

When the Insulin Isn't Working: II. Management of the Insulin-Resistant Patient

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Insulin resistance (IR) is usually considered in patients with diabetes mellitus (DM) which do not show the expected response to exogenously administered insulin, manifesting as persistence of hyperglycemia and persistence of clinical signs suggesting insulin ineffectiveness. In these patients which do not show satisfactory response to insulin, it is important to address ALL of the many factors, including IR, which may impair the patient's apparent response to treatment. In fact, factors OTHER than IR are more common causes of poor glycemic control in the initial months of treatment.

First, it is critical that, at the time of initial diagnosis of DM, the patient is fully assessed for the presence of other related or unrelated abnormalities that may impact response to treatment. A thorough medication history is important since administration of some drugs (corticosteroids, other steroid hormones, cyclosporine), including topical preparations, may interfere with response to insulin. Medications which other animals or humans in the household are receiving and to which the diabetic may accidentally be exposed must also be addressed, especially if, after beginning insulin therapy, the patient is not responding to treatment as expected. Identification of co-morbidities (dental disease, renal disease, cardiac disease) and conditions commonly developing as a consequence of the diabetic condition (urinary tract infection, hypertension) must be identified and resolved or managed to the degree possible. Any source of infection or inflammation may affect insulin responsiveness.

In deciding on the initial insulin type, dose and frequency of administration, it is important to recognize that recommended starting doses for the various insulin types are expected to be a starting point, erring on the "safer" side of insulin underdosage, and that adjustments upwards are expected. Owners should be fully advised of this in addition to being carefully schooled on proper handling and administration of insulin and at-home monitoring of the patient. Additionally, it is VITAL to understand that hyperglycemia itself, which obviously will be present in the newly-diagnosed diabetic, causes impaired insulin response, a phenomenon known as "glucose toxicity". The presence of high circulating glucose levels suppresses beta cell function (further suppresses release of any endogenous insulin) and induces IR in peripheral tissues, reducing insulin-stimulated glucose uptake. When insulin administration is initiated, it takes time for beta cells and peripheral tissues to fully respond to a particular dose of insulin (until the administration of insulin begins to correct the hyperglycemia, removing its suppressive effects). **THIS IS WHY WE DON'T CONTINUE INCREASING THE INSULIN DOSE IN THE FIRST 2 WEEKS OF TREATMENT** (we may reduce the dose if hypoglycemia occurs but DO NOT adjust the dose upward because of persistent hyperglycemia until the patient has been on that particular dose of insulin for at least 2 weeks). It is important to realize that sustained hyperglycemia in this period is not unexpected and does not indicate a need for extensive diagnostics to address IR.

Another factor to consider in patients not showing expected control is the manner in which they are being monitored and factors other than IR that may impact monitored parameters. Spot-check glucose measurements are not adequate for monitoring DM except to identify hypoglycemia. Even in more accurate assessments of response, such as serial blood glucose curves, we know that results vary significantly even on consecutive days in the same animal with the same dose of insulin. We need to acknowledge that there will be some day-to-day variation in diabetic control due to variations in how the insulin is administered and absorbed; total dietary intake and rate of absorption; dietary indiscretions; amount of exercise; and stress, especially in cats. Fructosamine levels may be misleading in patients with other processes impacting serum protein turnover (relatively decreased levels in hyperthyroidism, protein-losing enteropathy/nephropathy) or in patients experiencing a Somogyi response due to insulin overdosage (may have normal, slightly elevated or markedly elevated fructosamine level).

Once insulin therapy has been appropriately initiated and serial q2week increases in the dose +/- frequency (if initially given q24h with intermediate-acting insulin type) insulin have failed to achieve

expected glycemic control, the possibility of IR should be addressed as follows:

- § **Is it really insulin resistance or are owners not giving the insulin properly?** (Check insulin expiration, WATCH owners draw and administer insulin)
- § **Is diluted insulin being used?** (Switch to non-diluted)
- § **Is it impaired insulin absorption?** (In many of the diabetic animals referred for poor glycemic control, owners are administering insulin improperly in the nape of the neck rather than in varying sites on the lateral thorax.)
- § **Is it underdosage or inadequate duration of the insulin type?**
- § **Is it insulin overdosage?** (Insulin-induced hyperglycemia - Somogyi phenomenon - can produce the appearance of IR or actual IR.)

The possibility of a Somogyi phenomenon should be considered in ANY poorly-regulated diabetic regardless of the insulin dose or fructosamine level. Affected animals will show the same clinical signs as insulin underdosage although the underlying problem is life-threatening hypoglycemia from insulin overdosage. Cats are especially susceptible, in part because stress-induced hyperglycemia in this species may complicate accurate assessment of glycemic control.

- § **Is it progression of beta cell dysfunction?** (It is common for DM to 'get worse', with patients requiring a dose increase 6 months or more after they are initially regulated.)

Once these factors have been addressed, the presence of true IR should be considered. Any concurrent infectious, inflammatory, endocrine, renal, cardiac or neoplastic disease can interfere with tissue responsiveness to insulin by pre-receptor, receptor, post-receptor or multiple mechanisms. A comprehensive evaluation of the poorly-responsive patient is indicated to identify sources of IR.

