Hypoglycemia in Patients Without Diabetes Mellitus

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Introduction

Hypoglycemia is defined as a blood glucose concentration of < 60 mg/dl (3.3 mmol/L). Because of the effectiveness of defense mechanisms against falling glucose concentrations, hypoglycemia is an uncommon clinical event in non-diabetic adult dogs and cats, although two exceptions are xylitol toxicity and babesiosis caused by *Babesia canis rossi* in the dog. However, hypoglycemia does occur with regularity in neonates, toy and miniature breed dogs less than 6 months of age without portosystemic vascular anomalies (PCVA), and young dogs with PCVA. In addition, hypoglycemia is a very common complication in insulin-treated diabetic dogs and cats; the incidence of owner reported "occasional" hypoglycemic episodes ranges from 35 to 40%. Although animals with diabetes are not spared the risk for the same hypoglycemic disorders than those without diabetes, the vast majority of their hypoglycemic episodes are the result of treatment of their diabetes.

Maintenance of Normal Glucose Concentrations in Healthy Dogs and Cats

Cell function and metabolism are dependent on energy sources delivered via the circulation. There are two major sources of energy: meals (ingested carbohydrates, proteins, and fat) and glucose that is produced by the liver. The liver initially produces glucose by the breakdown of stored glycogen (glycogenolysis). As glycogen stores are depleted, glucose levels are augmented by gluconeogenesis. The whole process of gluconeogenesis is quite complex and is dependent on certain substrates such as amino acids and free fatty acids mobilized from muscle and adipose tissue. In addition, a normally functioning endocrine system is also necessary to maintain glucose homeostasis and prevent hypoglycemia. Insulin is the dominant glucose-lowering hormone. It suppresses endogenous glucose production and stimulates glucose utilization. The glucose-raising or counterregulatory hormones include epinephrine, glucagon, growth hormone (GH), and cortisol. These hormones increase hepatic glucose production by stimulating glycogenolysis and gluconeogenesis and also inhibit glucose utilization by tissues.

Because the brain cannot synthesize glucose, store glycogen, or use physiologic circulating concentrations of alternative fuels effectively, maintenance of brain function, and ultimately survival, requires a continuous supply of glucose from the circulation. That, in turn, requires maintenance of the plasma glucose concentration within the physiological range because blood-to-brain glucose transport is a direct function of the arterial plasma glucose concentration. Glucose counterregulatory mechanisms effectively prevent or rapidly correct hypoglycemia. These critical physiological defenses include 1) a decrease in insulin secretion as glucose levels decline within the physiological range; 2) an increase in glucagon secretion; or, in its absence, 3) an increase in epinephrine secretion, both occurring as glucose levels decline just below the physiological range. In addition, increased cortisol and GH secretion are involved in the defense against prolonged hypoglycemia. If these defense mechanisms fail, blood glucose levels will continue to fall, and as a result, insulin secretion is virtually completely suppressed at glucose levels < 60 mg/ml. In essence, hypoglycemia develops when the sum of glucose utilization from the circulation (largely by the brain but also by the renal medulla, red blood cells, and insulin sensitive tissues, such as muscle) exceeds the sum of glucose delivery into the circulation (from ingested carbohydrates and hepatic and renal glucose production).

Clinical Signs of Hypoglycemia

Clinical hypoglycemia is a blood glucose level low enough to cause symptoms, including impairment of brain function. For example, values below 50 mg/dl (2.8 mmol/L) are often accompanied by symptoms, but values below the lower end of the normal reference range may not be. Hence clinical hypoglycemia, which is also referred to as “the hypoglycemic syndrome”, is not defined by hypoglycemia alone, but according to Whipple’s triad – hypoglycemia accompanied by symptoms that are relieved by the administration of glucose or by feeding.

