pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 36(1) : 74-77 (2019)
http://dx.doi.org/10.17555/jvc.2019.02.36.1.74

Journal of Veterinary Clinics
www.ksvc.or.kr

Remission of Progesterone-induced Diabetes Mellitus after Ovariohysterectomy in an Intact Female Dog

Ill-Hwa Kim†, Jin-Young Choi†, Dae-Youn Hwang* and Hyun-Gu Kang[1]

Laboratory of Veterinary Theriogenology, Department of Veterinary Medicine, College of Veterinary Medicine, Chungbuk National University, Cheongju 28644, Korea
**Department of Biomaterials Science, College of Natural Resources and Life Science/Life and Industry Convergence Research Institute, Pusan National University, Miryang, Gyeongsangnam-do 50463, Korea*

(Received: November 09, 2018 / Accepted: January 25, 2019)

Abstract : A 10-year-old, 8.28 kg, intact female Cocker Spaniel was presented with continuous polyuria and polydipsia. The dog had proestrus bleeding 5 weeks earlier, and hyperglycemia, glucosuria, ketouria, and high level of serum fructosamine in laboratory findings. Based on hyperglycemia, glucosuria, ketouria, and ketosis, the patient was tentatively diagnosed as diabetes mellitus (DM) with ketouria. After diagnosis, 5 to 7 U/body porcine lente insulin was administered during 11 days from initial presentation as the remission of DM for the dog. But, blood glucose was still high level. Because there was no reaction to porcine lente insulin, it was replaced by 4-10 U/body neutral protamine Hagedorn (NPH) during 3 days. But, NPH also did not regulate blood glucose level. Because insulin therapy failed to regulate blood glucose level, the dog was considering insulin-resistant diabetes. The dog was tentatively diagnosed with progesterone-resistant DM on the basis of the history that had revealed proestrus bleeding 5 weeks earlier. Progesterone level was moderate high (43.7 ng/ml; reference range, 15.0-90.0 ng/ml). Ovariohysterectomy (OHE) was performed to remove the cause of the dog's diabetes. After OHE 11 days, blood glucose was gradually declined by insulin treatment. Consequently, blood glucose was well controlled in reference range without insulin treatment after 2 months. This case is a report on progesterone-induced DM treated with OHE and insulin treatment during the diestrus.

Key words **:** progesterone, diabetes mellitus, insulin, ovariohysterectomy, dog.

Introduction

Diabetes mellitus (DM) is a one of syndromes that cause many complications and decrease the quality of patient's life (1). Clinical signs of DM are mainly polyuria, polydipsia, polyphagia, and weight loss (14). DM is a group of metabolic disorders characterized by hyperglycemia with disturbance of metabolism of carbohydrate, protein, and fat (6). In human, DM is triggered about 40 causes. Among them, there is also gestational diabetes mellitus (21). Gestational diabetes mellitus related to increase of circulating progesterone level during pregnancy. High progesterone concentration increases insulin resistance and declines of insulin sensitivity and β-cell function that cause DM (15,17). Dogs also have DM related diestrus that is similar human gestational DM (8,10,17).

As monoestrus animal, dogs have diestrus dominated by progesterone for about 60 days whether pregnancy or not (14). In diestrus, progesterone of sex hormones especially is secreted a lot (14). Long period exposure of high level of progesterone produces more growth hormones (GH) in mammary gland (19). Circulating GH level is increased by endogenous progesterone in diestrus (5) and exogenous progesterone after ovariohysterectomy (OHE) (19). High level of progesterone and GH has anti-insulin effect that causes insulin resistance and hyperglycemia (11).

Generally, DM is diagnosed based on persistent fasting hyperglycemia (65-118 mg/dL or > 8 mmol/L) and clinical signs that are polyuria, polydipsia, and weight loss (8). Metabolic DM is a disorder associated with persistent hyperglycemia due to dysfunction or loss of insulin secretion by β-cell in pancreas, decreased insulin sensitivity in tissues, or both (1). In addition, it associated with pancreatitis, vacuolar degeneration, and immune-mediated destruction (1). In intact female dogs, hormones usually trigger transient or persistent DM by insulin resistance in diestrus (1,17). In dogs with no therapeutic response, hormonal DM is diagnosed by endogenous progesterone and GH level after checking effect of endogenous or exogenous progesterone (8,17). The criteria to confirm the remission of DM was maintenance of fasting blood glucose level in normal range after stop of insulin therapy (10).

