Nutrients and Botanicals in the Treatment of Diabetes in Veterinary Practice

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Abstract
Diabetes mellitus can be frustrating to treat in veterinary practice, but botanical and nutritional supplements may offer assistance in stabilizing difficult patients. While dogs are typically subject to type 1 diabetes, cats develop type 2 diabetes as much as 70 percent of the time. Whereas treatment adjuncts to insulin may address carbohydrate metabolism from glucose absorption to insulin receptor function, success may depend on the type of diabetes present in the patient.
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Regulators of Glucose Absorption

Dietary therapy has been and will remain a mainstay of diabetes treatment. Dietary fiber has been shown to reduce glucose absorption from the gut, increasing glycemic control. Insoluble fiber (in the form of 12-percent cellulose incorporated into the diet) was shown to reduce glucose absorption in cats[1] and dogs[2] in randomized, crossover trials. Another study in dogs with insulin-dependent diabetes compared fiber content of several diets and their effect on insulin dosage and blood glucose concentrations. Dogs were randomly assigned either a low-fiber diet, a high insoluble-fiber diet, or a high soluble-fiber diet. While there was no significant difference in insulin requirements among the three groups, the insoluble-fiber diet resulted in significantly lower blood glucose concentrations, compared to the low-fiber and soluble-fiber diets.[3]

On the other hand, another study found soluble fibers, such as guar gum, to offer possible protection for diabetes and hyperlipidemia. Healthy beagles were fed a diet of seven-percent fiber: either guar gum, inulin, or sugar beet fiber. While neither sugar beet fiber nor inulin had a metabolic effect on the dogs, guar gum resulted in decreased postprandial insulin and fasting cholesterol. The researchers concluded that "Guar gum would be a suitable ingredient for dietary therapy of chronic diseases such as diabetes mellitus or hyperlipidemia in the dog."[4] Some of these same researchers found both sugar beet fiber and fructo-oligosaccharides (fermentable fibers) fed to healthy beagles resulted in a significant decrease in triglycerides and postprandial glucose.[5] Sources of soluble fiber are legumes (one of the best), whole grains, vegetables, and fruits – most of which also contain some insoluble fiber. Insoluble fiber supplementation may be supplied via vegetables and whole grains.

In humans it appears insulin resistance may develop (in part) from a high carbohydrate diet,[6] a theory particularly interesting considering the typical dry diet fed veterinary patients. Cats (obligate carnivores) and dogs (facultative carnivores) may, in fact, have innate insulin resistance mechanisms, making them less tolerant of the highly digestible carbohydrate diets

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recommended in principle for humans, and provided by typical dry commercial diets. It is well to remember that cats have no requirement for carbohydrates whatsoever; therefore, insulin resistance may have developed in this species as a mechanism for coping with exogenous glucose shortages. It is possible the progression of diabetes is hastened by feeding diabetic cats and dogs a high-carbohydrate dry diet.

While the role of obesity in the development of diabetes is well recognized, the connection between veterinary weight loss diets and obese diabetic pets has not received sufficient attention. The development of insulin resistance is seen particularly in cats, possibly due to a lifetime of dry, high-carbohydrate commercial foods. On the other hand, the overweight (and normal weight) diabetic cat is usually fed a low-fat, free choice, high-carbohydrate weight loss diet. Since many overweight cats return to a non-diabetic state when their weight is normalized, dietary management of these cats is of particular concern. Managing overweight cats is often complicated, as hepatic lipidosis occurs easily and is potentially fatal. A discussion of weight management in these cats is beyond the scope of this paper, but should be undertaken with care.

In any event, the time has come to re-evaluate dietary recommendations for the overweight diabetic veterinary patient. To this end, some are feeding a high-quality maintenance diet – prescription or homemade – with quality meat protein and lower digestible carbohydrate levels, adding insoluble fibers (vegetables, wheat bran) to take advantage of fiber's effect on glycemic control. This is particularly important when a pet is a so-called "picky" eater or has nutritional needs not covered by a commercial, high-fiber, weight-loss diet (e.g., food allergies, renal failure, etc.). Recently, one pet food manufacturer introduced a low-carbohydrate diet specifically for managing diabetes in cats.

Regulators of Insulin Availability or Release

Botanicals

Gymnema sylvestre is an herb that has been used in Ayurvedic medicine for 2,000 years in treating diabetes. Recent clinical and experimental studies suggest this use is warranted. Numerous case series reports indicate that Gymnema improves glucose tolerance and clinical status in human diabetics. Gymnema extract was shown to increase insulin secretion in pancreatic beta-cell lines by increasing membrane permeability.[7] In streptozocin-treated rats, administration of Gymnema extract was observed to increase serum insulin levels as well as the absolute number of pancreatic islet cells. The same group showed Gymnema improved glucose uptake in target tissues.[8,9] Clinical use suggests Gymnema must be administered for two to three months for maximum effect. Although the herb is available alone, it is more often used in combination with other herbs traditionally used in the treatment of diabetes, including *Momordica charantia* (bitter melon), fenugreek, and ginseng.

