Reliability of history and physical examination findings for assessing control of glycemia in dogs with diabetes mellitus: 53 cases (1995–1998)

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Objective—To evaluate the reliability of history and physical examination findings for assessing control of glycemia in insulin-treated diabetic dogs.

Design—Retrospective study.

Animals—53 insulin-treated dogs with diabetes mellitus.

Procedure—Medical records of insulin-treated diabetic dogs from June 1995 to June 1998 were reviewed, and information on owner perception of their dog's response to insulin treatment, physical examination findings, body weight, insulin dosage, and concentrations of food-withheld (ie, fasting) blood glucose (FBG), mean blood glucose (MBG) during an 8-hour period, blood glycosylated hemoglobin (GHb), and serum fructosamine was obtained. Owner's perception of their dog's response to insulin treatment, physical examination findings, and changes in body weight were used to classify control of glycemia as good or poor for each dog. The FBG, MBG/8 h, blood GHb, and serum fructosamine concentrations were compared between well-controlled and poorly controlled insulin-treated diabetic dogs.

Results—Presence or absence of polyuria, polydipsia, polyphagia, lethargy, and weakness were most helpful in classifying control of glycemia. Mean FBG and MBG/8 h concentrations, blood GHb concentrations, and serum fructosamine concentrations were significantly decreased in 25 well-controlled diabetic dogs, compared with 28 poorly controlled diabetic dogs. Most well-controlled diabetic dogs had concentrations of FBG between 100 and 300 mg/dl, MBG/8 h ≤ 250 mg/dl, blood GHb ≤ 7.5%, and serum fructosamine ≤ 525 μmol/L, whereas most poorly controlled diabetic dogs had results that were greater than these values.

Conclusions and Clinical Relevance—Reliance on history, physical examination findings, and changes in body weight are effective for initially assessing control of glycemia in insulin-treated diabetic dogs. (*J Am Vet Med Assoc* 2000;217:48–53)

Insulin-dependent diabetes mellitus (IDDM) is the most common type of diabetes identified in dogs.[1,2] Insulin treatment is required to maintain glycemic control of IDDM. Goals of insulin treatment include resolution of owner-observed clinical signs that result from hyperglycemia and glycosuria and avoidance of acute and chronic complications associated with diabetes mellitus and its treatment.[1,2] These goals are usually attained when the blood glucose concentration is kept between 100 and 250 mg/dl.[1-3] Hospitalization to determine serial blood glucose concentrations has become a routine part of the evaluation of control of glycemia in diabetic dogs, and changes in the insulin treatment regimen are often made on the basis of blood glucose results independent of the history and physical examination findings. Unfortunately, results of serial blood glucose concentrations are affected by many variables including stress, inappetence, variability in the quantity of insulin administered and absorbed from injection sites, and insulin antagonism caused by diabetogenic hormones.[1-4] Inaccurate blood glucose concentration results can lead to inappropriate adjustments in insulin treatment and development or perpetuation of poor control of glycemia.

Measurement of blood glycated proteins (ie, serum fructosamine, **glycosylated hemoglobin [GHb]**) concentration are not affected by some variables that affect determination of serial blood glucose concentrations and have been recommended in conjunction with serial blood glucose concentrations for assessing control of glycemia in diabetic dogs.[5-9] Serum fructosamine and blood GHb concentrations may be measured during routine evaluation of glycemic control or several weeks after changing the insulin treatment regimen to evaluate the effect of the change on control of glycemia.[5,7]

Intuitively, emphasis should be placed on owner perception of response to treatment, physical examination findings, and changes in body weight when initially assessing control of glycemia in diabetic dogs.[1,2,10] Most diabetic dogs that do not have clinical signs caused by hyperglycemia or hypoglycemia have a stable body weight, and no abnormalities detected on physical examination, as they pertain to complications of diabetes, should have a blood glucose concentration between 100 and 250 mg/dl, and a change in insulin treatment regimen is presumably not indicated. Hospitalization of these dogs for determination of serial blood glucose concentrations may not be warranted. In contrast, it is presumed that most diabetic dogs have a blood glucose concentration > 250 mg/dl if the owner reports clinical signs of hyperglycemia, an unplanned weight loss has been observed, or abnormalities suggesting poor control of glycemia are identified on physical examination. Hospitalization for determination of serial blood glucose concentrations is warranted in these dogs.

