

Evaluation of serum microRNA-375 concentration in dogs with diabetes mellitus: A pilot study

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Abstract

Serum microRNAs (miRNAs) serve as diagnostic and prognostic biomarkers for various diseases. The serum concentration of miRNA-375 (miR-375), which is abundantly expressed in pancreatic islet cells, is increased in dogs with experimentally induced pancreatic injury and naturally occurring acute pancreatitis. However, this has not been reported in dogs with diabetes mellitus (DM). This study aimed to compare the expression of serum cfa-miR-375 between dogs with DM and healthy dogs and examine changes in serum cfa-miR-375 levels after insulin administration in dogs with DM. Twenty dogs with DM and 18 healthy dogs were included. The relative expression of serum cfa-miR-375 using reverse transcription and real-time PCR were evaluated. The primary endpoint was the comparison of serum cfa-miR-375 expression between dogs with DM and healthy dogs. The mean $\pm$ standard deviation (SD) fold change (FC) of serum cfa-miR-375 was significantly higher ($P = 0.048$) in dogs with DM (2.30 ± 2.018) than in healthy dogs (1.294 ± 0.560). The FC of serum miR-375 was significantly increased ($P = 0.01$) after treatment (4.017 ± 2.054) than before treatment (2.322 ± 2.608) in dogs with DM. The percentage change in cfa-miR-375 levels was positively correlated with the concentration of serum fructosamine post-treatment ($r = 0.62$, $P = 0.01$). Increased serum miR-375 levels may be associated with direct leakage from the damaged pancreas and pathological glucose regulation in canine DM.

Keywords: canine, diabetes mellitus, glucotoxicity, microRNA, serum biomarker

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Introduction

Diabetes mellitus (DM) is a common endocrine disease in dogs whose treatment demands committed efforts by veterinarians and clients. The clinical diagnosis of DM is generally based on clinical signs, blood glucose concentration, and the presence of glucosuria. However, dogs in the early stages of subclinical DM appear normal, have a constant weight, and usually present normal laboratory evaluation (Behrend *et al.*, 2018). Therefore, an accurate and reliable blood biomarker for the diagnosis of and treatment response to DM in dogs is needed, especially in the early stages of subclinical DM.

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by binding to mRNAs (Bartel, 2009). miRNA expression is tissue-specific, and miRNAs can be released into body fluids when the tissue is injured (Condrat *et al.*, 2020). Additionally, miRNAs are stable in serum, making them potential biomarkers for the detection and monitoring of conditions such as cancer, viral infections, and inflammation (Wang *et al.*, 2016). MiR-375 is highly expressed in the canine pancreatic islets of Langerhans (Koenig *et al.*, 2016). The expression of serum miR-375 increases significantly in response to pancreatic damage in dogs treated with cerulein (Rouse *et al.*, 2017). Additionally, massive beta-cell loss elicited by the administration of streptozotocin in C57BL/6 mice causes a dramatic increase in circulating levels of miR-375 (Erner *et al.*, 2013). Furthermore, the serum expression of miR-375 could be associated with inflammatory processes in dogs with acute pancreatitis (AP) (Lee *et al.*, 2023). Because AP and DM frequently occur concurrently in dogs, it is necessary to establish the relationship between serum miR-375 and DM to utilize it as a biomarker for AP. However, to our knowledge, no study has evaluated the serum expression levels of miR-375 in dogs with naturally occurring DM or in experimental DM models.

Therefore, the primary objective of this study was to compare the expression of miR-375 in the serum of dogs with DM and healthy dogs and examine changes in serum miR-375 concentration after insulin administration in dogs with DM.

Materials and Methods

Study group: This cross-sectional study included 20 client-owned dogs with DM and 18 client-owned healthy dogs. The dogs used in this study visited our institution between May 2017 and March 2023. This study was approved by the University Ethics Committee (CBNUA-2232-24-03). DM was diagnosed if the dogs presented with (a) consistent pre-prandial hyperglycemia (>180 mg/dL), (b) glucosuria, and (c) at least two of the following clinical signs: polyuria, polydipsia, polyphagia, and weight loss (Behrend *et al.*, 2018). This study excluded dogs that had clinical signs of AP, increased specific canine pancreatic lipase (IDEXX Reference Laboratory Inc., Westbrook, Maine, USA) (Reference interval, 0–200 µg/L), and ultrasonographic evidence of AP (Hammes and Kook, 2022). For the healthy control group, client-owned clinically healthy dogs that visited the institution for routine health examination were included in the study

based on unremarkable findings in physical examinations, complete blood count, serum biochemistry profiles, specific canine pancreatic lipase levels, C-reactive protein levels, urinalysis, survey radiography, and abdominal ultrasonography.

