Breed distribution of dogs with diabetes mellitus admitted to a tertiary care facility

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Objective—To determine which dog breeds are at low and high risk for developing diabetes mellitus (DM).

Design—Cohort study.

Animals—Hospital population of 221 dogs with DM and 42,882 dogs without DM during 5.5 years.

Procedure—165 breeds (including a mixed-breed category) were represented in the hospital population. Breed-specific expected numbers of dogs with DM were calculated by multiplying the proportion of all dogs admitted to the hospital that were determined to have DM during the study period by the breed-specific totals during the study period. Breeds or breed groups evaluated in the analysis (n = 20) were restricted to those that had a combined observed and expected count > 5 to document breeds at low and high risk for developing DM. Proportionate changes in the risk of developing DM by breed were calculated and presented using exact odds ratios, 95% confidence intervals, and *P* values. Mixed-breed dogs were chosen as the reference breed.

Results—Samoyeds, Miniature Schnauzers, Miniature Poodles, Pugs, and Toy Poodles were at high risk for developing DM. Dog breeds found to be at low risk for developing DM were German Shepherd Dog, Golden Retriever, and American Pit Bull Terrier.

Conclusion and Clinical Relevance—The finding that certain dog breeds are at low or high risk for developing DM suggests that some genetic defects may predispose dogs to development of DM, whereas other genetic factors may protect dogs from development of DM. (*J Am Vet Med Assoc* 2000;216: 1414–1417)

The cause of insulin-dependent **diabetes mellitus (DM)** in people is multifactorial and includes environmental and genetic components.[1] The genetic component is not fully understood; however, it is known that a number of genes are involved in the pathogenesis of insulin-dependent DM in people.[1] The most important genes involved in insulin-dependent DM in people are **major histocompatibility complex (MHC)** genes that determine immune responsiveness and are located on chromosome 6.[1,2] One of the theories regarding the action of MHC genes is that in people at high risk for developing insulin-dependent DM, MHC genes favor positive selection for antipancreatic T cells, whereas in people at low risk for developing insulin-dependent DM there is selection for T cell nonresponsiveness to pancreatic cells.[3] Although there is evidence that DM in dogs is also an immune mediated disease,[4,5] involvement of MHC-like genes in dogs (ie, dog leukocyte antigens), has not been found.[a]

Additional genes involved in the pathogenesis of insulin-dependent DM in people have been identified but are probably less important than the MHC genes.[1] Some of these other genes vary among different ethnic, national, or geographically located groups of people.[6] This is probably the result of a small and unique genetic pool found in these groups of people compared with the human population at large. Similarly, it is possible that various purebred dogs may have distinct genes involved in the pathogenesis of DM. However, prior to investigating genetic particularities of dogs with DM, populations or breeds at low or high risk for developing DM must be identified.

The mode of inheritance of DM in dogs is also incompletely understood, and may vary in different breeds. Familial DM has been described in Keeshonds, Golden Retrievers, Miniature Poodles, and Samoyeds.[7-9,b,c] Results of pedigree analyses in Keeshonds indicate that the mode of inheritance of the particular form of DM observed in this breed is likely autosomal recessive.[8] The forms of DM described in Keeshonds and Golden Retrievers are unique in that most described Keeshonds were affected before 6 months of age and Golden Retrievers were affected by 8 weeks of age.[8,c] However, most other dogs with naturally occurring DM develop the disease when they are 7 years of age or older.[10]

The purpose of the study presented here was to identify dog breeds at low or high risk for developing DM. Identification of such dog breeds may focus pedigree analyses, foster the understanding of modes of inheritance, and help research genetic components of DM.

Materials and Methods

A computer search of all dogs admitted to the Veterinary Hospital of the University of Pennsylvania between January 1993 and May 1998 identified 295 dogs with an incident diagnosis of DM. Medical records were reviewed in detail by a board-certified internist (RSH). Upon review of medical records, 221 dogs with DM were included in the study. Inclusion criteria for these 221 dogs consisted of clinical signs suggestive of DM (observed in all 221 dogs) and persistent hyperglycemia with glucosuria (observed in 174 [79%] of these dogs), or persistent hyperglycemia in face of insulin treatment (observed in 47 [21%] dogs).