Treatment of DM is elimination of main causes. In dogs, exogenous insulin should be administrated to remission of DM (1). Generally, porcine insulin is used for starting dose of 0.25 U/kg q 12 hours (16). If the patient have ketosis, 24-hour intensive care and aggressive treatment should be started (1,16). Though OHE is recommended to dog that have progesterone related DM to decline insulin resistance, there are few case report that DM is in remission after OHE (17). In this case, we describe that the dog with diabetes mel-

†These authors contribute equally to this work
[1]Corresponding author.
E-mail : kang6467@cbu.ac.kr

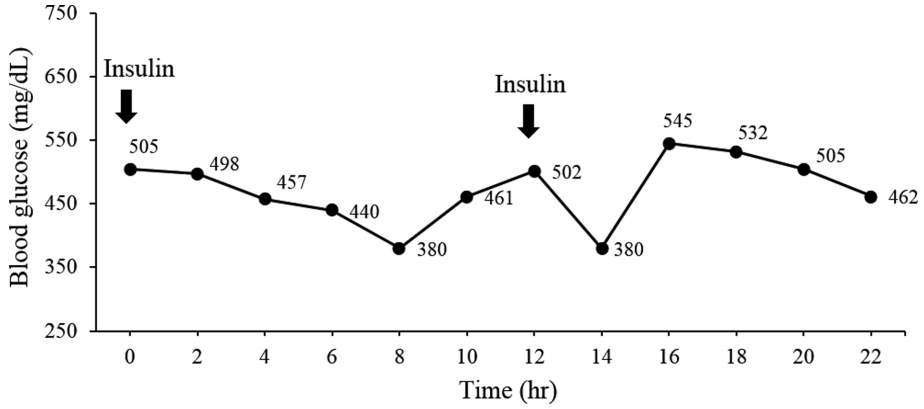

Fig 1. Blood glucose levels of patient during 24 hours before ovariohysterectomy. Fasting glucose level at initial presentation was 505 mg/dL. At initial presentation, porcine insulin 7 U/body SC was administered. Because of no reaction of insulin, porcine insulin was changed to neutral protamine Hagedorn (NPH) 4 U/body SC in 12 hours after presentation. Likewise, Administration of NPH 4 U/body SC didn't show insulin effectiveness. Blood glucose was higher than the normal range.

litus and history of estrus bleeding 1 month ago was treated with OHE because there was no insulin therapy response.

Case

A 10-year-old, weighing 8.28 kg, intact female Cocker Spaniel was presented with continuous polyuria and polydipsia from 4 weeks ago. The dog had proestrus bleeding 5 weeks earlier, and good appetite and vitality. Physical examination was unremarkable. But, body condition score (BCS) was 6/9 that means mild overweight. Blood glucose analysis revealed severe hyperglycemia (679 mg/dL; reference range, 65-118 mg/dL). Also, hyperlipidemia (576 mg/dL; reference range, 135-270 mg/dL), hyponatremia (138 mmol/L; reference range, 141-152 mmol/L), hyperproteinemia (7.5 g/dL; reference range, 5.4-7.1 g/dL), mild anemia (33.2%; reference range, 37.3-61.7%), increased ALP (1782IU/L; reference range, 29-97 IU/L), increased BUN (27.1 mg/dL; reference range, 7-25 mg/dL), hyperkalemia (6.8 mmol/L; reference range, 3.6-5.8 mmol/L), and hypochloremia (100 mmol/L; reference range, 105-115 mmol/L) were revealed in complete blood count, blood chemical analysis and blood electrolyte analysis (Table 1). Serum fructosamine level was severe high (573 μmol/L; reference range, 260-378 μmol/L). Venous blood gas analysis was unremarkable. In urinalysis, glucosuria and ketouria were revealed at the time of presentation. Ketone level was mildly increased (2.7 mmol/L; reference range, less than 0.6 mmol/L). In ACTH stimulation test, cortisol level was measured for 16.4 μg/dL in post-ACTH injection (reference range, 6-16 μg/dL in post-ACTH injection). So, hyperadrenocorticism (Cushing syndrome) was rolled out in the patient.

Based on hyperglycemia, glucosuria, ketouria, and ketosis, the patient was tentatively diagnosed as DM. After diagnosis, 3 U/body porcine insulin was prescribed as subcutaneous injection because appetite and vitality were good without acidosis. For resolution of overweight, feed was replaced with low fat diet (Hill's prescription Diet w/d canine®, Hill's pet nutrition, United States).