Pre-treatment assessment: The expression of selected serum miRNAs after insulin treatment (n = 17) was compared with that before insulin treatment in dogs with DM. The post-treatment period was defined as the time following insulin administration, characterized by the improvement of clinical signs consistent with DM based on the clinical parameters, including body weight stability, results of physical examinations, and assessments of glycemic control as considering the owner's observations, and stabilization of serum fructosamine concentrations (350–450 µmol/dL). A dog that did not meet the above criteria, serum obtained at the last visit was evaluated as the post-treatment sample.

Serum collection and RNA extraction: Blood samples were collected from the jugular or cephalic veins in serum-separating tubes. After the samples were centrifuged at 2000 g for 10 minutes, the serum was separated and stored at -80°C within 1 h of collection until further use. Total RNA was extracted from serum samples using commercial kits for miRNA extraction (miRNeasy serum/plasma kit, Qiagen, Valencia, California, USA) in accordance with the manufacturer's instructions.

Reverse transcription and real-time quantitative PCR (RT-qPCR): Herein, RT-qPCR was performed as described in a previous study (Lee *et al.*, 2023). After RNA extraction, cDNA was synthesized using the miRCURY LNA RT kit (Qiagen, Valencia, California, USA). RT-qPCR for relative quantification was performed using the miRCURY LNA SYBR Green PCR Kit (Qiagen, Valencia, CA) and the miRCURY LNA miRNA PCR assay (Qiagen, Valencia, California, USA). All analyses were performed using a StepOnePlus Real-Time PCR System (Applied Biosystems, Waltham, Massachusetts, USA), and all samples were analyzed in triplicates. The miRNA sequence was as follows: cfa-miR-375 (UUUGUUCGU UCGGCUCGCGUGA) (Rouse *et al.*, 2017). All samples were normalized to the synthetic spike-in control cel-miR-39-3p (UCACCGGGUGUAAAUCAGCUUG). All processes were performed according to the manufacturer's instructions.

Analysis of miRNA expression: The RT-qPCR results were expressed as the cycle threshold (Ct), which was determined as the second-derivative maximum cycle and was calculated by the software. If miRNAs were not detected after 40 cycles of RT-qPCR, the Ct value was set to 40 (Ji *et al.*, 2009). The relative expression is miR-375 (fold change [FC], $2^{-\Delta\Delta Ct}$) was normalized to the expression levels of the control gene (cel-miR-39-3p) according to the following formulas: $\Delta Ct = Ct \text{ value of the target gene} - Ct \text{ value of the control gene}$; $\Delta\Delta Ct = \Delta Ct \text{ value of the target sample} - \text{average of } \Delta Ct \text{ value of the control sample}$; and the estimated expression ratio = $2^{-\Delta\Delta Ct}$ (Livak and Schmittgen, 2001).

The percentage change in the fold change (PC) of serum cfa-miR-375 was calculated as follows:

$$PC = \frac{(\text{post treatment fold change (FC)} - \text{pre treatment FC})}{\text{pre Treatment FC}} * 100$$

Statistical analyses: Statistical analyses were performed using the commercial statistical software Prism 6 (GraphPad Software Inc., La Jolla, California, USA). The Shapiro-Wilk test was performed to determine the normality of data distributions. Normally distributed data are expressed as mean $\pm$ standard deviation (SD) and skewed distributed data are expressed as median and interquartile range (IQR). Student's t-test was used to compare miRNA expression levels between dogs with DM and healthy dogs. A paired t-test was performed to compare miRNA expression levels before and after treatment. The Mann-Whitney U test was used to compare age and body weight between dogs with DM and healthy dogs. The correlation between the concentration of fructosamine or blood glucose and the expression

levels of serum miR-375 was assessed using Spearman's rank correlation test. The correlation between insulin dosage or treatment period and the percentage change in serum miRNAs was evaluated using Spearman's rank correlation test or Pearson's correlation test, respectively. A P value < 0.05 was considered statistically significant.

