Hypoglycemia

Thomas Schermerhorn, VMD, DACVIM (SAIM)
Kansas State University

Hypoglycemia is a manifestation of a pathologic process—not a diagnosis. It is always secondary to a disorder that disrupts or overwhelms one or more of the homeostatic mechanisms responsible for maintenance of normoglycemia.

Background & Pathophysiology

Glucose is a dietary carbohydrate used as a substrate for adenosine triphosphate production via anaerobic and aerobic pathways. Its use as a cellular source of fuel requires regulation at multiple points during metabolism. As a result, glucose homeostatic pathways are highly integrated to maintain blood glucose levels within precise physiologic limits.[1]

Hypoglycemia is defined as a decrease in blood glucose below the physiologic range and is considered clinically relevant when levels decrease below 60 mg/dL.[2]

Blood Glucose Regulation

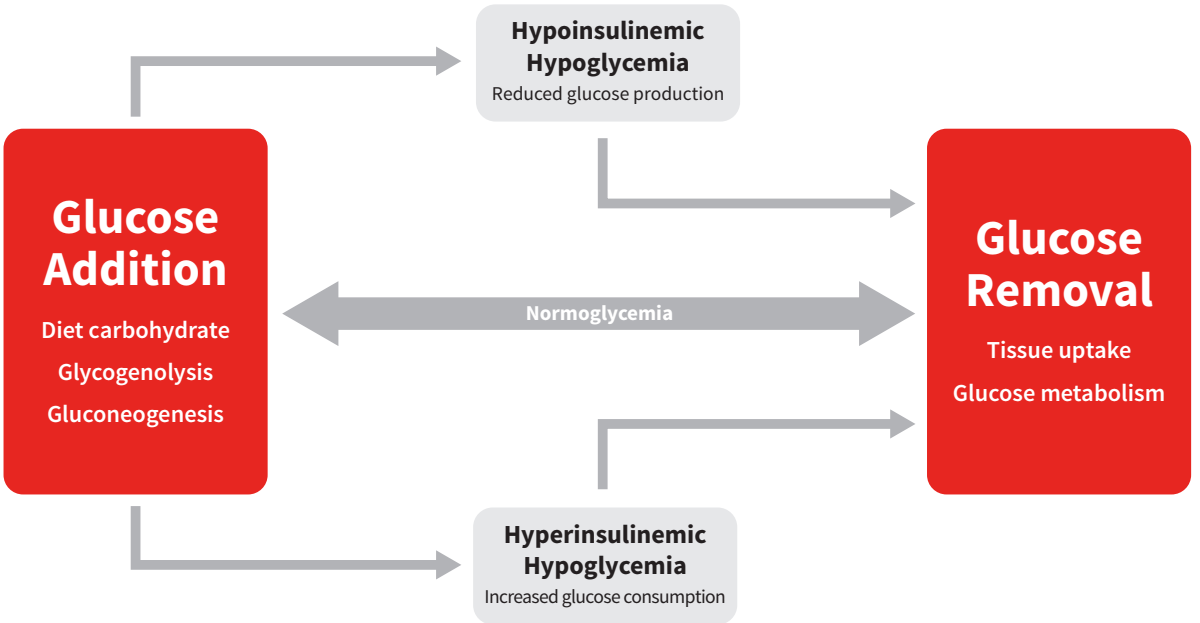
Normoglycemia is maintained by the actions of multiple hormones that regulate the metabolic pathways responsible for glucose addition and removal from blood (***Figure***). Insulin and glucagon are the most important hormones involved in glucose homeostasis. The major pathways through which glucose is added to blood are intestinal absorption of dietary glucose and hepatic glucose production via glycogenolysis and gluconeogenesis.[3] Insulin and glucagon play opposite roles in blood glucose regulation. Insulin exerts hypoglycemic effects through actions that stimulate glucose uptake by target tissues and reduce hepatic glucose output.[3] Glucagon has no effect on cellular glucose uptake but potently increases the rate of glucose appearance in blood through stimulation of glycogenolysis and gluconeogenesis.[4] It is the balanceof these hormones—the insulin:glucagon ratio—that determines whether there is a net gain or loss of glucose from blood.

