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Preventing Insulinomas in Pet Ferrets

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Islet cell cancer (insulinoma) is common in pet ferrets in the United States. Islets are the areas of the pancreas that make insulin to regulate blood sugar. I first stumbled upon ferret islet cell tumors in 1987, a year after graduation from veterinary school. Our clinic ferret "Josh" was gradually becoming lethargic, and one day he began having seizures. Remembering a question on the board exams, I checked his blood glucose, and it was less than 40 mg/dl. Surgery confirmed the presence of an insulinoma and we cured Josh's hypoglycemia. From that point on I began recognizing islet cell tumors in many of my ferret patients (which we had previously been diagnosing with a vague cortisone-responsive neurologic condition). Needless to say, insulinomas were one of the most common ferret tumors in the U.S. even back then, and they remain so today. The question is, why?

Islet cell tumors are uncommon in most species; there is probably a predisposition for insulinomas in ferrets compared to other companion animals. This species tendency might be worsened if breeders unwittingly selected stock with a higher genetic risk for the tumors. The current situation in the U.S., wherein one or two breeding facilities produce most of the pet ferrets sold, is ripe for genetic anomalies, due to inbreeding and an overall loss of genetic diversity. However, I saw numerous cases of islet cell tumors in pet ferrets prior to the era of the 'mega-breeders', back when many ferrets we saw were produced by small scale local breeders. Therefore this is one disease syndrome we probably cannot blame primarily on the large-scale breeder facilities. Whatever tendency ferrets have for islet tumors appears to be widespread, and not just the result of a few breeders with 'defective' breeding lines. This means that buying a ferret from a small scale breeder may not significantly reduce the odds of that animal developing an insulinoma.

Islet cell tumors are reportedly less common in some other parts of the world, where ferrets are fed diets of whole mice and similar prey, instead of commercial food. We will assume, for discussion's sake, that the lower reported incidence in Europe, Australia, etc., is not due to lack of awareness of the disease in those regions (one must remember, insulinomas were extremely common but virtually unrecognized in the U.S., until published reports opened practitioners' eyes). If insulinomas are truly less common outside the U.S., this would suggest a possible dietary (or genetic) component to the disease.

In addition, I have submitted extensive pancreatic histopathology samples as a consequence of performing numerous insulinoma surgeries, some of which included removal of sections of the pancreas. The pathology noted in many of those cases was not limited to the small insulinomas we removed; there was often widespread islet hyperplasia (pre-cancerous enlargements) present in the remaining pancreas tissues as well. This is counter-intuitive on the face of it; the excess insulin output from the islet tumor(s) should produce a negative feedback on the pancreas, or at the very least a lack of need to make further insulin. The remaining normal pancreas tissue should therefore appear normal to under-active, due to lack of insulin production. Instead we see the opposite, and the non-cancerous islets appear to be enlarged instead of shrunken. This enlargement seems to be a precursor for cancer development in the islets, suggesting that multiple islet areas throughout the pancreas may be heading towards cancerous growths. Why would this occur?

One mechanism hypothesized by myself and others is that dietary carbohydrate overload (too much sugar intake) may stimulate higher than normal production of insulin (to process the excessive dietary sugars). Overworking the islets may eventually result in islet enlargement, and in

some cases, growth into tumors. Ferrets are strict carnivores, but like many domesticated pets, they can demonstrate a sweet tooth in captivity. Their loving owners may give them treats (often marketed for ferrets) such as raisins, yogurt chews, or "FerretVite" (basically relabeled Nutrical or High-Cal, which are used as *short-term* high energy supplements in underweight dogs & cats). These are heavily carbohydrate-loaded and *not* appropriate for long term use in carnivores. However, as easy as it is to place blame on these sugary treats, they may not be the primary sources for carbohydrate overload in most ferrets. If not, then what is? Answer: their dry kibble diet.

Historically, and until fairly recently, all kibble formulas for dogs, cats and ferrets were relatively high in carbohydrates. The reason for this was that starch was added to the formulas, not for nutritional purposes, but to act as 'glue' so that the kibble would bake into a hard, cohesive shape. Therefore a dry food was higher in starch (carbs) than the canned formula of the same brand. Ferrets usually are raised on, and therefore prefer, dry kibble instead of canned food. There are advantages to this: kibble reduces the 'messiness' that is produced by ferret eating habits (they love to dig in food and spread it around). Spoilage is also not an issue, which allows food to be left out for long periods; ferrets tend to be nibblers that feed multiple times in a day, rather than consuming a large meal all at once. Plaque build up on teeth might be reduced a bit on kibble versus a strictly soft food diet. But the high starch content of traditional kibble diets may be contributing to insulinoma development, so changes may be needed.