Results

Study group: Dogs with DM consisted of seven Maltese, five Poodles, three mixed-breed dogs, two Spitzs, two Pomeranians, and one Yorkshire terrier. Healthy dogs consisted of three Beagles, three Poodles, two Pomeranians, two Maltese, two Cocker Spaniels, two mixed-breed dogs, and one each of the Bichon Frise, Yorkshire Terrier, Shiba, and Labrador Retriever. Other demographic characteristics, serum glucose and fructosamine concentrations, treatment periods, insulin dosages, and insulin types are presented in Table 1. Dogs with DM (6.5 [3.9–9.4]) were significantly older ($P < 0.01$) than healthy dogs (9.5 [7.8–12.3]).

Table 1 Characteristics and demographics of subjects included in the present study.

Parameters	Healthy dogs (n = 18)	Dogs with DM (n = 20)
Age (years)	6.5 (3.9–9.4)	9.5 (7.8–12.3)
Body weight (kg)	6.3 (4.7–11.4)	4.8 (4.1–6.6)
Sex (number)		
Intact male	2	1
Castrated male	8	11
Intact female	4	2
Spayed female	4	6
Blood glucose (mg/dL)	111.0 (107.3–113.8)	408.0 (291.3–506.8)
Fructosamine ($\mu\text{mol/L}$)	NA	404.0 (266.0–481.0)
Treatment period (days)	NA	220.0 (65.0–641.0)
Dosage of insulin therapy (IU/kg)	NA	0.5 (0.4–0.7)
Type of insulin (number), lente/ NPH/ glargine/ untreated	NA	7/10/2/1

Note: Data is expressed as medians (interquartile ranges).

DM, diabetes mellitus; NA, not applicable; NPH, neutral protamine.

Comparison of expression levels of serum miR-375 between dogs with DM and healthy dogs: The mean $\pm$ SD FC of serum cfa-miR-375 was significantly higher in dogs with DM (2.30 ± 2.018) than in healthy dogs (1.294 ± 0.56) ($P = 0.048$; Hedges' $g = 0.650$, 95%

confidence interval = 0.0095–1.290; Fig. 1). Before the onset of diabetes, the median (IQR) FC of cfa-miR-375 was not significantly increased (1.768 [1.265–4.433]) in dogs with DM ($n = 7$) compared with in healthy dogs (1.284 [0.884–1.606]) ($P = 0.11$).

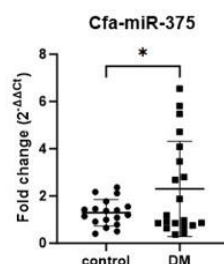


Figure 1 Scatterplot of expression levels of the serum cfa-miR-375 in healthy dogs and dogs with diabetes mellitus (DM). Significantly higher ($P = 0.048$) expression of the serum cfa-miR-375 is observed in dogs with DM ($n = 20$) compared with healthy dogs ($n = 18$). The horizontal bars show means $\pm$ standard deviations of circulating levels of cfa-miR-375. $*P < 0.05$. Student's T-test.

Correlation between expression levels of miR-375 and blood glucose or fructosamine at the time of diagnosis in dogs with DM: Serum cfa-miR-375 expression did not significantly correlate with blood glucose concentration ($r_s = 0.35$, $P = 0.13$). In addition, no

correlation was observed between the serum fructosamine concentration and cfa-miR-375 expression at the time of diagnosis ($r_s = 0.08$, $P = 0.73$).

Comparison of pre- and post-treatment serum miRNA expression levels in dogs with DM: A significantly higher mean $\pm$ SD FC of serum cfa-miR-375 was observed after treatment (4.017 ± 2.608) compared with

before treatment (2.322 ± 2.054) in dogs with DM ($n = 17$) ($P = 0.01$; Fig. 2).

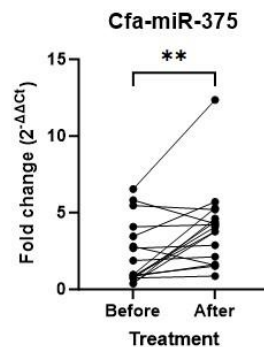


Figure 2 Comparison of expression levels of serum cfa-miR-375 between before and after treatment in dogs with diabetes mellitus ($n = 17$). Paired t-test. ** $P < 0.01$.

Correlation of PC of miR-375 with post-treatment fructosamine, dosage of insulin, and treatment period in dogs with DM: The PC exhibited a moderate positive linear relationship with the post-treatment fructosamine concentration ($r = 0.62$, $P = 0.01$; Fig. 3).

No statistically significant correlation was observed between PC and insulin treatment dosage or treatment period ($r_s = 0.35$, $P = 0.17$ and $r = 0.40$, $P = 0.11$, respectively).

