Intensified insulin therapy in cats with diabetes mellitus

Reusch, C
Intensified insulin therapy in cats with diabetes mellitus

Claudia E. Reusch, DVM, Professor, DiplECVIM-CA
Clinic for Small Animal Internal Medicine, Winterthurerstrasse 260, 8057 Zurich

It is currently assumed that approximately 80% of diabetic cats suffer from a type 2-like diabetes mellitus. Similar to human type 2 diabetes mellitus, feline type 2 diabetes mellitus is a heterogeneous disease attributable to a combination of impaired insulin action in liver, muscle and adipose tissue (insulin resistance) and β-cell failure. Environmental as well as genetic factors are thought to play a role in the development of both defects.

The hallmark of diabetes is the presence of hyperglycemia. In human medicine, various clinical trials have established that high blood glucose increases susceptibility to infections and hyperglycemia is the most important cause of diabetic microvascular and macrovascular complications. However, chronic hyperglycemia also has a negative impact on the diabetes itself. In contrast to acute hyperglycemia, which stimulates insulin secretion and glucose utilization, chronic hyperglycemia impairs the secretion of insulin and contributes to insulin resistance and thereby perpetuates the diabetic disease.

These damaging effects of chronic hyperglycemia have been referred to as glucotoxicity. The cellular mechanism by which chronic hyperglycemia affects insulin secretion and insulin sensitivity are only partly understood. Amongst others inflammatory cytokines and oxidative stress seem to play an important role.

The concept of glucotoxicity (and possibly lipotoxicity) is very important to understand because immediate treatment of diabetes may reverse the negative effects of glucose and increase the chance of remission. Remission, which is defined as normalisation of blood glucose and fructosamine levels and resolution of clinical signs and glucosuria without antidiabetic therapy, occurs within the first 3 months after initiating therapy in most cats. Up till now no tests have been established suitable to predict remission. Insulin concentrations (baseline levels as well as after IV glucagon or IV arginine) are usually low at the time of diagnosis because of the suppressive effects of glucose. Therefore, the appropriate approach is to aim for optimal metabolic control.

In humans with type 2 diabetes various studies have shown the positive effects of intensive insulin therapy. In newly diagnosed type 2 diabetic patients, a 2 – 3 week period of intensive insulin therapy
by multiple daily insulin injections induced prolonged clinical remission (i.e., 50% were still in remission after 1 year). In another study 73% of patients were in remission 3 months after a 2-week period of intensive insulin therapy with continuous subcutaneous insulin infusion. A multicentre randomized study with transient intensive insulin therapy compared against oral hypoglycaemic agents showed that the former induced remission in almost 50% of patients compared to 25% with the latter. With regard to potential mechanisms by which intensive insulin therapy enables diabetic remission, the most accepted is the relief of glucotoxicity resulting in increasing capacity to secrete endogenous insulin. In particular, the first phase of insulin secretion is clearly augmented after reducing excessive glucose levels, and in addition the ratio between proinsulin and insulin decreases.

In cats with diabetes mellitus the mainstay of therapy is insulin administration and feeding a high-protein diet.

Today it is well accepted that good glycemic control improves pancreatic insulin response and partially corrects insulin secretion defects. It has been postulated by some researchers that the remission rate is higher in cats treated with insulin Glargine (Lantus) than with other types of insulin (e.g. Lente types, such as Vetsulin/Caninsulin). However, the number of studies (in particular prospective randomized trials) is still too small to allow a definitive conclusion. In our hospital remission rate is approximately 50% in newly diagnosed diabetic cats when BID insulin therapy (Lantus or Caninsulin) and a high protein diet are used. Re-checks and adjustment of insulin dosage is done relatively frequently (every 1 – 2 weeks) during the first three months of therapy according to a specific protocol. Other investigators recently reported higher remission rates of 64% using Lantus BID and a high protein diet during an internet-based study. Close monitoring was performed, i.e. owners were required to measure blood glucose at least 3 times daily and insulin dosage was constantly adjusted. Despite the very good results it has to be considered that the regimen is suitable for only a selected group of owners.

We are currently exploring the effect of tight glycemic control during a limited period of hospitalisation, comparable to that described in humans. The protocol includes continuous intravenous infusion of crystalline insulin and monitoring of interstitial glucose concentration with a continuous glucose monitoring system (Guardian REAL-time CGMS). Only cats with newly diagnosed diabetes are included and the blood glucose is targeted between 5 and 9 mmol/l throughout 24 hours. After one week cats are switched to standard subcutaneous insulin (i.e. Lantus). The aim of the study is to
investigate whether starting therapy with the intensive insulin protocol improves the rate of remission compared to cats in which therapy is started on standard (BID) insulin therapy. We hypothesize that tight control of blood glucose levels is crucial for functional recovery of beta-cells in the early clinical stage of the disease. Preliminary results show that cats that started with the intensive insulin protocol are more likely to achieve remission than cats that started with the standard insulin therapy (71% vs. 50%, respectively). Approximately one month after starting therapy, cats in the intensive regimen group received, on average, 0.5 U of subcutaneous insulin BID whereas the group of cats started on standard insulin therapy needed at least twice as much. These preliminary results suggest a beneficial effect of intensified insulin therapy in newly diagnosed diabetic cats.