"Natural wild diets," e.g. fresh killed (or live) rodents, bird chicks, etc, have their own drawbacks, including availability, messiness, owners' distaste for feeding prey species to their pet, and potential for disease transmission (parasites and *Salmonella* come to mind). Diet-related disease is much more commonly reported in parts of the world utilizing such diets in pet carnivores. Home made meat-based diets are fraught with problems as well, most notably the difficulty balancing nutrients such as calcium and phosphorous; rickets is seen much more commonly in animals on 'home made' diets compared to those on commercial formulas with precisely balanced Ca/P ratios. In my opinion, having seen every imaginable health problem resulting from home-made raw or cooked carnivore diets, a commercial food is still the best choice for the vast majority of owners who lack extensive training in animal nutrition.

If we are going to use a commercial food, and probably a dry food, then what can be done to reduce carbohydrate load? Over the years most traditional ferret diets have mimicked cat or kitten foods fairly closely. They tend to be high in starch, and moderately high in protein and fat. Protein content usually ranges from 35-43% in modern ferret kibbles, and most of these formulas have changed little in the past 15 years. Things are improving, however.

More recently, food manufacturers have found ways to make cohesive kibble without the added starch. This has resulted in a few modified feline and ferret diets that have lower carbohydrate content than previously available; these foods also tend to contain higher protein levels.

At this time there are no good studies that prove how much impact diet has on ferret blood glucose or insulinoma development. However, we have anecdotal evidence that suggests that high protein/low carb diets are indeed helpful, even after insulinomas have developed. An example is a recent ferret patient of mine, with insulinomas which were being treated medically (the owners had declined surgery). As with most such patients, medical management was a gradual losing battle, and as the tumor(s) grew, it became more difficult to control his blood sugar. The patient in question had been on increasing doses of both diazoxide and prednisolone for months, and had exceeded the usual maximum dosing limits for both drugs. Even on such high doses, his condition was so advanced that a severe hypoglycemic episode would occur daily (he would lose consciousness, and required oral glucose to be administered to revive him). This patient was switched over to a strict diet of Purina D-M feline kibbles. Over the next 3 to 4 months, with no increase in drug doses, the owners noted a gradual but steady improvement. The ferret still required medications, but after 4 months the severe hypoglycemic episodes were reduced to once every 3 weeks. The likely explanation is that the insulinomas persisted, but the over-active (pre-cancerous) islets in the rest of the pancreas had gradually shrunk, reducing their insulin output due to the reduction in dietary carbs. This reduced the overall insulin levels, not to normal, but

enough that significant clinical improvement was seen. If diet can achieve this on an advanced insulinoma patient, then there is a strong potential for preventing islet pathology with diet as well. As a side benefit, ferrets with inflammatory bowel disease (a very common chronic digestive disorder) also benefit from a high protein/low carb diet.

My current recommendation, barring kidney disease, is that all ferrets should be fed kibbles with high protein content (50%+), and significantly reduced starch load. There are many high quality high protein ferret and cat kibbles on the market today. Mixing more than one food in the daily diet may reduce imprinting on any one formula, making future diet changes easier. A good formula would be high protein/low carb, with only 1 or 2 meat sources, a moderate amount of a single grain, and no simple-sugar sources (fruit, beets, etc). A well formulated commercial food has many advantages: minimal mess, reliable nutrition with little risk of rickets or other deficiencies, no risk of bacterial or parasitic infections from the food, and convenience. It should also be noted that peas should not be present in the diet ingredients, as they can cause kidney damage leading to dangerous cysteine bladder stones.

As more nutritional research is conducted, formulas may still improve in the future, but right now there are good diet choices available for the informed ferret owner. More work needs to be done regarding the role of diet in insulinoma disease, but in the past few years using these improved formulas, I have already seen a reduction in insulinoma cases in my practice. Combined with other medical advances, we are now able to reduce the incidence of all three common ferret cancers: insulinoma, adrenal tumors, and lymphoma. Long live our ferrets!