When glucose decreases below its physiologic set point, insulin secretion is typically inhibited and glucagon secretion is stimulated; when the decrease in glucose levels is rapid, a marked counterregulatory response serves to rescue the organism from severe hypoglycemia.[5] The counterregulatory response is mediated through the actions of hormones such as cortisol and other glucocorticoids, catecholamines, and growth hormone, which induce a degree of insulin resistance that helps increase blood glucose. Hypoglycemia occurs when the rate of glucose removal exceeds the rate of its addition to blood.[1] Endogenous or exogenous substances that mimic or potentiate insulin action or enhance or accelerate glucose metabolism increase glucose removal, whereas failure of endogenous glucose production decreases the rate of glucose addition to blood. Disruptions of the pathways responsible for glucose addition or removal may overwhelm homeostatic mechanisms and produce clinical hypoglycemia.

Mechanisms of Action

Hypoglycemia has been associated with a variety of clinical conditions but is a consistent feature of relatively few disorders. Because artifactual and factitious causes for hypoglycemia are fairly common, it is important to rule out the possibility of preanalytic (eg, improper sample collection, handling or storage) or analytic (eg, inaccurate glucometer) errors before accepting the validity of a test result consistent with hypoglycemia, especially when clinical signs are lacking or the finding is unexpected. Confidence in the result can be improved by repeating the analysis or using a different technique to measure glucose. Clinical disorders produce hypoglycemia through one or more pathophysiologic mechanisms. Clinical hypoglycemia can be broadly divided into several categories: hyperinsulinemic hypoglycemia, hypoinsulinemic hypoglycemia, and miscellaneous disorders (***Table*** 1, next page).[6]

Hyperinsulinemic hypoglycemia is the most common mechanism of hypoglycemia in dogs and cats, with relative or absolute insulin excess being a common feature (***Table 1***, next page). Exogenous insulin administered to diabetic patients is



▲ **FIGURE** Normoglycemia represents balance between glucose addition and removal from the blood. Hypoglycemia results when the rate of glucose addition falls below the removal rate (ie, hypoinsulinemic hypoglycemia) or when the rate of removal exceeds the addition rate (ie, hyperinsulinemic hypoglycemia).

TABLE 1

PATHOPHYSIOLOGIC MECHANISMS & MAJOR CAUSES OF HYPOGLYCEMIA

	Mechanism of Action
Hypoinsulinemic hypoglycemia	
Congenital portosystemic shunt	Reduced hepatic glycogen storage and gluconeogenesis
Liver failure (acute or chronic) of any cause, including feline hepatic lipidosis	Impaired or reduced hepatic glucose production due to hepatocellular dysfunction, injury, or loss
Hypoglycemia of fasting	Limited hepatic glycogen stores are exhausted after a short fast. Hepatic glucose production is less efficient in young puppies and kittens than in adults due to reduced glycogen stores and limited gluconeogenic substrates. Fasting does not cause hypoglycemia in healthy adult animals.
Glycogen storage disorders	Genetic condition that causes impaired glycogen metabolism
Counterregulatory hormone deficiency	Deficiency results in decreased antagonism of insulin action, which favors development of hypoglycemia.
Polycythemias	Increased cellular glucose use
Hyperinsulinemic hypoglycemia	
Insulin overdose	Accidental or intentional administration of excess dose of exogenous insulin
Insulinoma	Neuroendocrine tumor of islet cells secretes endogenous insulin in excess
Paraneoplastic hypoglycemia	Tumor produces an insulin-like substance.
Xylitol toxicity	Stimulation of insulin release in dogs
Miscellaneous	
Sepsis	Cause is not fully understood; multiple mechanisms have a role.
Infections, toxins, and drugs	Various mechanisms
Idiopathic or episodic hypoglycemia	Unknown cause; multiple factors (eg, prandial state, level of anxiety/excitement, level of exertion, diet) are likely to be involved.