Symptoms of hypoglycemia are categorized as neuroglycopenic (lack of glucose supply to the brain) or autonomic (largely the result of the sympathoadrenal discharge triggered by hypoglycemia). The neuroglycopenic signs range from lethargy, weakness, ataxia and unusual behavior to seizures and coma. Clinical signs resulting from stimulation of the sympathoadrenal system include restlessness, muscle tremors and hunger. Clinical manifestations are dependent on the duration and severity of hypoglycemia. For example, in healthy people, symptoms of hypoglycemia develop at a mean plasma glucose concentration of 55 mg/dl. However, people with recurring fasting

hypoglycemia appear to tolerate low blood glucose levels for prolonged periods (e.g., < 40 mg/dl) without exhibiting clinical signs. This adaptive process to chronic severe hypoglycemia also occurs in animals.

Etiology/Pathophysiology

Identification of randomly obtained or a fasting blood glucose concentration below 60 mg/dl is cause for concern in dogs or cats. Although this finding is not always diagnostic of organic disease, normal dogs and cats have consistently been shown not to have blood glucose concentrations decline below this level. Therefore, once artifactual hypoglycemia has been ruled out as a possible cause, organic disease is a likely cause of persistent hypoglycemia. Failure in any one of the key steps in the production or conservation of glucose may result in hypoglycemia and clinical signs of hypoglycemia.

Artifactual hypoglycemia

Artifactual hypoglycemia, which is also referred to as pseudohypoglycemia, is not a clinical syndrome but rather a result of artifactually low blood glucose concentration in vitro, mainly in the presence of leukocytosis, polycythemia, or both. In dogs, it has been reported that the glucose concentration in whole blood kept at room temperature can decrease in by as much as 10 mg/dl/hour. Presumably this decrease in glucose concentration is due to continuing utilization of glucose by cells present in the blood. Therefore, whole blood obtained for glucose determination should be centrifuged within an hour after collection, separated and refrigerated or frozen to minimize artifactual lowering of blood glucose concentration. In addition, the practice of measuring glucose in whole blood immediately after collection using portable hand-held glucometers specifically designed and manufactured for measuring human blood glucose, while quick and convenient, is less accurate than measurements by an accredited veterinary laboratory. Because dogs, cats, and humans have different ratios of glucose between the plasma and red blood cells, if a portable hand-held glucometer is used to determine the blood glucose, it is recommended to use the Alpha-TRAK glucometer (Abbott Animal Health, Abbott, Illinois) which is calibrated specifically for dogs and cats.

Another cause of artifactual hypoglycemia is laboratory error. Incorrect values can occur with any assay, and therefore, it is always wise to confirm a finding of hypoglycemia by evaluating another blood sample before more sophisticated or extensive studies are performed.

Other less common causes of pseudohypoglycemia are seen with the following conditions:

1. Leukemias (e.g., chronic lymphocytic leukemia) and benign forms of leukocytosis (e.g., leukemoid reactions)

2. Chronic hemolytic anemia accompanied by a high (> 3%) nucleated red blood cell count

3. Polycythemia vera: an 87% decrease in blood glucose levels over 4 hours has been reported

4. Hypovolemic shock: poor capillary circulations leads to increased glucose transit time promoting increased glucose extraction by the tissue. Capillary blood sampling from the ear or paw pads are low compared to central venous glucose levels which are normal.

Congenital hepatic disease: Portosystemic vascular shunts, microvascular dysplasia, and glycogen storage disease.

The most common congenital cause of hepatic-induced hypoglycemia is portosytemic vascular anomalies (PSVA). PSVA is really an "umbrella term" which includes dogs with extra-hepatic shunting (PSVA-E) or intra-hepatic shunting (PSVA-I). In addition, many small breed dogs with PSVA have concurrent microvascular dysplasia (MVD). The prevalence of hypoglycemia in dogs with PSVA varies from 5-10%. The hypoglycemia associated with PSVA is presumably caused by chronic hepatic hypoperfusion which leads to insufficient glycogen stores and inadequate hepatocellular function to support gluconeogenesis.