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To our knowledge, there is little information on the reliability of owner perception of effectiveness of insulin treatment and physical examination findings for assessing control of glycemia during routine evaluation of diabetic dogs. The purpose of the study reported here was to compare concentrations of food-withheld (ie, **fasting**) **blood glucose (FBG)**, **mean blood glucose (MBG)** during an 8-hour period, blood GHb, and serum fructosamine in well-controlled versus poorly controlled insulin-treated diabetic dogs when control of glycemia was determined by owner perception of response to treatment and physical examination findings obtained at the time dogs were admitted to the veterinary hospital for routine evaluation of control of glycemia.

Criteria for Selection of Cases

Medical records from all dogs evaluated for diabetes mellitus between June 1995 and June 1998 at the Veterinary Medical Teaching Hospital at the University of California, Davis were reviewed. Dogs were included in the study on the basis of the following 5 criteria: 1) the dog was an insulin-treated diabetic admitted to the hospital for evaluation of control of glycemia, 2) the medical record contained a complete history, physical examination findings, and body weight 4 to 8 weeks prior to and at the time of admission, 3) concentrations of serum fructosamine, blood GHb, and FBG had been measured, 4) blood glucose concentration had been measured every 2 hours for 8 hours after administration of insulin, and 5) the dog had a hematocrit between 35 and 50%, serum albumin concentration between 2.5 and 4.0 g/dl, and total serum bilirubin concentration < 0.3 mg/dl on the day control of glycemia was evaluated.[11-13]

Procedures

Data collected from the medical records included owner perception of their dog's response to insulin treatment, physical examination findings, body weight, results of urinalysis, and concentrations of FBG, MBG/8 h, blood GHb, and serum fructosamine. The FBG was measured in the morning before feeding or administration of insulin. The MBG/8 h was determined by measuring blood glucose concentrations every 2 hours for an 8-hour period after feeding and administration of insulin.

Classification of control of glycemia—Owner perception of their dog's response to insulin treatment, findings on physical examination, and changes in body weight were used to classify control of glycemia as good or poor for each diabetic dog. Good control of glycemia was defined by owner-perceived normal behavior of their dog in terms of intake of water, frequency of urination, activity level, stable body weight, and lack of physical examination abnormalities suggestive of poor control of glycemia. Poor control of glycemia was defined by owner-perceived abnormal behavior in terms of persistent polyuria, polydipsia, polyphagia, and low activity level. Identification of recently acquired abnormalities on physical examination (eg, thin, and dry flaky skin, poor coat, muscle wasting) and loss of body weight were considered further evidence for poor control of glycemia.[1,2]

Analytical methods—Serum glucose concentration was determined by use of the glucose oxidase method.[a] Mean (± SD) serum glucose concentration measured from blood samples obtained randomly and independent of the preprandial state in 40 healthy dogs was 104 ± 10 mg/dl. Using the mean serum glucose concentration ± 2 SD, the reference range for serum glucose concentration in healthy dogs was 84 to 124 mg/dl. Blood GHb concentration was determined using affinity chromatography.[5,b] Mean (± SD) blood GHb concentration previously described for 63 healthy dogs was 3.3 ± 0.8%.[5] Using the mean blood GHb concentration ± 2 SD, the reference range for blood GHb concentration was 1.7 to 4.9%. Serum fructosamine concentration was determined using the nitroblue tetrazolium reduction method.[7-9,c] Mean (± SD) serum fructosamine concentration in 40 healthy dogs was 293 ± 35 µmol/L. Using the mean serum fructosamine concentration ± 2 SD, the reference range for serum fructosamine in healthy dogs was 223 to 363 µmol/L.