Clinical Notes

Signs observed at young age. Breed conveys risk in dogs. Signs are similar for intra- and extrahepatic shunt locations.
Frequently accompanied by elevated levels of hepatic transaminases and bilirubin; however, blood levels of other hepatic function markers (eg, urea, albumin, cholesterol) will be low.
Most common cause for hypoglycemia in neonatal and young puppies and kittens
Type 1 (von Gierke's disease) and type 3 (Cori's disease) are rare conditions that have been described in dogs.
Clinical disorders include cortisol deficiency (hypoadrenocorticism) and growth hormone deficiency (eg, pituitary dwarfism).
Infrequent complication of hematologic cancers and other disorders associated with marked erythrocytosis (eg, polycythemia vera) or leukocytosis (eg, leukemias)
Affected patients have a history of diabetes mellitus; many are considered poorly regulated diabetics. Inadvertent overdose of prescribed insulin is the most common error. Using insulin to cause intentional harm is reported in humans but appears rare in veterinary medicine.
Vague, nonspecific signs may precede onset of hypoglycemia. Recent weight gain is reported before diagnosis in some patients.
Some nonpancreatic tumors release a humoral factor that causes hypoglycemia; tumor may produce other signs along with hypoglycemia. Increased glucose consumption by very large tumors may also contribute to hypoglycemia.
Hypoglycemia is secondary to increased insulin secretion but may be exacerbated in dogs with xylitol-associated liver failure.
Hypoglycemia is related to more severe cases of sepsis and may signify a worse prognosis.
Infections infrequently associated with hypoglycemia include bartonellosis and babesiosis.[2] Hypoglycemia can result from ethylene glycol toxicity or ethanol intoxication (rare in dogs and cats) and has been observed in a dog after oleander ingestion.[2] Hypoglycemia due to drugs (other than insulin), including oral hypoglycemic drugs, is rare in dogs and cats.
Episodes of hypoglycemia occur in an otherwise healthy animal. Triggering events or circumstances may be identified; clinical examples include small-breed hypoglycemia and hunting dog hypoglycemia. Hypoglycemia may rarely develop during pregnancy in dogs.

responsible for most cases of hyperinsulinemic hypoglycemia in veterinary medicine; typically, the cause is insulin overdose, although pharmacologic doses of insulin given to diabetic cats may result in onset of diabetes remission with subsequent hypoglycemia.[7,8] Accidental or nefarious injection of insulin has been described in nondiabetic humans but is an unlikely cause of hyperinsulinemic hypoglycemia in animals.[9]

Insulinoma, a neuroendocrine tumor of the pancreas, is the most common disorder associated with hyperinsulinemic hypoglycemia due to excess production of endogenous insulin.[10] Insulin excess due to islet cell hyperplasia has been suspected in some dogs.[11,12] In humans, oral hypoglycemic drugs (eg, sulfonylureas) that stimulate release of endogenous insulin can cause hyperinsulinemic hypoglycemia. However, these drugs are infrequently used in veterinary medicine, so this effect is unlikely to be encountered clinically.[13]

Ingestion of xylitol, an artificial sweetener used in many products intended for human use, causes profound hypoglycemia in dogs.[14] Uniquely in dogs, xylitol is a potent stimulator of insulin release, and toxicity occurs after ingestion of more than 0.1 g/kg.[15,16] Hypoglycemia results from insulin excess with or without concurrent failure of hepatic glucose output, which is caused by xylitol-induced liver damage.