The herb *Momordica charantia* has a long history of use in China, India, and Africa for the treatment of human diabetes. The hypoglycemic constituents may include charantin, and a polypeptide which has been called p-insulin (plant insulin or polypeptide-p).[10] P-insulin has been compared structurally and pharmacologically to bovine insulin. In type 1 diabetics, Baldwa et al studied the effect of p-insulin on nine human diabetic patients and found its onset of action at about 30-60 minutes and a peak hypoglycemic effect after four hours.[11] Animal studies have had conflicting results.[12-15] The hypoglycemic effects of this plant may involve increased glucose utilization by the liver;[13] decreased glucose synthesis by depression of the two key gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-biphosphatase; and

Table 1. Nutrients and Botanicals for Managing Diabetes

COMPOUND	DOSE	ADVERSE OR OVERDOSE EFFECTS
Vanadium	0.2 mg/kg/day	Anorexia, vomiting, possible renal toxicity[22]
Vanadyl sulfate	1 mg/kg/day	Anorexia, vomiting, possible renal toxicity[22]
Chromium	50-400 mcg/day	anorexia, vomiting, possible renal toxicity[22]
Fish oil	100 mg of combined EPA/DHA per kg of body weight, divided daily	Nausea, possible platelet effects that have not proven clinically significant
alpha-Lipoic Acid	Cats: no more than 25 mg/day. Dogs: up to 200 mg/day for large dogs	Anorexia, disorientation, seizures at high doses
Vitamin C	50 mg/kg, up to 3000 mg daily in large dogs	Diarrhea at large doses
Gymnema	100-400 mg of extract divided daily or 250-1500 mg dried herb divided daily	None reported
Fenugreek	Published doses vary widely; 20-100 gm of seed powder daily in divided doses with meals in human studies (adjust dose by weight of animal)	Probably safe; may cause GI distress in high doses
Panax ginseng	50-1000 mg three times daily	Long term use at high doses may lead to agitation, hypertension, diarrhea, but appears rare
Panax quinquefolius	50-1000 mg three times daily	No reports of adverse effects but may be similar to those of P. ginseng

enhancement of glucose oxidation through the shunt pathway via activation of glucose-6-phosphate dehydrogenase.[14]

The defatted seeds of *Trigonella foenum-graecum* (fenugreek) have been shown to lower blood glucose in both humans and dogs.[16] Fenugreek seeds contain fiber thought to slow glucose absorption from the gut. Since aqueous extracts have also shown hypoglycemic activity in rats, this herb may work by a

number of mechanisms. In a study of rats given alloxan to induce diabetes, both water and alcohol extracts of fenugreek had some hypoglycemic activity.[17] Since alloxan destroys pancreatic beta-cells, it was presumed that fenugreek either stimulated insulin release from remaining beta-cells or had insulin-receptor activity.

Two species of ginseng have shown promise in managing diabetes. *Panax ginseng* (Chinese or Korean ginseng) and *Panax quinquefolius* (American ginseng) have been shown to reduce hyperglycemia in type 2 human patients.[18,19] The mechanism of action by which ginseng works is unknown, but effects on insulin secretion and receptor sensitivity have been suggested.[18]

Although herbal medicine offers potential in the treatment of diabetes in dogs and cats, few studies on efficacy and safety have been published. They still, however, may be useful in regulating difficult diabetic patients. Doses for some of these herbs are given in Table 1.

Glandulars

Glandular therapy is another alternative occasionally recommended. A glandular is an extract of a specific organ or gland, given to support the functioning of that organ. For example, pancreatic glandulars contain freeze-dried pancreatic tissue, as well as small amounts of pancreatic enzymes.

Recent research in immune tolerance has led to the investigation of oral tolerization in the treatment of autoimmune disease, including diabetes in humans.[20] The specific mechanism of action is unknown, but may involve deletion, anergy, or active suppression of T-lymphocytes that initiate immune destruction of target tissues. Since 40-50 percent of dogs have autoantibodies to islet cell antigens, administration of pancreatic glandulars may be a rational approach in this species. Recently, questions have arisen regarding the safety of glandular therapy, as oral tolerization may exacerbate the immune response to autoantigens instead of tolerizing T-lymphocytes.[21] Glandular therapy is best used early in the disease to decrease destruction of pancreatic beta-cells. This author has observed few positive results using glandular therapy.

