Hypoglycemia (blood glucose <70 mg/dl) can cause a wide variety of clinical signs ranging from generalized weakness to seizures and death. Insulinoma is the malignancy most commonly associated with hypoglycemia in dogs, but a wide variety of other non–islet cell tumors have also been shown to cause hypoglycemia in humans and dogs by inducing ectopic hormone production. Non–islet cell tumors that have been reported to cause hypoglycemia include hepatocellular carcinoma, hepatoma, plasma-cytoid tumor, lymphoma, leiomyosarcoma, oral melanoma, hemangiosarcoma, and salivary gland adenocarcinoma.

Insulinomas produce excessive quantities of insulin, which causes very low blood glucose levels. In contrast, hypoglycemia of extrapancreatic tumors in dogs has been associated with low to low-normal insulin levels. Extrapancreatic tumors cause hypoglycemia by secreting an insulin-like substance, accelerating the utilization of glucose by the tumor, and causing failure of gluconeogenesis or glycogenolysis by the liver. The most common nonmalignant causes of hypoglycemia are hyperinsulinism, hepatic dysfunction, adrenocortical insufficiency, hypopituitarism, extrapancreatic tumors, starvation, and sepsis. Laboratory error is perhaps the most common cause of hypoglycemia.

**DIAGNOSTIC CRITERIA**

Currently, it is not possible to identify the cause of hypoglycemia in many extrapancreatic tumors. Insulin-producing tumors, such as insulinomas, may be diagnosed by identifying normal to elevated insulin levels in association with low blood glucose concentrations. For accurate diagnosis, some patients require frequent evaluation of glucose and insulin concentrations during a 72-hour fast. Although controversial, the amended insulin:glucose ratio has been advocated as a method to help diagnose insulin-producing tumors in pets:

\[
\text{Amended insulin:glucose ratio} = \frac{\text{Serum insulin (µU/ml)} \times 100}{\text{Serum glucose (mg/dl)} - 30}
\]

Values above 30 are highly suggestive of an insulinoma or other insulin-producing tumor.

**Historical Information**

- Weakness.
- Confusion.
- Seizures.
- Coma.

**Physical Examination Findings**

- Clinical signs are often paroxysmal and subtle in the earlier phases of the disease and are followed by seizures, coma, and death.
- Neurologic signs, including weakness, disorientation, behavioral changes, seizures, coma, and death, predominate in dogs with hypoglycemia secondary to a malignancy. These clinical signs generally occur in dogs when blood glucose falls below 45 mg/dl. Death may also occur.
- Catecholamines, growth hormone, glucocorticoids, and glucagon are released secondary to hypo-
glycemia and activate compensatory mechanisms to combat hypoglycemia by promoting glycogenolysis.

**Laboratory Testing**
- Complete blood count.
- Biochemical profile.
- Urinalysis.
- Fasting blood glucose and insulin levels.

**Other Diagnostic Testing**
- Radiography.
- Abdominal ultrasonography.
- Computed tomography.
- Magnetic resonance imaging.
- Exploratory surgery.
- Biopsy.

**TREATMENT RECOMMENDATIONS**
- Treat the underlying cause.
- Give frequent feedings of a complex carbohydrate food.
- Administer glucose infusion, prednisone, and diazoxide with or without hydrochlorothiazide.
- Propranolol may be of value in refractory cases.

**Surgical Treatment**
- Surgery is the only method of eliminating the underlying cause of malignancy-associated hypoglycemia. However, metastases are common with most malignant tumors associated with this condition. Therefore, surgery often is not curative.
- If an insulinoma is suspected, a partial pancreatectomy may be indicated. Complications include iatrogenic pancreatitis and diabetes mellitus.

**Medical Management**
- Medical management of the hypoglycemia is essential before, during, and after surgery because of the serious consequences of hypoglycemia and the high metastatic rate.
- Dogs with severe cases of hypoglycemia should be treated with IV administration of 2.5% to 5% dextrose in parenteral fluids, such as 0.9% NaCl or Ringer’s solution. Dogs that are convulsing should be given IV 0.5 g/kg dextrose slowly over 5 minutes.

**Combined Surgical and Medical Management**
Combined surgical and medical management of pancreatic tumors has been associated with remission periods of 1 year or more. The following agents may be useful in the medical management of hypoglycemia:
- **Prednisone:** 0.5–2.0 mg/kg PO divided bid can induce hepatic gluconeogenesis and decrease peripheral utilization of glucose.
- **Diazoxide:** 10–40 mg/kg PO divided bid, with or without hydrochlorothiazide (2–4 mg/kg PO daily), may be effective in elevating blood glucose levels by inhibiting pancreatic insulin secretion and glucose uptake by tissues, enhancing epinephrine-induced glycogenolysis, and increasing the rate of mobilization of free fatty acids. Diazoxide is expensive and difficult to obtain. Hydrochlorothiazide enhances the hyperglycemic effects of diazoxide.
- **Propranolol:** 0.2–1.0 mg/kg PO tid may be effective in increasing blood glucose levels by blocking insulin release through the blockade of β-adrenergic receptors at the level of the pancreatic β cell; inhibiting insulin release by membrane stabilization; and altering peripheral insulin receptor affinity.
- **Streptozotocin** (streptozocin): This is a nitrosourea chemotherapeutic agent that is specifically toxic to β cells and therefore specific for the treatment of insulinomas. It is being evaluated by a number of oncologists. Streptozotocin can induce nephrotoxicity unless given with aggressive saline diuresis. The drug is also extremely emetogenic; pretreatment with butorphanol, metoclopramide, or ondansetron is required.
- **Glucagon:** 5 ng/kg/min can be used to increase gluconeogenesis. Glucagon can be used by reconstituting 1 mg of lyophilized glucagon with the diluent provided. This material can be added to 1 L of 0.9% NaCl. The resulting solution will have a 1-µg/ml concentration, which allows for convenient administration rates. This treatment is most effective for the hypoglycemic crisis, but it may provide sustained benefits after infusion in some cases.

**PROGNOSIS**
- Survival times for dogs with insulinomas range widely in reported studies, based on the treatment selected (surgery alone, medical therapy alone, or both) and tumor stage. The stages are stage 1 (pancreatic nodule only), stage 2 (regional lymph node metastasis), and stage 3 (distant metastasis, usually the liver). In one study of 73 dogs, dogs with stage 1 tumors had a median disease-free interval (no hypoglycemia) of 14 months; those with stage 1 or 2 tumors had similar median survival times of 12 to 18 months; and those with stage 3 tumors lived an average of 6 months. Five dogs lived between 24 and 36 months (two stage 1 tumors, three stage 2 tumors). Younger dogs generally had a poorer prognosis than older dogs.
Dogs with insulinomas managed surgically (with or without postoperative medical therapy) generally survive longer than those managed with medical therapy alone. Debulking metastatic disease increases survival times. In one study, the median survival with surgery was 381 days in 26 dogs compared with 70 days in 13 dogs treated with medical therapy alone. In another study, 31 dogs with resectable tumors or metastases had a median survival of 258 days. Dogs in that study that were hyperglycemic or normoglycemic after surgery had a median survival of 680 days; dogs that were hypoglycemic had a median survival of 90 days. In a third study, 18 dogs that were normoglycemic after surgery lived for more than 435 days. Eleven dogs that were hypoglycemic after surgery and were treated medically survived a median of 215 days (with one dog alive after 704 days).

RECOMMENDED READING