Hypoinsulinemic hypoglycemia describes hypoglycemia that develops independent of insulin; in associated conditions, blood insulin is appropriately low with hypoglycemia. Non-insulin–mediated hypoglycemia may develop via one of several mechanisms (***Table 1***, page 30). Several tumor types (eg, hepatomas, hepatocellular carcinomas, leiomyomas, leiomyosarcomas) produce humoral insulin-like substances (eg, insulin-like growth factor-1) that promote hypoglycemia.[2,6,17] Hypoinsulinemic hypoglycemia can also occur with disorders that increase use of glucose by body tissues or those associated with failure of hepatic glucose production.[18]

History & Clinical Signs

Hypoglycemia is a manifestation of disease rather than a specific diagnosis. Patient age and breed, previous diagnoses (eg, diabetes), and information about the conditions that elicit signs (eg, fasting, exercise) provide clues about possible causes. Patients may not share a consistent history except when the only signs displayed are those of hypoglycemia. Signs of hypoglycemia can be divided into signs related to impaired tissue energetics (neuroglycopenic) and those related to sympathetic activation (neurogenic; see ***Signs of Hypoglycemia***).[19] Acute hypoglycemia can produce a variety of nonspecific signs, including muscle tremors or weakness, ataxia, nausea, vomiting, behavior changes, confusion, collapse, seizures, and coma.[2] Chronic or intermittent hypoglycemia is often associated with vague signs of decreased activity or reduced energy, which may be accompanied by signs that are usually associated with acute exacerbations.[19]

Diagnosis

Hypoglycemia is diagnosed when the measured blood glucose level is below the reference range, which is generally centered around 90 to 100 mg/dL and ranges from 70 to 120 mg/dL. Clinically, signs are most likely to appear when the glucose level is ≤60 mg/dL.[2,19] Hypoglycemia may be documented using a variety of clinical testing methods, including serum chemistry profile, whole blood testing using a portable glucometer, or interstitial fluid analysis using a continuous glucose monitor. Artifactual hypoglycemia is a preanalytic error that occurs when glucose in the sample is consumed by blood cells during processing. Some examples include consumption by RBCs when clot removal is delayed during serum processing or by WBCs when severe leukocytosis is present.[20] If laboratory error is eliminated as a cause, persistent or recurrent hypoglycemia should be investigated. Because recognition of hypoglycemia per se is not sufficient to make a diagnosis, patient history, physical examination, and other diagnostic findings must be carefully evaluated to identify the underlying cause. A diagnosis of clinically relevant hypoglycemia is

confirmed by satisfying the criteria of Whipple's triad: 1) clinical signs of hypoglycemia, 2) concurrent biochemical hypoglycemia, and 3) resolution of clinical signs with correction of hypoglycemia. In many cases, a series of diagnostic tests and imaging studies are needed to identify an underlying cause for hypoglycemia.

Treatment & Management

Treatment aims to eliminate the clinical signs of hypoglycemia and address any underlying pathology (***Table 2***, next page). Mild hypoglycemia may be alleviated by feeding, especially in young animals or small-breed dogs in which hypoglycemia may develop due to rapid depletion of glycogen. Blood glucose can be increased rapidly via oral or IV glucose supplementation. Oral glucose is usually provided as corn syrup or honey, both of which contain large amounts of glucose in the form of simple sugars.[19] IV glucose is usually supplied via bolus injection or CRI of a glucose solution prepared from a sterile 50% dextrose solution. Infusion of glucagon, a hormone that antagonizes insulin-mediated inhibition of gluconeogenesis and promotes hepatic glucose production, has been used to treat hypoglycemia associated with insulin overdose and insulinoma in dogs.[21,22]

Some medications are useful for addressing chronic hypoglycemia associated with specific disorders. Glucocorticoids (eg, prednisone, dexamethasone) are used as replacement therapy for cortisol deficiency that accompanies hypoadrenocorticism.[23] Given at doses sufficient to induce insulin resistance, these drugs are also used as adjunctive treatment for insulinoma-associated hypoglycemia.[10] Anecdotally, L-carnitine supplementation may help ameliorate hypoglycemic events in susceptible small-breed puppies, including those with hypoglycemia caused by portosystemic shunting.