Seventy-four dogs identified as diabetic on the computer search were excluded from the study. Forty-three dogs had insufficient data for a diagnosis of DM, mostly a result of a single measurement of hyperglycemia and no urinalysis. Ten dogs were found to be nondiabetics that were erroneously coded as diabetic dogs. This happened mostly in dogs with dilated cardiomyopathy (coded as DCM) that were mistaken for dogs with DM (coded as DM). Six dogs were excluded because they developed DM while receiving glucocorti-

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coids.[11,12] Two dogs developed DM as a result of treatment for insulinoma. Two other dogs had transient DM, and insulin treatment was discontinued 3 weeks after ovariohysterectomy in 1 dog and 1 month later in another dog. The later dog was thought to have hyperadrenocorticism, although the diagnosis was never confirmed. An additional 11 records were not available for review.

Ultimately, the case series included 221 dogs with DM that were admitted to the hospital between January 1993 and May 1998. The comparison group consisted of all dogs without DM admitted to the hospital during the same period and amounted to 42,882 dogs.

Data analysis—One hundred sixty-five breeds (including a mixed-breed category) were represented in the hospital population during the period studied. Breed-specific expected numbers of dogs with DM were calculated by multiplying the proportion of all dogs admitted to the hospital that were found to have DM during the study period by the breed-specific totals during the study period. Breeds or breed groups evaluated in the analysis (n = 20) were restricted to those that had a sum of observed and expected counts > 5 dogs to ensure that there were sufficient numbers of dogs to document breeds at low and high risk for developing DM.

Proportionate changes in the risk of diabetes by breed, which quantify the measure of association, were calculated and presented using exact **odds ratios (OR)**, and 95% **confidence intervals (CI)**. Mixed dog breeds were chosen as the reference breed. Two-sided *P* values were calculated for the null hypothesis that breed-specific OR = 1.00.[d]

Results

Forty-eight dog breeds were identified among 221 dogs with DM. Of these 48 breeds, 16 breeds had a summed observed and expected count > 5 and were included in the analysis (**Table 1**). The following 32 breeds of diabetic dogs were not included in the analysis, because their combined observed and expected count was ≤ 5: Australian Terrier (2 dogs), Collie (2), Keeshond (2), Standard Poodle (2), West Highland White Terrier (2), Australian Sheep Dog (1), Basset Hound (1), Beagle (1), Bearded Collie (1), Bearded Terrier (1), Boston Terrier (1), Brittany Spaniel (1), Bullmastiff (1), Bull Terrier (1), Cairn Terrier (1), Chow Chow (1), Dalmatian (1), English Cocker Spaniel (1), Eskimo (1), German Setter (1), Siberian Husky (1), Jack Russell Terrier (1), Maltese (1), Miniature Dachshund (1), Pekingese (1), Pomeranian (1), Saluki (1), Scottish Terrier (1), Shetland Sheepdog (1), Toy Fox Terrier (1), Weimaraner (1), and Whippet (1).

The comparison group included 165 dog breeds and comprised all 48 diabetic breeds and an additional 117 dog breeds. Most of the 117 dog breeds had a summed observed and expected count that was ≤ to 5 and, therefore, were not included in the analysis. However, 3 breeds from the control group that were not represented among diabetic dogs were included in the analysis. The American Pit Bull Terriers, German Shepherd Dogs, and Golden Retrievers had an observed count of zero, but a summed observed and expected count > 5, because of their high expected count (Table 1).

Samoyeds (OR, 11.83; 95% CI, 5.50 to 23.26; $P < 0.001$), Miniature Schnauzers (OR, 9.87; 95% CI, 5.96 to 15.99; $P < 0.001$), Miniature Poodles (OR, 4.01; 95% CI, 2.14 to 7.10; $P < 0.001$), Pugs (OR, 3.87; 95% CI, 1.20 to 9.68; $P = 0.026$), and Toy Poodles (OR, 3.27; 95% CI, 1.42 to 6.70; $P = 0.007$) were found to be at high risk for developing DM (Table 1). Dog breeds at low risk for developing DM were German Shepherd Dogs (OR, 0; 95% CI, 0.00 to 0.31; $P < 0.001$), Golden Retrievers (OR, 0; 95% CI, 0.00 to 0.30; *P* value < 0.001), and American Pit Bull Terriers (OR, 0; 95% CI, 0.00 to 0.53; $P = 0.002$).