Glycogen storage disease

Glycogen storage diseases (GSD) are rare congenital hepatic disorders in which hypoglycemia results from the inability to convert glycogen to glucose because of the absolute or relative deficiency of the enzymes necessary for the breakdown of glycogen stores in the liver. Type III GSD (Cori's disease), a deficiency of amylo-1,6-glucosidase, was documented in puppies with massive hepatomegaly caused by glycogen accumulation, failure to thrive and muscle weakness. Type I GSD (von Gierke's disease) has been documented in the Maltese breed. This uncommon disorder is a deficiency of glucose-6-phosphatase caused by a defect in the glucose-6-phosphatase gene. Affected puppies develop progressive hepatomegaly characterized by diffuse hepatocellular vacuolization,tremors, weakness, and neurologic signs when hypoglycemic. Biochemical abnormalities include fasting hypoglycemia,

hypercholesterolemia, hypertriglyceridemia, and elevated uric acid levels. Confirmatory tests include histologic evaluation of liver biopsies and specific enzyme assays that are rarely performed in veterinary medicine. And lastly, GSD type IV has been documented in a family of Norwegian forest cats. It leads to death as a result of perinatal hypoglycemic collapse or late-juvenile-onset neuromuscular degeneration.

Idiopathic Causes of Liver-Associated Hypoglycemia in young Animals: Neonatal and Juvenile Hypoglycemia

Neonatal hypoglycemia: The blood glucose concentration in the healthy neonate falls during the first few hours after birth because of the loss of continuous transplacental infusion of glucose. Thereafter, the neonate is dependent on glycogenolysis and gluconeogenesis to maintain euglycemia between feedings. Limited glycogen stores, small muscle mass, and lack of adipose tissue as alternative energy sources place the neonate at risk for hypoglycemia. That said, the ill neonate should always be evaluated for hypoglycemia, especially if sepsis, toxic milk syndrome, or starvation is suspected or hypothermia is noted. Orally administered glucose or frequent bottle feeding can help correct or prevent hypoglycemia

Juvenile hypoglycemia: Hypoglycemia of toy and miniature breed dogs younger than 6 months of age is common. Deficiency of gluconeogenic precursors such as the amino acid alanine, or an age-related transient malfunction or deficiency of enzymes responsible for gluconeogenesis is implicated in this syndrome. Insufficient food supply of any cause such as starvation or gastrointestinal disturbances may cause hypoglycemia within 24 hours of fasting. In addition, underlying conditions such as PSVA that cause anorexia or impaired liver function may contribute to the precipitation of this syndrome. Many of these puppies have a history of being recently purchased along with a recent change in environment and diet. Presenting signs may include weakness, depression, vomiting and diarrhea with or without intestinal parasites, ataxia, stupor and seizures. Similar forms of juvenile hypoglycemia have not been well documented in kittens.

Treatment and Prognosis

Intravenous administration of a 20% or 50% dextrose solution (0.8 ml to 0.2 ml per 100 g body weight respectively) is indicated if there are neurologic signs. If the pup can take the glucose solution orally, this is administered at regular intervals until appetite returns. The small amounts of food are given at intervals of 2 h. If tube feeding is needed, oral rehydration is guided by electrolyte measurements. Clinical improvement occurs rapidly

following glucose administration. The prognosis is good if hypoglycemia is corrected before brain damage occurs. The risk of developing hypoglycemia deceases with increasing age and body weight.

Non-islet Cell Tumor-Induced Hypoglycemia

Hypoglycemia can be a manifestation of neoplastic disease. Tumors related to the occurrence of hypoglycemia can, as a general rule, be divided into 3 groups. First, tumors can produce excess insulin such as pancreatic insulinomas or ectopic insulin-producing tumors. Second, hypoglycemia can be caused by tumor-related factors such as destruction of the liver by massive tumor infiltration. And lastly, there now is convincing evidence that secretion of IGF-2 and incompletely processed insulin-like growth factors (e.g., pro-IGF-2 or "big"-IGF-2) cause hypoglycemia in humans. This mechanism has also been documented in a few cases of hypoglycemia in dogs. Non-islet cell tumor induced hypoglycemia (NICTH) can arise in virtually every benign and malignant tumor. However, it mainly occurs in patients with solid tumors of mesenchymal (e.g., leiomyosarcoma, fibrosarcoma) and epithelial origin (e.g., hepatoma, hepatocellular carcinoma), but rarely in patients with tumors of hematopoietic or neuroendocrine origin. The most frequent nonpancreatic tumors associated with hypoglycemia are leiomyoma, leiomyosarcoma, hepatoma, hepatocellular carcinoma, and tumors with extensive hepatic metastasis.