Prognosis

Correction of hypoglycemia is readily accomplished with glucose supplementation. However,

SIGNS OF HYPOGLYCEMIA[19]

- Signs may be triggered under such circumstances as fasting, stress, or exercise.
- Severity of signs depends on hypoglycemia duration and severity.
- Marked hypoglycemia may be tolerated in dogs and cats with chronic or episodic hypoglycemia.

Neurogenic Signs

- Restlessness
- Hunger/food seeking
- Nausea/vomiting
- Tachycardia
- Tremors
- Signs reported in humans include feeling shaky, sweating, and anxiety, but equivalent signs are difficult to define in dogs and cats.

Neuroglycopenic Signs*

- Weakness
- Unusual behaviors, confusion, apparent vision abnormalities
- Ataxia
- Lethargy
- Seizure
- Coma

*Severe or prolonged neuroglycopenia may be fatal.

TABLE 2

TREATMENT OF HYPOGLYCEMIA

Treatment	Formulations & Dosing Guidelines
Food	A small snack or meal portion of a commercial balanced diet is a source of carbohydrates as well as substrates that support gluconeogenesis.
Glucose-containing syrup	• Corn syrup or honey contains a high percentage of glucose as the simple sugar. • 50% dextrose for injection (0.5 g glucose/mL); can be given PO if IV access is not available • Apply liberally along gingiva and buccal mucosa; allow ingestion if patient is able to swallow.
Glucose solution	50% dextrose for injection (50-mL vial); each vial contains 25 g dextrose **Glucose bolus** • IV injection is administered at 0.5-1.0 g/kg (1-2 mL/kg) over 10-15 minutes; the dose is diluted 1:4 with 0.9% sodium chloride before administration. **Glucose CRI** • A 5% glucose infusion solution is prepared by adding 25 g dextrose/500 mL isotonic fluid (eg, lactated Ringer's solution). • A glucose bolus may be given at the start of CRI. • The infusion rate is started at 2-3 mL/kg/hour and titrated to achieve normoglycemia.
Glucagon	Available in 1-mg vials for rescue treatment of hypoglycemia in diabetic humans; drug is administered via CRI for veterinary applications **CRI preparation and dosing** 1. Glucagon is reconstituted using supplied diluent. 2. The infusion solution (1 µg glucagon/mL) is prepared by adding the entire reconstituted volume (containing 1 mg glucagon) to 1 L bag of 0.9% sodium chloride solution. 3. A bolus injection of glucagon (0.05 µg/kg) IV can be given before starting CRI. 4. The initial CRI dose is 0.005-0.01 µg/kg/min IV and is titrated to achieve normoglycemia. 5. Blood glucose should be monitored hourly until normoglycemia is achieved. 6. CRI can be maintained until blood glucose is stable and the rate tapered with monitoring to ensure normoglycemia is sustained.
Adjunctive treatment	
Glucocorticoids	**Prednisone** • Dose for hormone replacement is 0.1-0.2 mg/kg daily. • Dose to induce insulin resistance is 1-2 mg/kg daily (higher dose is also immunosuppressive). **Dexamethasone** • More potent than prednisone and requires appropriate dose reductions • Replacement dose is 0.01-0.02 mg/kg/day. • Dose sufficient to induce insulin resistance is 0.1-0.2 mg/kg/day.
L-carnitine	A recommended empiric dose is 50 mg/kg twice daily. The use of L-carnitine for this purpose is based on anecdotal reports and the author's clinical experience.

Clinical Notes

- Only indicated for treatment of mild hypoglycemia
- Requires patient to be alert and have the ability to swallow normally
- Not suitable for emergency treatment of hypoglycemia
- Small meals fed frequently may be part of an effective strategy for hypoglycemic management in some patients.