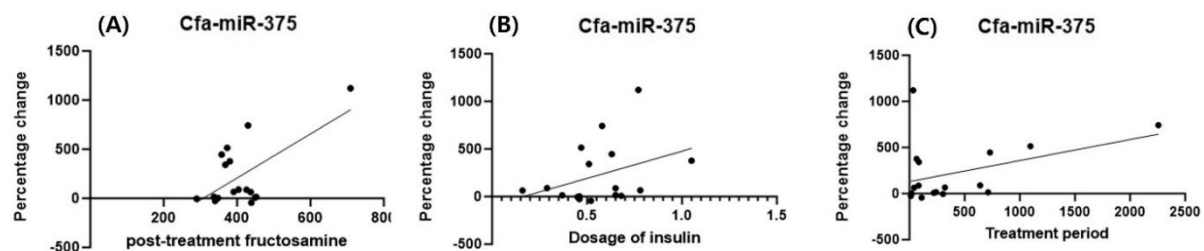


Figure 3 Correlations between PC of cfa-miR-375 and post-treatment serum fructosamine concentration (A), dosage of insulin (B), and treatment period (C). Pearson's correlation test. PC, percentage change.

Discussion

This study investigated serum cfa-miR-375 concentrations in dogs with DM. Serum cfa-miR-375 expression was significantly higher in dogs with DM than in healthy dogs. In addition, the expression of serum miR-375 significantly increased after insulin administration, and the PC of miR-375 showed a positive linear relationship with post-treatment fructosamine concentration in dogs with DM. These findings suggest that cfa-miR-375 may be a potential biomarker in dogs for the diagnosis of and evaluation of treatment response to DM.

MiR-375, which is highly expressed in pancreatic islets of Langerhans, regulates beta-cell proliferation and glucose-dependent insulin secretion (Poy *et al.*, 2009). The results of the present study corroborate those of previous studies on increased serum miR-375 compared with controls in human and murine subjects with type 1 DM (Erener *et al.*, 2013; Seyhan *et al.*, 2016). Increased serum concentrations of miR-375 have been associated with beta-cell death in the murine models of DM (Erener *et al.*, 2013). Prolonged or repeated exposure to increased blood glucose concentrations may exert toxic effects on beta-cells through complex mechanisms such as beta-cell overstimulation, endoplasmic reticulum stress, and hypoxia (Bensellam

et al., 2012). It is reasonable that glucotoxicity may cause beta-cell apoptosis and direct leakage of miR-375 from pancreatic tissue. In addition, a previous study has shown that miR-375 negatively regulates glucose-stimulated insulin secretion via myotrophin inhibition (Poy *et al.*, 2004). Myotrophin is a protein that controls the secretion of the neurotransmitter catecholamine and is involved in insulin vesicle exocytosis (Kumar *et al.*, 2012). Therefore, the increased expression of miR-375 might be due to the high-glucose-exposed environment to prevent overstimulation of beta-cells in dogs with DM. However, a previous study showed that the expression of miR-375 was increased in dogs with AP (Lee *et al.*, 2023), and the association between DM and AP has been reported (Kim *et al.*, 2019; Kim *et al.*, 2023). Therefore, increased miR-375 expression in dogs with DM could result from concurrent subclinical pancreatitis or glucotoxicity-induced beta-cell damage. Pancreatic histopathological examination to assess the integrity of beta-cells is necessary to verify the mechanism underlying increased miR-375 expression in dogs with DM.

A previous study using murine models of DM showed that serum miR-375 concentrations were increased 2 weeks before diabetes onset and suggested its usefulness as a screening tool for predicting early-stage DM (Erener *et al.*, 2013). In the early stages of

subclinical DM, dogs might appear normal, have a constant weight, and present with normal laboratory evaluations (Behrend *et al.*, 2018). Therefore, if serum miR-375 concentration is increased before DM onset in dogs having risk of DM, it might be a potential biomarker for early-stage DM. However, in the present study, serum miR-375 concentrations measured in stored serum samples of dogs with DM before the onset of diabetes were not significantly different from those in healthy dogs. It was challenging to accurately assess how early miR-375 reflects endocrine pancreatic function because miR-375 concentrations were not measured longitudinally. Additional studies, including a larger number of dogs and serial measurements of the serum concentration of miR-375 over time to the onset of DM, are necessary to elucidate whether serum miR-375 could be an early biomarker for DM in dogs.