Hypoadrenocorticism

Hypoadrenocorticism should always be on the rule-out list for hypoglycemia. Of 506 dogs diagnosed with hypoadrenocorticism at UC Davis Veterinary Medical Teaching Hospital, 116 dogs (25%) were hypoglycemic at the time of diagnosis. Interestingly, however, clinical signs attributable to hypoglycemia appear to be uncommon. In this cohort of cases, hypoglycemic seizures and other clinical signs that may have been caused by hypoglycemia such as ataxia and disorientation were observed in only 30 dogs (6%).

Critical Illness and Hypoglycemia: Renal failure, Acquired Liver Disease, Sepsis, and Virulent Babesiosis

Renal failure

Renal failure is associated with hypoglycemia in critically ill diabetic and non-diabetic human patients, however the impact of renal failure on the blood glucose concentration is unpredictable in dogs and cats. In most cases the blood glucose concentration is normal. However, hyperglycemia may develop as a result of uremic-induced carbohydrate intolerance and insulin resistance in a dog or cat with impaired insulin secretion; this phenomenon has been referred to as "pseudodiabetes''. Alternatively, renal failure may induce hypoglycemia. Several mechanisms for the development of hypoglycemia during renal insufficiency have been proposed. These include reduced renal gluconeogenesis and decreased caloric intake related to inappetence. Normally, renal gluconeogenesis may supply as much as 45 percent of new glucose during prolonged starvation. Additional defects in glucose homeostasis occur in renal insufficiency, including an increased insulin half-life related to decreased renal degradation or excretion of insulin, impaired hepatic glycogenolysis and gluconeogenesis, inadequate glucose counterregulatory responses, or a combination of these factors. It should be emphasized that hypoglycemia is rarely the cause of death in the critically ill patient with renal failure and is considered more a marker for multisystem failure than a cause of mortality.

Acquired Hepatic Dysfunction

Hypoglycemia has been associated with a wide spectrum of liver diseases in people. These disorders include everything from type 1 glycogen storage disease, cirrhosis, viral hepatitis, procainamide-induced hepatitis, cholecystitis, and metastatic infiltration to fulminant liver failure after cardiac arrest. In dogs and cats hypoglycemia often results from severe destruction of the liver from bacterial infection, hepatotoxins, neoplasia, and chronic fibrosis/cirrhosis with the development of acquired portosystemic shunts. The underlying cause of hypoglycemia results from inadequate amounts of functional liver tissue for optimal gluconeogenesis and glycogen storage to maintain normal blood glucose levels. The diagnosis of acquired liver dysfunction is usually quite straightforward. Common CBC, serum biochemical profile and urinalysis abnormalities may include microcytosis, low serum albumin, BUN and cholesterol concentrations, elevated serum bilirubin levels, elevated paired serum bile acid concentrations, ammonium biurate crystals in the urine, and radiographic evidence of abnormal liver size, and/or ultrasonographic changes consistent with abnormal echotexture or liver size. A liver biopsy is necessary to determine the exact cause of the liver disorder and may help guide specific treatment options such as the selective use of antibiotics, glucocorticoids, copper chelation, cyclosporine, lactulose, and dietary therapy.

Sepsis-induced Hypoglycemia

Systemic illness caused by microbial (usually bacteria) invasion of normally sterile parts of the body is referred to as sepsis. Sepsis plus organ dysfunction or hypoperfusion is termed severe sepsis. And severe sepsis accompanied by hypotension is termed septic shock. Impaired glucose homeostasis has been well documented in patients with sepsis. Hyperglycemia is the most common blood glucose abnormality seen early in the course of bacterial sepsis. In pre-terminal sepsis, profound hypoglycemia may occur because of hyperinsulinemia, increased tissue uptake of glucose, and the failure of hepatic glucose production. It is postulated that sepsis-related hypoglycemia is a manifestation of non-specific inflammatory responses mediated by high levels of cytokines, including tumor necrosis factor and interleukin-6. The signs and symptoms of sepsis are highly variable. They are influenced by the virulence and "bioburden' (the amount) of the organism, the portal of entry (e.g., skin, gut, urinary tract) and host susceptibility (the young and very old and patients with weakened immune systems are most at risk). Patients with sepsis can present with a fever or hypothermia and CBC findings may show a leukocytosis with a left shift or leukopenia. Common causes of sepsis-induced hypoglycemia include parvovirus infection, prostatic and liver abscesses, pyothorax, pyometra, hemorrhagic gastroenteritis, and gram-negative bacteremia. The diagnosis of sepsis-induced hypoglycemia is often one of suspicion or identification of an infection based on history, physical examination and CBC findings, and other diagnostics such as bacterial cultures, radiography and ultrasonography, and resolution of hypoglycemia after initiation of antibiotic therapy.