Regulators of Insulin Receptor and Post-Receptor Effects

Unpublished research from Colorado State University's School of Veterinary Medicine[22] lends support to the use of vanadium in treating diabetes in cats. Vanadium appears to have insulin-like effects in both people and experimental animals. Vanadium may be of most use in type 2 diabetes, where it is thought to activate tyrosine kinase intracellularly to act as an insulin co-factor. In one study, vanadium as an adjunct to PZI insulin therapy resulted in lower insulin doses, lower serum fructosamine values, and fewer clinical signs including polyuria and polydipsia in diabetic cats.[23]

Chromium is thought to increase receptor number, receptor sensitivity, and receptor phosphorylation. Recent unpublished research by the Iams Company suggests chromium is effective at improving glucose tolerance in dogs. In a study of eight dogs fed chromium tripicolinate at 300 ppb in their diet, glucose clearance from the blood increased by 10 percent compared to another eight dogs fed the same diet not supplemented with chromium.[24]

Other studies have not found significant benefit from chromium supplementation. In a study on non-diabetic obese and non-obese cats, chromium was supplemented at 100 mcg elemental chromium daily for six weeks. Intravenous glucose tolerance tests were administered prior to supplementation and at the end of the test period. Chromium supplementation did not affect glucose tolerance in either group.[25] In a study of seven obese diabetic cats, six normal weight diabetic cats, and six non-

diabetic, normal weight cats, supplementation of 100 mcg chromium as picolinate did not result in clinically significant changes.[26]

A different group examined the effects of supplementing up to 400 mcg twice daily (20-60 mcg/kg/day) to naturally occurring diabetic dogs for a period of three months. In this study, there were no differences in serum fructosamine, blood glycated hemoglobin concentration, body weight, insulin dosage, 10-hour mean blood glucose concentration, or daily caloric intake when dogs were administered chromium plus insulin versus insulin alone.[27]

Prevention and Treatment of Complications of Diabetes

There is little doubt that diabetes imposes oxidative stress on many tissues and organs, although the effects of oxidative stress and endothelial dysfunction are much more evident in human conditions such as diabetic cataracts, peripheral vascular disease, and diabetic nephropathy. Supplementation of various antioxidants, including vitamins C and E, has support in the human medical literature.[28] Vitamin E improves vascular reactivity and oxidative stress indices in human diabetics,[29] while vitamin C reduces plasma free radicals as well as insulin levels in human type 2 diabetic patients.[30]

Alpha-lipoic acid has been shown to improve neuropathic deficits of diabetes in humans,[31] but efficacy in feline diabetic neuropathy has been questionable in practice. Alpha-lipoic acid has also been used to slow the progression of cataracts in humans. Caution should be advised with this nutrient, however, as unpublished research from the University of California at Davis has shown that cats may demonstrate signs of neurologic toxicity when doses exceed 25 mg per day.[32]

Oxidative stress likely affects many tissues and functions, including insulin resistance and beta-cell destruction.[33] The role of antioxidants has not been examined in diabetic dogs and cats, but it is reasonable to postulate that antioxidants may be helpful and should be strongly considered. Veterinary antioxidant supplements are readily available and appear safe for long-term use.

Marine fish oil, a source of the omega-3 fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), has been suggested to increase insulin sensitivity, preventing insulin resistance.[34] It has been suggested as a treatment for diabetic neuropathy as well.[35,36] Possible mechanisms of action by which fish oil exerts these effects may be via changes in cell membrane composition or transmembrane ion transport.[37,38] Because cats are more prone to type 2 diabetes and diabetic neuropathy than dogs, fish oil seems especially appropriate as a supplement for feline diabetes mellitus.

Practical Use of Supplements

While only anecdotal experience is available as a guide on proper use of these and other adjunctive diabetes treatments, most of these supplements are quite safe, even in combination. In the author's experience, vanadium, fish oil, and antioxidants are relatively safe and appear effective for most diabetic patients. While it is unclear how much time should elapse before changing or instituting new treatment, some interventions such as vanadium have appeared to alter insulin requirements quickly – within a matter of days to weeks. On the other hand, the time required to improve longstanding tissue changes secondary to chronic hyperglycemia might be expected to take weeks to months. This author usually assesses response to therapy one to two months after instituting a new supplement.

For those pet owners willing to give a larger number of oral medications, other nutrients, herbs, and Chinese herbal combinations may be helpful. Knowledge of mechanisms of action, when available, will be helpful in guiding small animal veterinarians, since

dogs and cats often experience (in general) different forms of the disease. Except in occasional cases, it is important to keep in mind these supplements are experimental and cannot be relied on to maintain control of diabetes in the absence of insulin therapy.

Conclusion

The nutrients and botanicals described above may aid in regulation of glucose levels in difficult cases of diabetes. Other supplements are being investigated, including niacin, arginine, magnesium, and other herbs. They have the potential to reduce insulin requirements and provide more even glycemic control. The case can be made for using most of these supplements early in the disease, in hopes of slowing beta-cell destruction and amyloid deposition.

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