded based on histopathology findings in all dogs included in the study. One of this study's limitations is that diagnoses are based on postmortem findings. However, histopathologic diagnosis was needed in order to ensure an accurate diagnosis of atherosclerosis and glomerulopathy and also in order to verify that dogs that had atherosclerosis were excluded from the control groups. Glomerular disease may be difficult to diagnose antemortem as many dogs with glomerular disease have no clinical signs, and have normal physical examinations and clinicopathologic findings.[6,20] Similarly, the gold standard for diagnosis of atherosclerosis is histopathology. It is possible that with increased awareness of canine atherosclerosis and recognition of risk factors associated with this condition, antemortem diagnosis and therapy will be practiced more commonly.

Rottweilers were observed significantly more commonly in the group of dogs with atherosclerosis and glomerulopathy compared to all 3 control groups combined. Rottweilers have also recently been shown to be at increased risk for myxedema coma.[26] It is possible that Rottweiler dogs are over-represented in the group of dogs with atherosclerosis because profound metabolic abnormalities (such as severe hypercholesterolemia) associated with a

hypothyroid crisis increase the risk of atherosclerosis. Other Rottweiler breed peculiarities may also be associated with increased risk for atherosclerosis. Miniature Schnauzers and Shetland Sheepdogs, which have been shown to be at increased risk for primary hyperlipidemia,[27,28] were not found to be at increased risk for atherosclerosis.

The clinical significance of these findings is not known. It is possible that knowledge of the association between atherosclerosis and glomerular disease will prompt clinical investigations directed at recognizing vascular disease in these patients. Such future diagnostic evaluations may lead to further understanding of the clinical significance of atherosclerosis in dogs with glomerular disease.

The results of this study suggest that dogs with atherosclerosis have significantly more glomerulopathy and significantly higher serum cholesterol concentrations compared with dogs with no evidence of atherosclerosis. These findings are true even when comparing dogs with atherosclerosis to dogs with endocrinopathies that increase the risk of hypercholesterolemia, indicating that there are factors other than diabetes mellitus and hypothyroidism that increase the risk for spontaneous atherosclerosis in dogs.

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