Virulent babesiosis

Hypoglycemia has been identified as a life-threatening metabolic complication in almost 20% of severely ill dogs suffering from babesiosis caused by *Babesia canis rossi*. This highly virulent subspecies of *Babesia canis* is endemic only to South Africa. Clinical signs include pale mucous membranes, depression, tachycardia, tachypnea, anorexia, weakness, splenomegaly and fever. The clinical signs are attributed to tissue hypoxia resulting from anemia and a concomitant systemic inflammatory response syndrome caused by marked cytokine release. The severe form of the disease is characterised by hemolytic anemia and severe acid-base derangements, with secondary multiple organ failure and complications such as acute renal failure, hepatopathy with marked icterus, hypoglycemia, acute respiratory distress syndrome, cerebral pathology and additional immune-mediated erythrocyte destruction. Mortality is around 12%. A feature of the disease is that, in contrast to babesiosis in other domestic

species, pups and immature dogs are also severely affected. Only one case of *Babesia canis rossi* has been reported in a dog in the United States and that was a dog imported from South Africa.

Several contributing factors have been implicated as causes of the hypoglycemia. These include increased peripheral requirement for glucose during febrile and critical illness, obligatory demands of the parasites that use glucose as their major fuel, hyperinsulinemia, failure of hepatic gluconeogenesis and glycogenolysis, and increased glucose consumption by anaerobic glycolysis because of tissue hypoxia.

Blood glucose concentration should ideally be measured in all dogs requiring inpatient treatment for babesiosis, but is mandatory in collapsed dogs, puppies and dogs with severe anemia, vomiting, or icterus. Many dogs have probably been misdiagnosed with cerebral babesiosis in the past, and hypoglycemia should be suspected in any dog with coma or other neurological signs. Response to treatment with selected antibabesial compounds such as imidocarb dipropionate, atovaquone, azithromycin, clindamycin, and doxycycline is variable, and intravenous dextrose does not reliably improve glycemic status or survival.

Persistent Hyperinsulinemic Hypoglycemic Syndrome

In humans, persistent hyperinsulinemic hypoglycemia of infancy (PHHI) represents the most common cause of hyperinsulinism in neonates and children; currently, many authors prefer the term congenital hyperinsulinism (CHI). Severe recurrent hypoglycemia associated with an inappropriate elevation of serum insulin defines CHI. This disturbance of the normal relationship between glucose concentration and insulin secretion is caused by a variety of genetic mutations. If left untreated, CHI can lead to brain damage or death secondary to severe hypoglycemia. Although it was initially thought to affect only infants and children, numerous cases have been reported in adults of all ages but at a much lower incidence. CHI is often poorly responsive or unresponsive to medical management, necessitating 95% or near-total pancreatectomy.

Recently, a persistent hyperinsulinemic hypoglycemic syndrome, not associated with sepsis or insulinoma, was diagnosed in two dogs. Both dogs were less than 12 months of age. The clinical signs in these dogs were similar; hypoglycemic–induced seizures unresponsive to intravenous glucose administration and anticonvulsant therapy. The owners of these dogs elected euthanasia because of poor response to therapy and poor prognosis. Blood was cultured from one dog using a special enrichment PCR media to rule in or rule out an infection caused by a

fastidious bacteria; *Bartonella hensalae* was amplified and sequenced from this dog's blood. In the other dog, *Bartonella kohlerae* was amplified and sequenced retrospectively from paraffin-imbedded tissue. Despite isolating *Bartonella* sp. from both dogs, it is unclear whether *B. hensalae* and *B. kohlerae* contributed to the pathogenesis of this unusual and rare hypoglycemic syndrome. That said, persistent hyperinsulinemic hypoglycemic syndrome should be suspected in any young dog with hypoglycemia refractory to intravenous glucose. Moreover, until more is known about the cause of this syndrome, testing and treating for *Bartonella* sp. should be a diagnostic and therapeutic consideration.

