Inadequate response to insulin, or insulin resistance, has many potential causes and may lead to diabetes mellitus or may complicate management of diabetic patients. To address insulin resistance, it is important to consider insulin and glycemic control under normal conditions.

Insulin is synthesized and secreted by pancreatic beta cells and released into the portal circulation to be distributed to the liver and subsequently to the systemic circulation. The primary target tissues for the actions of insulin are the liver, skeletal muscle and adipose tissue. Endogenous insulin secretion occurs in two phases. The basal phase refers to continuous low-level secretion serving to limit lipolysis and hepatic gluconeogenesis during fasting. The bolus phase is the post-prandial release of insulin in response to the presence of nutrients at the level of the beta cell. The amount of insulin released in the bolus phase, or degree of beta cell response, is impacted by the nutrients present and modified by hormonal and nervous system input. The bolus phase of secretion serves to temper postprandial elevations in blood glucose by stimulating muscle uptake of glucose and inhibit hepatic glucose output.

The effects of insulin at the tissue level are moderated by insulin receptors, which are transmembrane receptors on target tissues which are activated by the binding of insulin and, to a lesser extent, by binding of insulin growth factors (IGFs). Activation of the insulin receptor results in a cascade of intracellular events resulting in incorporation of glucose transporters (GLUT4), necessary for cellular uptake of glucose into insulin-dependent cells, into cell membranes to allow entry of glucose. It is important to note that, in the liver, glucose uptake is independent of insulin and occurs via GLUT2, a non-insulin dependent transporter. Muscle tissue has an exercise-induced GLUT4 in addition to insulin-dependent GLUT4, allowing active muscle cells to take up additional glucose over insulin-stimulated uptake; this becomes important in managing the diabetic patient as variations in degree of physical activity can alter glycemic control (requirements for exogenously-administered insulin decrease with increased physical activity).

Insulin resistance (IR) refers to the condition in which a normal amount of insulin produces a subnormal insulin response, or “decreased sensitivity to insulin”. Contrary to common belief, it is NOT defined by a particular insulin dose, although we often don’t start thinking about the possible presence of insulin resistance until we are treating a diabetic patient and find them to require a relatively high insulin dose (>1.5U/kg in dog and >6-8U/cat), when clinical signs persist despite insulin therapy or when patients require varying insulin doses with requirements changing every few weeks. It is important to recognize the limitation of fructosamine measurements in identifying IR. A very high fructosamine indicates poor glycemic control but does not identify the nature of the problem underlying the poor glycemic control, which may be an insulin OVERDOSAGE (Somogyi phenomenon), underdosage or inadequate duration of effect (presuming administration errors have been eliminated).

Causes of IR may be categorized as pre-receptor (interference with insulin response arising before interaction of insulin with insulin receptor such as increased degradation of insulin or insulin-binding antibody), receptor (abnormal number or concentration of insulin receptors, abnormal insulin-insulin receptor binding), or post-receptor (obesity, increased levels of insulin antagonistic hormones). In conditions of IR, often the problem occurs at multiple levels i.e co-existing receptor and post-receptor effects. The manifestations are the same: a normal amount of insulin produces a subnormal response. We usually are referring to the glucose-lowering effects of the insulin (inhibition of gluconeogenesis, stimulation of glucose uptake by adipose and muscle cells) but other insulin actions (inhibition of ketogenesis and lipolysis; stimulation of protein synthesis, glycogen synthesis, potassium and phosphate uptake into cells) are also impaired.

It is important to think of IR as a continuum that is likely present in many non-diabetic animals and may actually be the CAUSE of a diabetic state (secondary diabetes mellitus) rather than something to be
addressed only in diabetic animals requiring high doses of exogenous insulin. IR increases the demand on the beta cell for insulin secretion. If the beta cells are able to adequately increase insulin synthesis and secretion, the animal may be able to maintain normal glucose levels in the face of insulin antagonism and therefore remain non-diabetic, at least for a period of time. However, if the demand on beta cells is sustained, beta cell function may become impaired and the animal may become diabetic. If the beta cells are NOT able to adequately increase insulin synthesis and secretion to meet the increased demand for insulin to overcome insulin antagonism, the animal will become hyperglycemic. This secondary diabetes mellitus is initially reversible if the cause of IR is corrected but, if insulin antagonism persists, permanent diabetes mellitus may develop.

Persistent hyperglycemia itself suppresses beta cell function, causing decreased insulin secretion, and induces peripheral insulin resistance, reducing glucose uptake by peripheral tissues and therefore worsening hyperglycemia. This phenomenon is called “glucose toxicity”. Correction of hyperglycemia reverses these effects, resulting in improved beta cell function (insulin secretion) and improves tissue responsiveness to insulin. These changes generally take a week or so: this is why we allow a 2-week equilibration period between dose changes and why, early in treatment, we do not see an immediate full response to a particular dose of insulin until the hyperglycemia is brought under control.