Data analysis—Statistical analysis of data was performed using a nonparametric Mann-Whitney comparison test. Statistical analysis was performed with statistical software.[d] A value of $P < 0.05$ was considered significant. All data are expressed as mean ± SD.

Results

Fifty-three diabetic dogs met the criteria for inclusion in our study. Control of glycemia was classified as good and poor in 25 and 28 of 53 diabetic dogs, respectively, on the basis of history, physical examination findings, and changes in body weight. Abnormalities identified from the history and on physical examination of diabetic dogs with good control of glycemia included cataracts (15 dogs), hepatomegaly (7), obesity (4), and seborrhea (1), and for diabetic dogs with poor control of glycemia included persistent polyuria/polydipsia (27), cataracts (18), weight loss (18), hepatomegaly (16), polyphagia (7), lethargy (5), muscle wasting (4), weakness (3), alopecia (3), and seborrhea, pyoderma, hyperkeratosis, panting, obesity, and keratoconjunctivitis sicca (1 each). Of the well-controlled diabetic dogs, body weight had increased 1% in 2 dogs and remained the same in 23 dogs, compared with body weight at the previous hospital visit. Of the poorly controlled diabetic dogs, body weight had decreased 2 to 13% (median, 5%) in 18 dogs and remained the same in 10 dogs, compared with body weight at the previous hospital visit. Urine collected by free catch had positive results for ketonuria in none of 17 well-controlled diabetic dogs and 9 of 22 poorly controlled diabetic dogs.

Sixteen of 31, 8 of 18, and 1 of 4 diabetic dogs treated twice each day with recombinant human insulin zinc suspension (lente preparation),[e] isophane insulin suspension (NPH preparation),[f] and extended insulin zinc suspension (ultralente),[g] respectively, were classified as well controlled; the remaining dogs were classified as poorly controlled. Mean daily insulin dosage and concentrations of FBG, MBG/8 h, blood

Table 1—Insulin dosages and laboratory values for 25 well-controlled diabetic dogs and 28 poorly controlled diabetic dogs

	Well-controlled diabetic dogs*			Poorly controlled diabetic dogs*		
Variable	**Mean ± SD**	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**
Insulin (U/kg/24 h)†	1.3 ± 0.6‡	1.2	0.5–2.5	1.9 ± 0.9	1.7	0.7–3.6
FBG (mg/dl)	234 ± 101§	246	42–462	362 ± 130	406	33–500
MBG/8 h (mg/dl)	207 ± 68‖	212	100–340	305 ± 89	295	119–490
GHb (%)	6.3 ± 1.5§	6.6	2.7–8.9	8.0 ± 1.5	7.9	5.2–10.5
Fructosamine (μmol/L)	460 ± 93‡	470	250–651	547 ± 97	544	337–763

*Dogs were classified as well-controlled or poorly controlled on the basis of history, physical examination findings, and changes in body weight. †Per kilogram of body weight (to convert dosage in kilograms to dosage in pounds, divide the dose by 2.2). ‡$P < 0.05$, compared with equivalent variable in poorly controlled diabetic dogs. §$P < 0.01$, compared with equivalent variable in poorly controlled diabetic dogs. ‖$P < 0.005$, compared with equivalent variable in poorly controlled diabetic dogs.

FBG = Food-withheld (ie, fasting) blood glucose concentration. MBG/8 h = Mean blood glucose concentration during an 8-hour period. GHb = Concentration of glycosylated hemoglobin in blood.