Discussion

Among breeds that had sufficient numbers of dogs to meet our sample size criteria for analysis, results of our study pointed to 5 dog breeds at high risk and 3 dog breeds at low risk for developing DM. The impor-

Table 1—Effect of dog breed on risk for diabetes mellitus

Breed	No. of affected dogs	No. of clinically normal dogs	Odds ratio	95% Confidence interval	*P* value
Samoyed	11	172	11.83	5.50–23.26	< 0.001
Miniature Schnauzer	27	506	9.87	5.96–15.99	< 0.001
Miniature Poodle	16	739	4.01	2.14–7.10	< 0.001
Pug	5	239	3.87	1.20–9.68	0.026
Toy Poodle	9	509	3.27	1.42–6.70	0.007
Lhasa Apso	6	492	2.26	0.79–5.25	0.13
Bichon Frise	4	349	2.12	0.56–5.78	0.26
Yorkshire Terrier	7	691	1.88	0.72–4.13	0.20
Chihuahua	4	497	1.49	0.39–4.05	0.62
English Springer Spaniel	3	418	1.33	0.27–4.11	0.83
Labrador Retriever	18	2,948	1.13	0.63–1.95	0.73
Dachshund	3	524	1.06	0.21–3.27	1.00
Mixed (reference)	58	10,753	1.00	NA	NA
Doberman Pinscher	3	877	0.63	0.13–1.95	0.63
Rottweiler	7	2,194	0.59	0.23–1.30	0.26
Cocker Spaniel	3	1,327	0.42	0.084–1.29	0.18
American Pit Bull Terrier	0	1,343	0.00	0.00–0.53	0.002
German Shepherd Dog	0	2,280	0.00	0.00–0.31	< 0.001
Golden Retriever	0	2,358	0.00	0.00–0.30	< 0.001
Other purebred dogs	37	13,666	NA	NA	NA

P values ≤ 0.05 were considered significant.
NA = Not applicable.

tance of ascertaining which dog breeds are at low or high risk for developing DM is 3-fold. Identification of such breeds may help focus investigations of pedigree analyses on breeds at high risk for developing DM. This may further the understanding of the mode of inheritance of DM in certain dog breeds. Additionally, studies of genetic alterations that may increase or decrease the risk for developing DM can be centered on breeds at low or high risk for developing the disease. Finally, breeds at low or high risk for developing DM may be studied in an attempt to identify concurrent conditions that increase the risk for developing DM or confer protection from developing DM.

Because of the importance of identifying breeds at low or high risk for developing DM, several groups of researchers have investigated breed predisposition to DM in dogs in the past. One study from the United States and Canada analyzed data from 15 veterinary hospitals and found Poodles to be at high risk for developing DM. German Shepherd Dogs, Cocker Spaniels, Collies, and Boxers were at low risk for developing DM.[13] Results of a study in California revealed that Dachshunds and Poodles are dog breeds at high risk for developing DM,[10] and results of another study from Scotland indicate that crossbreed Terriers, Miniature and Toy Poodles, and Cairn Terriers are dog breeds at high risk for developing DM.[14] Others report that Pulik and Miniature Pinchers are also at high risk for developing DM, while Pekingese and Rottweilers are added to the list of breeds at low risk for developing DM.[15]

One of the reasons for differences in the results of these studies may be inbreeding of purebred dogs in certain areas. Although purebred dogs are generally considered inbred, further inbreeding of certain dog breeds within geographic locations may result in high breed susceptibility in that area but not in another. Another reason for a difference may be that in our study, medical records were reviewed in detail, and dogs with an erroneous or inappropriate diagnosis were excluded from the study. This resulted in the exclusion of 74 (25%) dogs that a computer search identified as diabetic. In one of the other studies,[13] an internal medicine specialist did not review the medical records, and results of a computer search were relied on for inclusion of most affected dogs. Therefore, dogs that did not actually have DM may have been classified as diabetic in that study.[13] A third reason for differences in results is that other studies were performed 14 to 22 years ago,[10,14] and breed susceptibility to DM in dogs may have changed over time. Finally, it is possible that studies analyzing populations of dogs admitted to tertiary care facilities do not adequately reflect the population of diabetic dogs at large and, therefore, have differing results.