The most common cause of true IR is the presence of insulin-antagonizing hormones which results in receptor and post-receptor defects in insulin response. Elevated glucocorticoid levels (hyperadrenocorticism [HAC] or administration of glucocorticoid-containing medications) induce severe IR and represent the most common cause in dogs. HAC causes progressive worsening of glycemic control as the HAC progresses but is difficult to diagnose in the face of unregulated DM, which constitutes chronic 'stress'. HAC alters insulin responsiveness at the levels of the liver, muscle and bone and impairs beta cell function, potentially inducing DM.

Thyroidal disease impacts insulin response. Hyperthyroidism in cats induces IR that resolves with treatment of the hyperthyroidism. It is important to recognize that cats receiving insulin may require a decrease in their insulin dose when treatment for hyperthyroidism is initiated. Other considerations in hyperthyroid patients are 1) hyperthyroidism alters protein turnover, resulting in lower than expected fructosamine levels, and 2) poorly regulated diabetics may have T4 levels that are 'falsely' lowered by this concurrent disease ('euthyroid sick'). Low thyroxine levels in diabetic dogs are usually reflecting a 'euthyroid sick' condition. True hypothyroidism, which is uncommon, is associated with poor response to insulin which usually improves with of thyroid hormone administration; insulin dose will likely need to be reduced when treatment with levothyroxine is initiated.

Acromegaly, or growth hormone (GH) excess, induces severe IR. This condition is uncommon in cats, where it occurs in older male cats due to development of a GH-secreting pituitary macroadenoma, and rare in dogs, where it develops due to GH secretion from the mammary gland in intact females and resolves with ovariohysterectomy.

Progestogens, whether endogenous (progesterone-secreting tumor, diestrus or pregnant bitch) or exogenous (Depo-Provera, Ovaban) causes severe IR and, like HAC, may *cause* DM. Glucagonoma, a glucagon-secreting tumor of the pancreatic islet A cells, is an uncommon but potent cause of IR. Glucagon is an insulin antagonist that also contributes to the Somogyi response to hypoglycemia.

Catecholamine excess (pheochromocytoma in dogs, stress hyperglycemia in cats) acts at the levels of liver, muscle and kidney to counter the action of insulin but usually is not a significant contributor to IR because the catecholamine release is episodic.

Obesity causes a reversible form of IR that is usually relatively mild, readily overcome by increases in insulin dose and weight loss.

Cyclosporine administration induces severe IR. In patients being treated for immune-mediated disease, it is not unusual for glucocorticoids to be administered concurrently with cyclosporine, compounding the insulin-antagonistic effect of treatment superimposed on an inflammatory disease process and its associated IR. Additionally, immunosuppressive treatment is generally continued for long periods up to lifelong so the effect on beta cell function and insulin responsiveness of peripheral tissues is profound. Some of these patients do become overtly diabetic as a consequence but, even if they do not, they are certainly experiencing severe derangements in carbohydrate handling.

Pancreatic disease can interfere with response to insulin. Pancreatitis is a common co-morbidity in diabetic dogs (35%) and cats (50%) that can result in IR and variability in insulin requirements with variation in the level of pancreatic inflammation in chronic pancreatitis. Some patients with pancreatitis may be overtly diabetic then revert to a non-insulin requiring condition with the resolution of pancreatitis (dogs). EPI can interfere with regulation of the diabetic due to variable nutrient absorption.

Bacterial infections are common in diabetics as DM results in altered immune function and any bacterial disease results in IR by multiple mechanisms. Careful monitoring for and treatment of infections improves diabetic management.

Patients with renal insufficiency may show variation in insulin response. Renal disease results in changes in insulin responsiveness of peripheral tissue but also places these patients at an increased risk for hypoglycemia due to decreased renal clearance of insulin (prolonged insulin effect) and decreased renal gluconeogenesis. Additionally, the fact that these patients remain PU/PD due to their renal disease despite level of glycemic control complicates monitoring of DM.

Hypertriglyceridemia may be a cause or effect of poor diabetic control. Hypertriglyceridemia interferes with insulin binding to its receptor, alters receptor function and alters tissue response to insulin as well as resulting in increased hepatic release of glucose. Lack of adequate insulin causes alterations in lipid metabolism.

Non-endocrine neoplasia (lymphosarcoma, mast cell tumor) and cardiac disease are also associated with subnormal response to insulin.

Clearly, to address the many causes of IR, a comprehensive diagnostic work-up may be required. If none of these explanations for IR are evident, the presence of anti-insulin antibodies should be considered as a potential cause for poor insulin response. Development of anti-insulin antibodies appears to be uncommon with human recombinant or pork insulin but is common in dogs treated with bovine insulin. These antibodies have a variable effect and may enhance or impair response to insulin. Change of insulin type usually remedies this problem.

Finally, intrinsic defects in the insulin receptor or in post-receptor function and auto-antibodies directed against the insulin receptor have been identified which alter insulin responsiveness. None of these have yet been reported in the dog or cat.