A week later, porcine insulin 5 U/body was administered before presentation. Blood glucose level was lower rather than before, but it was still high level (482 mg/dL). In history taking, the patient seemed to be remission of polyuria and polydipsia because of decrease of drink amount. The body weight increased from 8.1 kg to 8.3 kg after 2-3 days, and then decreased to 7.7 kg after few days. Ketone level was in the reference range (0.2 mmol/L). For generating blood glucose curve, the patient was hospitalized that blood samples were collected every 2 hours and blood glucose level was analyzed. After porcine insulin 5 U/body administration, blood glucose level almost did not decline during 9 hours, so porcine insulin 7 U/body was changed to 5 U/body. In blood glucose curve, though dose of porcine insulin was higher than before, mean blood glucose concentration was about 500 mg/dL. On the following day, porcine insulin 7 U/body was administered at initial presentation. Because of no reaction of porcine insulin, NPH 4 U/body was replaced with porcine insulin. But, NPH 4 U/body also had no insulin effectiveness (Fig 1).

The next day, there was no insulin effectiveness of NPH 10 U/body. Because insulin treatment did not control the blood glucose level and the patient had estrus bleeding 7 weeks ear-

Table 1. Body weight, blood glucose, ketone, packed cell volume (PCV), total protein, alkaline phosphate (ALP), blood urea nitrogen, total cholesterol, potassium, sodium, and chloride value before and after ovariohysterectomy (OHE) for the patient

	Pre-OHE	Post-OHE
Body weight (kg)	8.28	6.90
Blood glucose (mg/dL)	679	61
Ketone (mmol/L)	2.7	-
PCV (%)	33.2	33.4
Total protein (md/dL)	7.5	6.4
ALP (IU/L)	1782	1143
Blood urea nitrogen (mg/dL)	27.1	43.9
Total cholesterol (mg/dL)	576	-
Potassium (mmol/L)	6.8	4.4
Sodium (mmol/L)	138	149
Chloride (mmol/L)	100	114

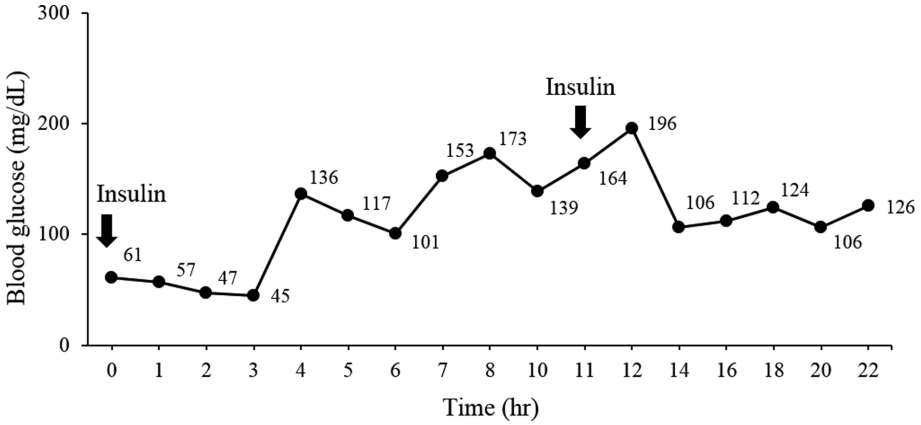

Fig 2. Blood glucose level of patient after 11 days of ovariohysterectomy (OHE). Porcine insulin 6 U/body SC was administered at morning of that day. As transient hypoglycemia was developed in 2-3 hours after presentation, 50% distilled water 5 ml and 0.9% normal saline were slowly injected. After patient took a meal in 11 hours after presentation, porcine insulin 3 U/body SC was administered at that time. Blood glucose level is lower than that of before OHE.

lier, patient was supposed to diestrus in estrous cycle. At that time, progesterone level was moderate high (43.7 ng/ml; reference range, 15.0-90.0 ng/ml). The increase of progesterone level was thought to trigger insulin resistance during diestrus, so blood glucose level was not controlled despite of insulin treatment. To decline progesterone level to reference range, OHE was performed as therapeutic trial. Eleven days later, porcine insulin 6 U/body was administered to the patient before presentation. Complete blood count, blood chemical analysis, blood electrolyte analysis and physical examination were performed after OHE (Table 1). After 2-3 hours of porcine insulin administration, suddenly transient hypoglycemia occurred, so 50% distilled water and 0.9% normal saline were slowly injected to the patient.

That afternoon, after porcine insulin 3 U/body was administered, the blood glucose curve showed good glycemic control (Fig 2).