GHb, and serum fructosamine were significantly lower in well-controlled diabetic dogs, compared with poorly controlled diabetic dogs (**Table 1**). Median daily insulin dosage and concentrations of FBG, MBG/8 h, blood GHb, and serum fructosamine were also lower in well-controlled diabetic dogs versus poorly controlled diabetic dogs. Despite significant differences in mean daily insulin dosage and concentrations of FBG, MBG/8 h, blood GHb, and serum fructosamine, individual results overlapped when well-controlled diabetic dogs were compared with poorly controlled diabetic dogs (**Fig 1 and 2**). There was no single value for concentrations of FBG, MBG/8 h, blood GHb, or serum fructosamine that consistently differentiated diabetic dogs with good versus poor control of glycemia. Eighty and 84% of 25 well-controlled diabetic dogs had concentrations of FBG between 100 and 300 mg/dl and MBG/8 h ≤ 250 mg/dl, respectively, whereas 79 and 86% of 28 poorly controlled diabetic dogs had concentrations of FBG > 300 mg/dl and MBG/8 h > 250 mg/dl, respectively. There was more overlap in concentrations of blood GHb and serum fructosamine than in concentrations of FBG and MBG/8h between well-controlled versus poorly controlled diabetic dogs. Eighty and 76% of 25 well-controlled diabetic dogs had concentrations of blood GHb ≤ 7.5% and serum fructosamine ≤ 525 μmol/L, respectively, whereas 61 and 64% of 28 poorly controlled diabetic dogs had concentrations of GHb > 7.5% and serum fructosamine > 525 μmol/L, respectively.

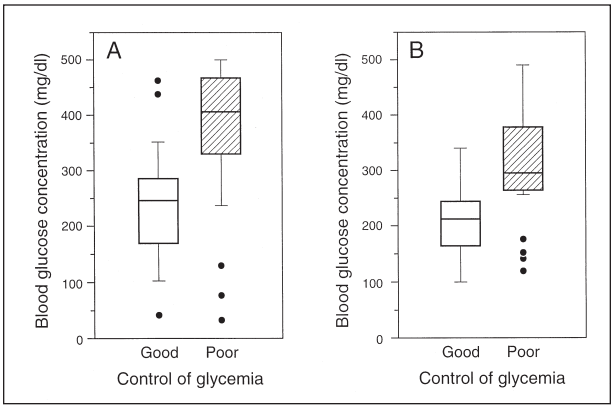

Figure 1—Box plots of food-withheld (ie, fasting) blood glucose (Part A, FBG) and mean of blood glucose (MBG) concentrations measured every 2 hours during an 8-hour period (Part B, MBG/8 h) in 25 well-controlled diabetic dogs and 28 poorly controlled insulin-treated diabetic dogs. Control of glycemia was classified as good or poor on the basis of history, physical examination findings, and changes in body weight. The box represents the interquartile range from the 25th to the 75th percentiles (ie, middle half of data). The horizontal bar within the box is the median value. Whiskers represent the main body of data with the outlying data points represented by circles.

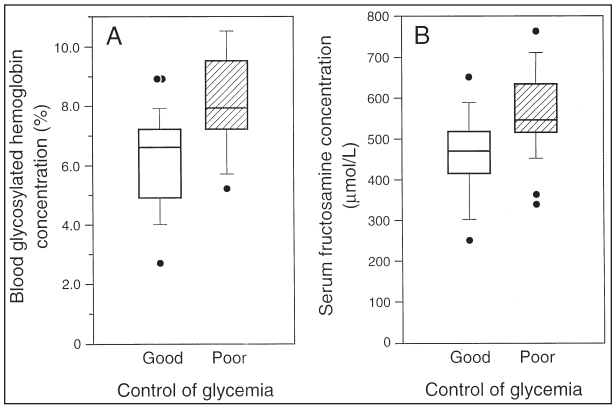

Figure 2—Box plots of concentration of glycosylated hemoglobin in blood (Part A) and serum fructosamine concentration (Part B) in 25 well-controlled and 28 poorly controlled insulin-treated diabetic dogs. Control of glycemia was classified as good or poor on the basis of history, physical examination findings, and changes in body weight. Data plotted as described in Figure 1.