Xylitol toxicity

Xylitol exposure, even in small amounts, can cause hypoglycemia and severe liver damage in dogs. Xylitol is a 5-carbon sugar alcohol that is used primarily as an artificial sweetener that has less than two-thirds the calories of most sugars. The two major sources of xylitol exposure are food and dental or medical products. Initially, exposure to xylitol in dogs was from ''sugar-free'' chewing gums. However, with demands from human diabetic patients, particularly because of the popularity of Atkins-like ''low-carb'' diets, many foods now contain xylitol. A large number of low carbohydrate foods, including a variety of breads, candies, gums, and deserts, have xylitol as the sweetener of choice. Xylitol has a wide margin of safety in mammals with the exception of dogs. Oral exposures as low as 0.1 mg/kg have induced hypoglycemia in the dog, and levels of 0.5 mg/kg have resulted in hepatotoxicity in some dogs. For example, one piece of Trident gum contains 0.22 g of xylitol and the popular breath mint Ice Breakers contains 1 g of xylitol per piece and therefore, 9 pieces of Trident or 2 Ice Breaker pieces could potentially cause xylitol toxicity in a 20 kg dog. The literature reports no cases of xylitol toxicity in cats.

The Diagnostic Approach to Disorders Associated With Hypoglycemia

After confirming the finding of hypoglycemia, the history (including exposure to insulin, sulfonylureas, or xylitol), signalment, physical exam findings, and a careful review of available laboratory data guide the evaluation. This information will either provide clues to the cause of hypoglycemia or exclude hypoglycemia caused by acknowledged drugs or toxins, critical illnesses, hormone deficiencies, or a non-islet cell tumor. A test of adrenocortical function is reasonable although hypoadrenocorticism is not commonly found as a cause of

hypoglycemia in dogs in the absence of other clinical clues. Non-islet cell tumor hypoglycemia is often associated with a large, clinically apparent mesenchymal tumor (e.g., leiomyoma and leiomyosarcoma) as well as epithelial tumors that are associated with the liver (e.g., hepatoma or hepatocellular carcinoma).

As part of the signalment, age of the animal can be quite useful in narrowing down the long list of rule outs for hypoglycemia. For example, hypoglycemia in a puppy or kitten is often idiopathic in origin or related to starvation, PSVA, or sepsis. In young adult dogs hypoglycemia is usually caused by hepatic insufficiency, hypoadrenocorticism, or sepsis. And in older dogs, hepatic insufficiency, insulinoma (see Chapter "X"), non-islet cell tumor induced hypoglycemia, hypoadrenocorticism, and sepsis are the most common causes of hypoglycemia.

The results of routine and specialized tests can also be quite helpful diagnostically. For example, dogs with adrenal insufficiency without the classic electrolyte changes of hyperkalemia and hyponatremia often have hypoalbuminemia, hypocholesterolemia and a resting cortisol < 2 mcg/dl; although an ACTH response test is required for a definitive diagnosis. Paired fasting and postprandial serum bile acids are diagnostic for virtually all dogs with a portosystemic shunt, and CBC findings which include a neutrophilic leukocytosis with a left shift in a hypoglycemic febrile dog or cat are highly suggestive of sepsis.

When the cause of the hypoglycemic disorder is not evident in a seemingly well adult dog, serum glucose and insulin concentrations should be measured during an episode of spontaneous hypoglycemia to rule out an insulinoma. The key pathophysiological feature of endogenous hyperinsulinism (e.g., an insulinoma) is the failure of insulin secretion to fall to very low rates as blood glucose concentrations fall to hypoglycemic levels.