After ten days, to confirm whether DM related insulin resistance of progesterone, insulin treatment was not prescribed to patient for three days. Three days later, blood glucose level was well controlled at presentation though insulin was not administrated for three days as highest blood glucose was 193 mg/dL and lowest blood glucose level was 95 mg/dL.

Discussion

Circulating blood glucose is controlled by insulin. But diabetes mellitus occurs when the blood glucose is not controlled normally. Human gestational DM is classified as type 1, type 2, monogenic type and other specific types (6). Type 1 DM is characterized by insulin deficiency, pancreatic β-cell autoimmunity, and idiopathy (1). Type 2 DM is associated with insulin resistance (1,6). Obesity often accompanies type 2 diabetes (6). Because the adipose tissue has expandability limit, excess lipid accumulates in other tissue (2). Increased free fatty acid from excess lipid damages muscle, liver and pancreatic β-cells (3). That triggers decreased glucose uptake in muscle, increased glucose production in liver and decreased insulin production in pancreas (2). These things are causes of DM (2). This form of DM accounts for 90-95% of human DM (20). Dogs also have DM related diestrus that is similar human gestational DM (8,10,17). In this case, the dog had hyperglycemia, estrus bleeding 5 weeks earlier, moderate high level of progesterone (43.7 ng/ml), and no therapeutic insulin effect. These findings revealed that the patient was supposed to be gestational DM during diestrus.

In progesterone-induced DM, progesterone prevents insulin from binding to the receptor, interferes with the tyrosine activity of the receptor, and induces apoptosis of insulin producing cells (15,17). Progesterone also stimulates secretion of mammary induced GH during diestrus (8,17,19). Generally, excessive GH is associated with hyperinsulinemia that induces impairment of kinase activity in insulin receptor and a reduction of insulin receptor levels (4). In the present case, increase of circulating progesterone (43.7 ng/ml) and growth hormone by mammary gland was believed to cause diabetes mellitus by insulin resistance (7).

In blood analysis, ketone level also increased (2.7 mmol/L) and the patient was with ketosis and ketouria. Ketone level increases when the body is metabolizing fat at a high rate. The shortage of insulin results in hypoglycemia at the target cell (liver, muscle, and adipose tissue) (16). So, the liver subsequently converts free fatty acids to ketone bodies and triglycerides. The ketone bodies can be used as energy in the tissues when there is a lack of nutritional intake or glucose (16). Consequently, insulin resistance induced ketosis and ketouria.

Serum fructosamine in dogs indicates the mean glucose concentration during the previous 2-3 weeks because of the half-life of the plasma proteins. Serum fructosamine are made through nonenzymatic reaction between serum protein and glucose (9,12). In the patient, serum fructosamine level was severe high (573 μmol/L). It suggested that blood glucose concentration was high before 2-3 weeks so, the patient had chronic DM.

Treatments of gestational diabetes mellitus in humans are weight loss for improvement of insulin sensitivity, insulin therapy, and administration of oral antihyperglycemic agent like glibenclamide (13). Generally, treatment of DM in dogs

is exogenous insulin therapy. If insulin therapy is ineffective, insulin resistance can be supposed. In dogs, there are many causes of insulin resistance (1); obesity (10), hypothyrodism (15), infection (1,15), hyperadrenocorticism (8,10), pancreatitis (3), and progesterone-induced (17). In this case, hyperadrenocorticism was rolled out because of result in ACTH stimulation test. Also, DM by obesity was excluded because the patient had normal body condition score despite of mild overweight. In blood analysis, as WBC was in normal range, infection was rolled out. However, moderate high level of progesterone was analyzed. Therefore, the patient was diagnosed with progesterone-induced DM based on resistance of insulin treatment and diestrus of the patient. OHE was performed to remove the cause of the dog's diabetes. After OHE, the patient was discharged with hyperglycemia, so we conclude that DM was in remission.

However, although performing OHE was effective remission of DM in this case, there were some possible limitations. Hypothyrodism and pancreatitis were overlooked that can be causes of DM (1). Methods of pancreatitis diagnosis are pancreatic lipase immunoreactivity assay, check trypsin-like immunoreactivity and serum amylase and lipase activity, and pancreatitis kit (22). Also, hypothyrodism is diagnosed when serum thyroid stimulating hormone (TSH) concentration is over 10 mU/L and free thyroxine 4 (fT4) is in normal or low range (18). In this case, progesterone-induced DM was diagnosed without test of these disorders. Therefore, there were some errors in the diagnosis. So, in the diagnosis of DM, it is believed that laboratory tests of the diseases that cause DM should be performed.