- Owners should be advised to start therapy as soon as hypoglycemia is recognized.
- Caregivers should be warned to take care not to be bitten during administration and to withhold treatment if patient is nonresponsive or unable to swallow.

- An indwelling catheter is recommended to avoid complications (eg, phlebitis, pain) associated with injection of hypertonic glucose solutions.
- Bolus injection will rapidly correct hypoglycemia but may stimulate insulin release in nondiabetic patients. In such cases, the effect of the bolus may wane rapidly, necessitating administration of multiple boluses; beginning a glucose CRI should be considered.
- In a study of insulin overdose in dogs and cats, glucose supplementation was continued for a median of 18 hours and 8.5 hours, respectively, until euglycemia was restored.[7] The same study found that the total amount of glucose needed to restore normoglycemia was >1 g/kg, with some patients requiring much greater quantities.

- Glucagon infusion is reported in dogs and has been used to treat hypoglycemia due to insulinoma[9,24] and insulin overdose.[9,25]
- Glucagon infusion is effective and well-tolerated in dogs[24] and should be considered when glucose infusion fails to maintain blood glucose.

- Use of low-dose glucocorticoids as hormone replacement is only indicated for treatment of hypoglycemia caused by cortisol deficiency associated with hypoadrenocorticism. The dose is insufficient to induce insulin resistance.
- Adverse effects (eg, polydipsia, polyuria, weight gain) occur when doses exceed the replacement dose.
- Glucocorticoid induction of insulin resistance is a helpful adjunctive treatment for insulinoma when definitive therapy is not pursued. Improvement or resolution of insulinoma-induced hypoglycemia is usually temporary, although some dogs will remain subclinical for several months.

- L-carnitine is believed to increase the metabolic efficiency of mitochondria and to improve cellular energy production.[26]
- L-carnitine is commercially available as a nutritional supplement. The powder form is easily given mixed with food.
- L-carnitine supplementation may be useful for decreasing the frequency and severity of hypoglycemia in young animals. Supplementation can usually be discontinued after the animal matures.
- Anecdotally, L-carnitine may provide similar benefits for animals with liver impairment secondary to portosystemic shunting and animals with some forms of idiopathic hypoglycemia.

initial improvement will wane if the underlying pathology of hypoglycemia is not addressed or resolved. Frequent or continuous glucose supplementation may be needed to support patients with hypoglycemia caused by insulin overdose until the exogenous insulin is fully metabolized. Insulin excess due to insulinoma causes a similar problem, but release of endogenous insulin from insulinoma is ongoing and may be unpredictable. Some of these tumors may retain the ability to secrete insulin in response to hyperglycemia, which may develop during bolus glucose administration. The severity of hypoglycemic episodes experienced by juvenile animals or small-breed dogs may decrease with treatment and time as the animal matures and grows.

Idiopathic hypoglycemia carries a good prognosis if triggering factors can be identified and avoided. Prognosis for paraneoplastic hypoglycemia depends on whether effective treatment of the underlying neoplasm is possible. Hypoglycemia secondary to liver failure subsequent to cirrhosis or other disorders carries a poor prognosis, whereas hypoglycemia in patients with portovascular anomaly is expected to resolve after shunt closure.