In the present study, post-treatment expression of serum miR-375 was significantly increased compared with that before treatment. This result was in line with that of a previous report on increased circulating levels of miR-375 in human patients with type 1 DM with controlled glycemia (Marchand *et al.*, 2016). Moreover, the PC of miR-375 showed a positive linear relationship with post-treatment fructosamine concentration, suggesting that the increase in miR-375 might be related to the overall elevated blood glucose concentration in dogs with DM. The dog that exhibited the highest PC had a post-treatment fructosamine concentration of 709 ng/mL and was the only subject that showed no clinical improvement after treatment. These results suggest that repeated hyperglycemia can cause glucotoxicity, which may induce miR-375 leakage from the pancreatic islets.

This study has some limitations. First, the number of dogs included was small, which may have contributed to the marginal statistical significance and relatively large SD observed in the comparison of miR-375 expression between dogs with DM and healthy controls. The sample size before DM onset ($n = 7$) was especially small, and thus, the evaluation of serum miR-375 before DM onset might lead to a false-negative result. Ideally, a priori sample size calculation should be performed before conducting a study. However, this was not feasible due to the lack of available data on serum miR-375 expression levels in dogs with DM. Nevertheless, the findings of the present pilot study will serve as preliminary data for future sample size calculations in studies designed to evaluate changes in miR-375 expression in dogs with subclinical DM or clinical DM concurrent with pancreatitis. Accordingly, the results should be interpreted with caution, and further investigation in larger, adequately powered studies is warranted. Second, serial serum samples collected at regular intervals before and after the diagnosis of DM were not in all DM dogs. Therefore, serial evaluations of miR-375 concentrations are needed to identify how early miR-375 can be utilized as a biomarker for the diagnosis of DM, especially in the early stages of subclinical DM. Furthermore, it should be verified whether the alteration of serum miR-375 is due to pancreatic injury via the comparison of serum miR-375 concentrations between dogs with diabetic and non-diabetic pancreatitis, because the

concentrations were elevated in dogs with pancreatitis (Lee *et al.*, 2023). Subclinical pancreatitis could not be completely excluded based on the exclusion criteria applied in this study. However, previous research has demonstrated no significant difference in miR-375 expression between dogs with mild pancreatitis and healthy controls (Lee *et al.*, 2023), suggesting that subclinical pancreatic inflammation may not substantially influence circulating miR-375 levels. Therefore, although DM can predispose dogs to pancreatitis (Kim *et al.*, 2019), the potential confounding effect of pancreatitis on miR-375 expression in the present study is likely to be limited. Third, dogs with DM in the present study were older than healthy dogs. In contrast to some miRNAs related to aging (Hooten *et al.*, 2013), no significant correlation between age and miR-375 was observed in the present study ($r_s = 0.06$, $P = 0.74$), consistent with previous studies (Lee *et al.*, 2023; Erger *et al.*, 2025). In addition, no correlation was observed between serum cfa-miR-375 expression and age in healthy and DM groups ($r_s = -0.30$, $P = 0.23$, and $r_s = 0.30$, $P = 0.19$, respectively). Nevertheless, the lack of age matching between the two groups may still have influenced the findings, given the potential effects of age-related low-grade inflammation or subclinical pancreatic degeneration. Finally, the type of insulin used varied among dogs. It cannot be excluded that the type of insulin used may have affected the results. Because the sample size of this study was small, this issue could not be verified.

In conclusion, increased serum miR-375 levels might potentially be associated with direct leakage from damaged pancreatic tissue and the pathological link between glucose regulation in canine DM and the expression of miR-375. Further studies evaluating the serial expression of miR-375 may help identify the potential of miR-375 as a diagnostic biomarker for subclinical DM in dogs.

Statement of Author Contributions

Hyeongyeong Lee: Conceptualization, Methodology, Visualization, Data curation, Investigation, Formal analysis, Writing—original draft. **Dohee Lee:** Methodology, Formal analysis, Investigation, Writing—review & editing. **Jayeon Park:** Data curation, Investigation, Visualization. **Yeon Chae:** Formal analysis, Visualization. **Byeong-Teck Kang:** Supervision, Writing—review & editing. **Taesik Yun:** Supervision, Writing—review & editing. **Hakhyun Kim:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing—review & editing.

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Declaration of Artificial Intelligence Use

The authors declare that no artificial intelligence tools were used in the preparation, writing, analysis, or production of this manuscript.

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