All blood glucose and glycated protein concentrations were consistent with good control of glycemia in 15 of 25 (60%) well-controlled diabetic dogs when the definition of good and poor control of glycemia for these blood variables was made on the basis of blood glucose and glycated protein concentrations. For the remaining 10 well-controlled diabetic dogs, FBG and MBG/8 h concentrations and 1 or both glycated protein concentrations indicated poor control of glycemia in 3 dogs, hypoglycemia (FBG, 42 mg/dl) in 1 dog, and results of either MBG/8 h concentration (1 dog; 299 mg/dl), blood GHb concentration (2 dogs; both 8.9%), serum fructosamine concentration (2 dogs; 540 and 588 μmol/L), or FBG and serum fructosamine concentrations (1 dog; 352 mg/dl and 538 μmol/L, respectively) indicated poor control of glycemia in 6 dogs. In contrast, all blood glucose and glycated protein concentrations were consistent with poor control of glycemia in only 11 of 28 (39%) poorly controlled diabetic dogs. The FBG and MBG/8 h concentrations and

both glycated protein concentrations indicated good control of glycemia in 2 dogs, and hypoglycemia was identified in 2 poorly controlled diabetic dogs (FBG, 33 and 77 mg/dl). The FBG and MBG/8 h concentrations indicated poor control of glycemia, but results of blood GHb concentration (4 dogs), serum fructosamine concentration (2), or both (4) indicated good control of glycemia in 10 poorly controlled diabetic dogs. The FBG concentration (2 dogs; 130 and 251 mg/dl) or FBG and serum fructosamine concentrations (1 dog; 269 mg/dl and 514 µmol/L, respectively) indicated good control of glycemia in the remaining 3 poorly controlled diabetic dogs.

Discussion

Classifying control of glycemia as good or poor on the basis of owner perception of their diabetic dog's response to insulin treatment, findings on physical examination, and changes in body weight was reliable for most diabetic dogs evaluated in our study. Diabetic dogs that had a stable body weight and lacked clinical signs and physical examination findings suggesting poor control of glycemia had significantly lower blood glucose and glycated protein concentrations, compared with diabetic dogs that lost weight and had clinical signs and physical examination findings suggesting poor control of glycemia. Presence or absence of polyuria, polydipsia, polyphagia, lethargy, and weakness were most helpful in classifying control of glycemia. Presence of unplanned weight loss and ketonuria supported poor control of glycemia, but absence of weight loss and ketonuria did not rule out poor control. Ten of 28 (36%) poorly controlled diabetic dogs did not have weight loss at the time of examination. Presence of polyuria, polydipsia, polyphagia, lethargy, and weakness is dependent on the severity and persistence of hyperglycemia and develops within hours to days after the onset of hyperglycemia. In contrast, weight loss is dependent, in part, on severity and persistence of hyperglycemia, changes in caloric intake, and the reason for poor control of glycemia, and may not be identified for several weeks after the onset of other clinical indicators of poor control of glycemia.

Ketonuria was identified less commonly than weight loss in poorly controlled diabetic dogs. Ketonemia and ketonuria result from insulin deficiency-induced excess of circulating free fatty acids and diabetogenic hormone-induced acceleration of hepatic ketone production,[14-16] the later developing as a result of concurrent disease.[1,2] Insulin treatment is often effective in preventing excess free fatty acids in blood, thereby minimizing ketone production by the liver and preventing ketonuria in most poorly controlled diabetic dogs, especially if concurrent disease is absent. However, ketonuria is an important marker of poor control of the diabetogenic state and, when identified, indicates an immediate need for change in insulin treatment and evaluation for concurrent diseases that may be promoting ketone production.[1,2]