References

1. Gerich JE. Physiology of glucose homeostasis. *Diabetes Obes Metab*. 2000;2(6):345-350.
2. Forcada Y. Hypoglycemia, hyperglycemia. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. St. Louis, MO: Elsevier Saunders; 2017:246-250.
3. Aronoff SL, Berkowitz K, Shriner B, Want L. Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectrum*. 2004;17(3):183-190.
4. Briscoe VJ, Davis SN. Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology and management. *Clin Diabetes*. 2006; 24(3):115-121.
5. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care*. 2013;17(2):305.
6. Kittah NE, Vella A. Management of endocrine disease: pathogenesis and management of hypoglycemia. *Eur J Endocrinol*. 2017;177(1):R37-R47.
7. Whitley NT, Drobatz KJ, Panciera DL. Insulin overdose in dogs and cats: 28 cases (1986-1993). *J Am Vet Med Assoc*. 1997;211(3):326-330.
8. Gottlieb S, Rand J. Managing feline diabetes: current perspectives. *Vet Med (Auckl)*. 2018;9:33-42.
9. Marks V, Wark G. Forensic aspects of insulin. *Diabetes Res Clin Pract*. 2013;101(3):248-254.
10. Goutal CM, Brugmann BL, Ryan KA. Insulinoma in dogs: a review. *J Am Anim Hosp Assoc*. 2012;48(3):151-63.
11. Polansky BJ, Martinez SA, Chalkley MD. Resolution of hyperinsulinemic hypoglycemia following partial pancreatectomy in a dog with nesidioblastosis. *J Am Vet Med Assoc*. 2018;253(7):893-896.
12 Breitschwerdt EB, Goldkamp C, Castleman WL, et al. Hyperinsulinemic hypoglycemia syndrome in 2 dogs with bartonellosis. *J Vet Intern Med*. 2014;28(4):1331-1335.
13. Mathew P, Thoppil D. Hypoglycemia. StatPearls website. https://www.ncbi.nlm.nih.gov/books/NBK534841/. Accessed June 6, 2020.
14. Piscitelli CM, Dunayer EK, Aumann M. Xylitol toxicity in dogs. *Compend Contin Educ Vet*. 2010;32(2):E1-E4.
15. Kuzuya T, Kanazawa Y, Kosaka K. Stimulation of insulin secretion by xylitol in dogs. *Endocrinology*. 1969;84(2):200-207.
16. Dunayer EK, Gwaltney-Brant SM. Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. *J Am Vet Med Assoc*. 2006;229(7):1113-1117.
17. Morgan RK, Cortes Y, Murphy L. Pathophysiology and aetiology of hypoglycaemic crises. *J Small Anim Pract*. 2018;59(11):659-669.
18. Idowu O, Heading K. Hypoglycemia in dogs: causes, management, and diagnosis. *Can Vet J*. 2018;59(6):642-649.
19. Schermerhorn T. Management of insulin overdose. *Standards Care Emerg Crit Care Med*. 2001;3:1-6.
20. Horwitz DL. Factitious and artifactual hypoglycemia. *Endocrinol Metab Clin North Am*. 1989;18(1):203-210.
21. Fischer JR, Smith SA, Harkin KR. Glucagon constant-rate infusion: a novel strategy for the management of hyperinsulinemic-hypoglycemic crisis in the dog. *J Am Anim Hosp Assoc*. 2000;36(1):27-32.
22. Datte K, Guillaumin J, Barrett S, Monnig A, Cooper E. Retrospective evaluation of the use of glucagon infusion as adjunctive therapy for hypoglycemia in dogs: 9 cases (2005-2014). *J Vet Emerg Crit Care (San Antonio)*. 2016;26(6):775-781.
23. Lathan P, Thompson AL. Management of hypoadrenocorticism (Addison's disease) in dogs. *Vet Med (Auckl)*. 2018;9:1-10.
24. Fischer JR, Smith SA, Harkin KR. Glucagon constant-rate infusion: a novel strategy for the management of hyperinsulinemic-hypoglycemic crisis in the dog. *J Am Anim Hosp Assoc*. 2000;36(1):27-32.
25. Koenig A. Endocrine emergencies in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2013;43(4):869-897.
26. Blanchard G, Paragon BM, Milliat F, Lutton C. Dietary L-carnitine supplementation in obese cats alters carnitine metabolism and decreases ketosis during fasting and induced hepatic lipidosis. *J Nutr*. 2002;132(2):204-210.