Clinical insulin resistance should be suspected in any dog or cat with diabetes mellitus (DM) in which marked hyperglycemia persists throughout the day despite insulin injections of >1 to 1.5 U/kg. A thorough review of the owner’s injection method is required; possible causes for a poor response to insulin treatment include inadequate mixing of the insulin prior to withdrawal into the syringe, misunderstanding how to read the syringe, and problems with technique of administration. Unrecognized insulin underdosage can result from administration of insulin that is outdated, inactivated because of overshaking or overheating, or improperly diluted.

If any of these is suspected, administer undiluted insulin taken from a new bottle and then measure several blood glucose concentrations over the course of a day. The diet and feeding
The scruff of the neck is a poor choice for insulin administration that is often made by owners. Insulin is not well absorbed from this site.

The schedule should also be reviewed. Dry foods that contain a moderate level of carbohydrates with added soluble fiber generally are recommended for dogs. Canned or low-carbohydrate, high-protein foods are recommended for cats.

Serial blood glucose monitoring or continuous interstitial glucose determinations (CGD) may define other problems that mimic insulin resistance, such as rapid metabolism of insulin (transient insulin action) or insulin-induced rebound hyperglycemia (Somogyi phenomenon). In the diabetic dog or cat receiving >1.5 U/kg/injection, a diagnosis of insulin resistance is confirmed by demonstrating persistent hyperglycemia (>300 mg/dL).

**Differential Diagnosis of Insulin-Resistant Diabetes in Dogs & Cats**

- **Poor subcutaneous absorption of insulin (subcutaneous insulin resistance).** Subcutaneous (SC) insulin absorption is known to be highly variable; only about 50% of intermediate-acting insulin and 30% of long-acting insulin is absorbed from SC sites. The scruff of the neck is a poor choice for insulin administration that is often made by owners. Insulin is not well absorbed from this site. Below the costochondral junction and behind the ribs are sites of optimal absorption. Poor absorption of insulin is likely to play a role if longer-acting insulins (ie, glargine insulin or PZI) are being administered.

- **Immunologic insulin resistance.** Development of clinical insulin resistance associated with insulin-binding antibodies is relatively uncommon in man and appears to be quite rare in animals.

- **Infection.** Diabetes reduces resistance to infections by increasing extracellular glucose, impairing phagocytosis, causing cellular malnutrition, and impairing microcirculation. Infection induces the increased secretion of cortisol, glucagon, and possibly epinephrine, all of which antagonize the action of insulin.

- **Ketoacidosis or concurrent illness.** As with infection, ketoacidosis, concurrent stress, or illness can also increase secretion of counter-regulatory hormones. Several disease conditions, including diabetic ketoacidosis, renal disease, hepatic insufficiency, cardiac insufficiency, chronic pancreatitis, and starvation, can be associated with insulin resistance.

- **Obesity.** Insulin resistance is a common characteristic of obesity. Correction of obesity decreases the daily insulin requirement of diabetic dogs and cats. In cats with sufficient pancreatic insulin secretor capacity, sufficient weight loss may result in prolonged or permanent discontinuation of insulin treatment.

- **Acromegaly.** In cats, chronic hypersecretion of growth hormone (GH) from pituitary tumors results in acromegaly, a disease characterized by overgrowth of connective tissue, bone, and visceras. In dogs, acromegaly is most often caused by endogenous or exogenous progestogens that induce GH overproduction. Acromegaly, in turn, predisposes cats and dogs to diabetes mellitus (DM) as a result of the antagonistic effect of GH on insulin. It is the most common endocrine cause of insulin resistance in cats.

- **Hyperadrenocorticism.** Hyperadrenocorticism should be suspected in any cat that has insulin-resistant DM, especially if other characteristic signs of Cushing’s syndrome (especially fragile skin) are also present. Overt DM occurs in dogs with hyperadrenocorticism in about 10% of patients. Caution must be used when interpreting low-dose dexamethasone suppression and ACTH stimulation test results, however, because the stress associated with poorly controlled DM alone can produce false-positive test results.

- **Hyperthyroidism in cats.** Hyperthyroidism will occasionally occur simultaneously with DM in cats. Treatment of hyperthyroidism tends to decrease the daily insulin requirements in such cats and allows for better regulation of the diabetic state.
Hypothyroidism in dogs. Hypothyroidism, the most common endocrine cause of insulin resistance in dogs, may occur simultaneously with DM in dogs as a result of a common inherited predisposition to autoimmunity. The mechanisms of glucose intolerance in states of thyroid hormone deficiency include a postreceptor defect in glucose transport, obesity, and hyperlipidemia. To confirm a diagnosis of hypothyroidism, one should measure endogenous thyroid-stimulating hormone (TSH) along with total thyroxine (TT₄).

Hyperlipidemia. Hypertriglyceridemia has been shown to impair insulin receptor binding affinity, promote down regulation of insulin receptors, and cause a postreceptor defect in insulin action. Primary (idiopathic) hypertriglyceridemia is rare in most dogs but is believed to be relatively common in the miniature schnauzer, Shetland sheepdog, and Doberman. Control of hyperlipidemia (eg, through diet) may also lessen insulin resistance and improve diabetic control.

Drugs. In dogs and cats, administration of...
either glucocorticoids or progestagens can lead to insulin resistance and overt DM.

Management of Confirmed Insulin Resistance

Once insulin resistance is documented, one should initiate an investigation to identify the underlying cause (Figure 1). The initial step in the diagnostic approach is a complete review of the history and a thorough physical examination (Figure 2). The next step is to repeat a diagnostic profile, which should include a complete blood count, serum chemistry analysis, and complete urinalysis, to rule out infection, ketoacidosis, and concurrent disease. Chest radiographs, abdominal ultrasonography, and urine bacterial culture should also be considered. In cats, thyroid function testing (eg, serum TT4 determination) should also be performed at this time to rule out hyperthyroidism. In dogs, the addition of endogenous TSH to TT4 determination will help rule out hypothyroidism. If initial procedures or testing fails to reveal the cause of insulin resistance, one should proceed in the flowchart to other known causes of insulin-resistant DM.

If the cause cannot be identified or definitive treatment of the underlying disorder is not possible, one can generally overcome insulin resistance and control marked hyperglycemia by administering large, divided doses of insulin. Use of a combination of short- and long-acting insulin administered in a 1:2 ratio (eg, 1/3 total dose given as regular insulin; 2/3 as NPH) may be required to control severe hyperglycemia. The added short-acting insulin helps to overcome severe insulin resistance and minimize postprandial hyperglycemia.

Suggested Reading