Presence of hepatomegaly and cataracts were not useful indicators of poor control of glycemia in our diabetic dogs. Hepatomegaly was identified in 28 and 57% and cataracts in 60 and 64% of well-controlled and poorly controlled diabetic dogs, respectively. Although development of cataracts and hepatomegaly suggests sustained hyperglycemia for a period, their presence may not reflect current status of glycemic control.[1,2] Daily insulin dosage was also not helpful by itself in classifying control of glycemia. Although mean daily insulin dosage was significantly lower in well-controlled diabetic dogs, compared with poorly controlled diabetic dogs, there was a large overlap in the range of insulin dosages between the 2 groups of dogs, especially at the low end of the insulin dosage range. Diabetic dogs with poor control of glycemia were grouped together regardless of the cause for poor control and included some diabetic dogs with an insulin dosage that was simply too low to attain control of glycemia. Eighty-four percent of well-controlled dogs had daily insulin dosage < 2 U/kg of body weight (0.9 U/lb/24 h)/24 h, whereas 36% of poorly controlled diabetic dogs had daily insulin dosage > 2 U/kg/24 h, suggesting that presence of a high daily insulin dosage, especially when other indicators of poor control of glycemia are present, supports performing additional diagnostics to verify poor control and determine the underlying problem.

Additional diagnostic tests to determine cause of poor control of glycemia are warranted in diabetic dogs classified as poorly controlled on the basis of the history, physical examination, and change in body weight. Measuring the blood glucose concentration at the time of the morning insulin injection may identify hypoglycemia and suggests the Somogyi phenomenon as the cause for poor glycemic control in some diabetic dogs.[1,2,4] Morning hypoglycemia was identified in 2 dogs and FBG of 130 mg/dl was identified in 1 poorly controlled diabetic dog, findings that are initially treated by decreasing the dosage of insulin and reevaluating the dog 7 to 14 days later. Hospitalization of the poorly controlled diabetic dog for determination of serial blood glucose concentrations is indicated if FBG is high (ie, > 300 mg/dl).[1-3]

Additional diagnostic tests to assess control of glycemia may not be warranted in dogs classified as well-controlled diabetics on the basis of evaluation of the history, physical examination, and change in body weight. All blood glucose and glycated protein concentrations were consistent with good control of glycemia in 60% of well-controlled diabetic dogs when the definition of good and poor control of glycemia for these blood variables was made on the basis of blood glucose and glycated protein concentrations identified in our study. Documenting a blood glucose concentration at the time of the morning insulin injection between 100 and 300 mg/dl further supports good control of glycemia, whereas documenting hypoglycemia indicates a need to decrease the insulin dosage. Determination of blood glycated protein concentration or hospitalization for serial blood glucose concentrations may be indicated when FBG concentration is > 300 mg/dl or < 100 mg/dl in well-controlled diabetic dogs. Hospitalization for serial blood glucose concentrations may also be warranted in well-controlled diabetic dogs with FBG between 100 and 125 mg/dl to

ensure that asymptomatic hypoglycemia is not developing during the day. Interestingly, 4 well-controlled diabetic dogs with FBG between 100 and 125 mg/dl did not develop hypoglycemia during the 8-hour period after morning insulin administration.

Blood glycated protein concentrations did not correspond with status of glycemic control as well as blood glucose concentrations did. Thirty-six percent of poorly controlled diabetic dogs with high FBG and MBG/8 h concentrations had 1 or both glycated protein concentrations in the range consistent with good control of glycemia when blood GHb and serum fructosamine concentrations of 7.5% and 525 µmol/L, respectively, were used to differentiate good from poor control of glycemia. A similar problem was identified in well-controlled diabetic dogs, where 20% of dogs with acceptable FBG and MBG/8 h concentrations had blood GHb or serum fructosamine concentrations in the range consistent with poor control of glycemia. Serum fructosamine and blood GHb concentrations reflect the mean blood glucose concentration during the prior 1 to 3 and 6 to 12 weeks, respectively.[5,7,9] As a consequence, there is a delay between change in control of glycemia and change in blood glycated protein concentrations. Recent improvement in glycemic control should be suspected when the history and physical examination suggest good control of glycemia, but blood glycated protein concentrations are in a range consistent with poor control and vice versa.