In our study, Samoyeds were found to be approximately 12 times more likely to develop DM than mixed dog breeds. Recently, familial DM has been described in Samoyeds[b]; however, familial DM is not necessarily associated with high risk for the breed at large. For example, the results of our study suggest that Golden Retrievers are at low risk for developing DM, however, familial DM has been described in this breed.[c] Therefore, the finding of high risk for developing DM in the Samoyed breed at large is separate from that of familial DM in Samoyeds. Samoyeds and Keeshonds are thought to be dog breeds that are related to one another.[16] Keeshonds have been characterized as having an early onset form of DM that is transmitted by an autosomal recessive mode of inheritance.[8] However, the Samoyeds in our study developed DM between 4 and 10 years of age, with a mean age of onset of 7 ± 2 years and a median of 7 years. Therefore, the form of DM observed in the Samoyeds in our study appeared to differ from that described in Keeshonds, and the importance of these 2 related breeds being affected by DM is not known.

Miniature Poodles and Toy Poodles were found to be at high risk for developing DM in our study. Other studies[10,13,14] analyzed these 2 types of Poodles in a single group, some of which also included Standard Poodles in their group of Poodles.[10,13] Although Standard, Miniature, and Toy Poodles are considered part of the same Poodle breed, the results of our study suggest that Standard Poodles are not at high risk for developing DM, whereas Miniature and Toy Poodles are at high risk, even when analyzed separately. It is possible that selective breeding of these 3 types of Poodles has protected Standard Poodles from DM, while increasing the risk for developing DM in Miniature and Toy Poodles.

One of our study's limitations was that breeds at low risk for developing DM may have been missed as a result of the small sample size of infrequently owned dogs. Another limitation of our study was that dogs with DM were not definitively determined to have insulin-dependent DM. It is accepted that most, if not all, dogs with DM have insulin-dependent DM.[15] Therefore, it is likely that most of the dogs in our study had insulin-dependent DM. However, because of the nature of our study (ie, review of medical records), it was not possible to confirm the diagnosis of insulin-dependent DM in these dogs. Additionally, DM may never be identified in affected dogs that are not brought to a veterinarian. These diabetic dogs were also not included in the study.

Our study was further limited because the study population was that of a tertiary care facility and may not accurately reflect the population of diabetic dogs at large. The population of dogs admitted to a tertiary care facility may be affected by availability of veterinary endocrinologists in such a facility, cost, perceptions of dog breeders or owners about the benefit of taking a dog to a tertiary care facility, and other factors.

The purpose of our study was to identify dogs at low or high risk for developing DM. Results of other studies of genes that may be associated with DM in dogs were not successful at identifying genetic alterations associated with the disease.[a] However, these studies involved a variety of dog breeds with and without DM, and did not focus on specific dog breeds at low or high risk for developing DM. Additionally, further sequencing of the dog genome in general and the dog leukocyte antigen region in particular has been accomplished since these original studies were performed.[17,18] Therefore, it is possible that by using the

information that has now become available, there will be greater success in genetic studies of DM in dogs. Another reason genetic studies of dogs with and without DM hold promise is that the genetic pool of purebred dogs may be smaller than that of humans. One of the difficulties in genetic studies of insulin-dependent DM in people is genetic heterogeneity.[6] It is possible that the genome of purebred dogs is less heterogeneous than that of people and may allow for a more focused investigation of genetic mutations associated with DM.

[a]Gerlach J, Bull RW. Evaluation of amplified DNA from IDDM dogs with epitope specific oligonucleotide probes (abstr). *J Vet Intern Med* 1989;3:121.

[b]Kimmel S, Ward C, Henthorn P, et al. Familial insulin-dependent diabetes mellitus in Samoyed dogs (abstr), in *Proceedings*. 17th Ann Vet Med Forum 1999;736:177.

[c]Williams M, Gregory R, Schall W, et al. Diabetes mellitus in a colony of golden retrievers (abstr), in *Proceedings*. Federation Proceedings, 1980;39:637.

[d]EGRET, CYTEL Software Corp, Cambridge, Mass.

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