This report provides the clinical information about onset of DM by high circulating progesterone and remission of progesterone related DM in intact female dog during diestrus. After OHE, DM was in remission in the patient and glucose level was in normal range. In some opinion, OHE should be performed as soon as possible to higher chance of remission of DM (9). However, OHE was performed as therapeutic trial after 18 days of DM diagnosis in our case. Consequently, we conclude that OHE is a key role of remission of DM by progesterone during diestrus in intact female dogs.

References

1. Behrend E, Holford A, Lathan P, Rucinsky R, Schulman R. 2018 AAHA Diabetes Management Guidelines for Dogs and Cats. J Am Anim Hosp Assoc 2018; 54: 1-21.
2. Colom C, Corcoy R. Maturity onset diabetes of the young and pregnancy. Best Pract Res Clin Endocrinol Metab 2010; 24: 605-615.
3. Davison LJ. Diabetes mellitus and pancreatitis-cause or effect. J Small Anim Pract 2015; 56: 50-59.
4. Dominici FP, Argentino DP, Munoz MC, Miquet J, Sotelo AI, Turyn D. Influence of the crosstalk between growth hormone and insulin signaling on the modulation of insulin sensitivity. Growth Horm IGF Res 2005; 15: 324-336.
5. Eigenmann JE, Eigenmann RY, Rijnberk A, van der Gaag I, Zapf J, Froesch ER. Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly. Acta Endocrinol 1983; 104: 167-176.
6. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003; 26: S5-S20.
7. Fall T, Hedhammar Å, Wallberg A, Fall N, Ahlgren KM, Hamlin HH, Lindblad-Toh K, Andersson G, Kämpe O. Diabetes mellitus in Elkhounds is associated with diestrus and pregnancy. J Vet Intern Med 2010; 24: 1322-1328.
8. Fall T, Johansson Kreuger S, Juberget A, Bergstrom A, Hedhammar A. Gestational diabetes mellitus in 13 dogs. J Vet Intern Med 2008; 22: 1296-1300.
9. Feldman EC, Nelson RW. Canine diabetes mellitus. In: Canine and Feline Endocrinology and Reproduction 3rd ed. St Louis: Saunders. 2004: 510-545.
10. Kim AY, Kang JH, Yang MP. Transient diestrus-related diabetes mellitus in a dog. J Biomed Res 2012; 13: 265-267.
11. Kopchick JJ. Growth and maturation. In: Endocrinology. Philadelphia: Saunders. 2001: 389-404.
12. Lutz TA, Rand JS, Ryan E. Fructosamine concentrations in hyperglycemic cats. Can Vet J 1995; 36: 155-159.
13. Mirghani Dirar A, Doupis J. Gestational diabetes A to Z. World J Diabetes 2017; 8: 489-511.
14. Nelson RW, Reusch CE. Animal models of disease: classification and etiology of diabetes in dogs and cats. J Endocrinol 2014; 222: T1-9.
15. Nunes VA, Portioli-Sanches EP, Rosim MP, Araujo MS, Praxedes-Garcia P, Valle MM, Roma LP, Hahn C, Gurgul -Convey E, Lenzen S, Azevedo-Martins AK. Progesterone induces apoptosis of insulin-secreting cells: insights into the molecular mechanism. J Endocrinol 2014; 221: 273-284.
16. Parker JA, Conway DL. Diabetes ketoacidosis in pregnancy. Obstet Gynecol Clin North Am 2007; 34: 533-543.
17. Poppl AG, Mottin TS, Gonzalez FHD. Diabetes mellitus remission after resolution of inflammatory and progesterone-related conditions in bitches. Res Vet Sci 2014; 94: 471-473.
18. Rabbiosi S, Vigone MC, Cortinovis F, Zamproni I, Fugazzola L, Persani L, Corbetta C, Chiumello G, Weber G. Congenital hypothyroidism with eutopic thyroid gland: analysis of clinical and biochemical features at diagnosis and after re-evaluation. J Clin Endocrinol Metab 2013; 98: 1395-1402.
19. Selman PJ, Mol JA, Rutterman GR, van Garderen E, Rijnberk A. Progestin-induced growth hormone excess in the dog originates in the mammary gland. Endocrinology 1994; 134: 287-292.
20. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997; 20: 1183-1197.
21. Wejdmark AK, Bonnett B, Hedhammar A, Fall T. Lifestyle risk factors for progesterone-related diabetes mellitus in elkhounds - a case-control study. J Small Anim Pract 2011; 52: 240-245.
22. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. J Small Anim Pract 2015; 56: 13-26.