Evaluation of sequential blood glycated protein concentrations is probably more valuable than interpretation of a single concentration, especially when blood glycated protein concentrations are used to evaluate the effect of changing insulin treatment or treating concurrent disease.[5,7] Results of blood glycated protein concentrations obtained at the time of routine evaluation of diabetic dogs may raise suspicion for persistent hypoglycemia (if the glycated protein concentration is in the lower half of or less than the reference range) or problems with owner observations (if blood glycated protein and glucose concentrations do not support the owner's perception of response to insulin treatment). All blood glucose and glycated protein concentrations indicated poor and good control of glycemia in 3 well-controlled diabetic dogs and 2 poorly controlled diabetic dogs, respectively. Presumably, owners of the 3 well-controlled diabetic dogs did not recognize clinical signs of poor control, and there were no physical examination findings that strongly supported poor control of glycemia. Although blood glucose concentrations were suggestive of poor control of glycemia, results may be spuriously high because of stress- or fear-induced hyperglycemia. Documenting high blood glycated protein concentrations in these dogs verified results of blood glucose concentrations, because results of blood glycated protein concentrations are not affected by stress-induced hyperglycemia.[5,7,8] Similar arguments for measuring blood glycated protein concentrations can be used when owners continue to report persistence of clinical signs despite lack of other indicators of poor control.

Most well-controlled diabetic dogs in our study did not have blood GHb and serum fructosamine concentrations within reference range; only 16% of blood GHb and 20% of serum fructosamine concentrations were in the reference interval in well-controlled diabetic dogs. The reference interval for glycated protein concentrations was established in healthy dogs that had blood glucose concentration presumably between 85 and 125 mg/dl for most of each day, a range that is difficult to maintain in insulin-treated diabetic dogs. For most diabetic dogs, good control of glycemia is achieved when the blood glucose concentration remains less than the renal tubular threshold for spillage of glucose (ie, < 180 to 220 mg/dl) for most of the day.[1,2] As a consequence, blood glycated protein concentrations are higher than the reference interval in most well-controlled diabetic dogs. Results of our study support the concept that good control of glycemia can be attained in most dogs despite blood glycated protein concentrations greater than the reference interval.

In summary, results of our study suggest that reliance on history, physical examination, and change in body weight is effective for initially assessing control of glycemia in diabetic dogs. Measurement of pretreatment blood glucose concentration and hospitalization for serial blood glucose concentrations are warranted in diabetic dogs with poor control of glycemia on the basis of results of the history, physical examination, and change in body weight. However, hospitalization for determination of serial blood glucose concentrations may not be warranted if glycemic control is determined to be good, especially if the blood glucose concentration measured prior to the morning insulin injection is between 100 and 300 mg/dl. Blood glycated protein concentrations often support results of the history, physical examination, and blood glucose concentrations, but discordant blood glycated protein results are common, presumably because of the delay between change in control of glycemia and change in blood glycated protein concentration.

[a]Beckman Glucose Analyzer 2, Beckman Instruments Inc, Fullerton, Calif.
[b]Glyc-Affin GHb, Isolab Inc, Akron, Ohio.
[c]Hitachi 705 adapted test kit, Boehringer Mannheim, Mannheim, Germany.
[d]Minitab Statistical Software, version 12, Minitab Inc, State College, Pa.
[e]Lente human insulin, Humulin-L, Eli Lilly Co, Indianapolis, Ind.
[f]NPH human insulin, Humulin-N, Eli Lilly Co, Indianapolis, Ind.
[g]Ultralente human insulin, Humulin-U, Eli Lilly Co, Indianapolis, Ind.

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