A Pilot Study of the Effect of American Ginseng Administration on Glycemic Control in Dogs with Insulin Dependent Diabetes Mellitus

A Thesis

Submitted to the Graduate Faculty

in Partial Fulfilment of the Requirements

for the Degree of Master of Science

in the Department of Companion Animals

Faculty of Veterinary Medicine

University of Prince Edward Island

E. C. R. Snead

Charlottetown, P. E. I.

September, 2006

Your file Votre référence
ISBN: 978-0-494-22830-2
Our file Notre référence
ISBN: 978-0-494-22830-2

SIGNATURE PAGE

16

REMOVED

SIGNATURE PAGE

REMOVED

Abstract

Background: Despite numerous preventative strategies and a wide array of conventional medications available for the treatment of diabetes mellitus, prevention and treatment of this disease remains unsatisfactory and the disease remains a serious health care problem in people and companion animals. There remains a need for development of new primary and adjunctive medical therapies to treat this disease. If left untreated or poorly regulated, diabetic patients are at high risk for the development of serious acute and chronic complications. Acute complications of diabetes mellitus in cats, dogs and people include the development of diabetic ketoacidosis, non-ketotic hyperosmolar diabetic ketoacidosis, and hypoglycaemia from an insulin overdose. Chronic complications in people include blindness from diabetic retinopathy, hypertension and related cardiovascular disease, renal failure from diabetic nephropathy, peripheral neuropathies, increased risk of secondary infections and a variety of dermatologic problems. Similar chronic complications can occur in diabetic dogs and cats but with the exception of diabetic cataracts in dogs, the incidence is much lower. To prevent such complications and to improve or maintain a diabetic patient's quality of life, many diabetic people and owners of diabetic pets turn to alternative medicines, including herbal remedies such as ginseng. Emerging evidence from human and experimental animal models for the use of American ginseng (AG) in the control of diabetes and high blood pressure has been encouraging.

Design: A placebo-controlled, blinded, crossover design study involving 8 dogs with well controlled insulin-dependent diabetes mellitus was performed to evaluate whether administration of a commercially available American ginseng (*Panax quinquefolius*) product has any antihyperglycemic and antihypertensive effects.

Results: In dogs with well controlled insulin dependent diabetes mellitus, no statistically significant differences in glycemic control or systemic blood pressure parameters were detected between placebo and American ginseng when either treatment was administered as an adjunct to the dog's prescribed insulin.

Conclusion: American ginseng did not demonstrate antihyperglycemic or antihypertensive effects in dogs with type I diabetes mellitus.

Acknowledgments:

The author wishes to thank the following persons for their help with the study:

Dr. Sherri Ihle, my graduate supervisor.

My husband, Jonathon Bowser.

Dr. Dan Ryan and Dr. Mary Leggett for their help with the statistical analysis.

The other members of my supervisory committee: Drs. Cathy Chan, James Miller, Shelley Burton, and Dan Ryan.

Donna Barnes, Chris Wilson, Dr. Tonya Stewart and the various fourth year students who helped me with collecting blood samples from the study dogs.

Kendra Day, University of Prince Edward Island Veterinary Teaching Hospital Pharmacy, for her assistance with randomization and dispensing of the placebo and study drug.

The Atlantic Veterinary College Companion Animal Trust Fund and the Atlantic Veterinary College Internal Research Fund for generously funding this study.

Table of Contents

Introduction

The use of herbal extracts for the treatment of diabetes mellitus in people has increased considerably in the last ten years. This has occurred despite the fact that the efficacy and the safety of most of these herbal remedies remain untested (1-2). The most recent estimates suggest that 75% of general medicine patients in the U.S. are now using complementary and alternative medicine (3). One of the strongest independent determinants of this behaviour is the use of complementary and alternative medicine to treat diabetes (4, 5). In one Canadian survey 1/3 of diabetic patients admitted to taking an alternative medicine (2). There is growing evidence from *in vitro* work, from studies in experimental diabetic rodent models, and from studies done with diabetic people that various species of ginseng, including American ginseng (*Panex quinquefolius*), have antihyperglycemic properties (2, 6-14). Reports of these antihyperglycemic properties have led to various species of ginseng becoming very popular as adjunctive treatments in people with diabetes mellitus (2, 5). Although some preliminary work has being done, more extensive blinded and placebo-controlled clinical trials are required in both people and animals to further test whether the preliminary findings are accurate. To date, no work has been published investigating whether administration of ginseng could be used as an effective antihyperglycemic adjunctive treatment for diabetes mellitus in dogs and cats.

Diabetes Mellitus

Diabetes mellitus is a heterogenous group of hyperglycemic disorders caused by an absolute or relative deficiency of the hormone insulin (15-16). An absolute or relative insulin deficiency results in chronic dysregulation of carbohydrate, fat, and protein metabolism in affected patients

(15-16). Deficient insulin secretion by pancreatic beta cells of the islets of Langerhans or peripheral resistance to the effects of insulin at the cellular level can be responsible (15-21). The similarities in the etiology, clinical syndrome, and the basic treatment of diabetes mellitus in dogs, cats, and people provides for valuable opportunities for comparative research which may benefit all three species (22).

Aside from the debilitating consequences of diabetes mellitus, management of the disease often represents a formidable challenge for affected people and owners of diabetic pets. The cost of insulin and related supplies, the need for regular monitoring, and the occurrence of secondary complications (e.g., diabetic cataracts in dogs, systemic hypertension-related organ damage, diabetic polyneuropathies) can lead to frequent visits to veterinarians and considerable financial expense. In addition to the financial costs, owners of diabetic pets are usually required to make inconvenient adjustments to their own life-style in order to optimize their pet's diabetic regulation. Because compliance with prescribed diet and treatment regimens can be poor, there is always a desire for novel adjunct treatments. Use of untested herbal remedies, including ginseng, has become increasingly popular in order to fill this perceived need.

Incidence and Medical Significance of Diabetes Mellitus in People

According to statistics published by the World Health Organization (WHO), over 135 million people worldwide have diabetes mellitus (8, 15). The public health and financial implications of the diabetic epidemic are staggering. In 2001, diabetes mellitus with its associated complications was the sixth leading cause of death from disease in people in the United States (23). The cost of treating these patients was estimated at $92 billion dollars in

2001 (23). With the increasing incidence of obesity, a known major risk factor for diabetes, the costs associated with treating diabetes mellitus will only increase (9). Indeed, the predicted rise in the incidence of diabetes mellitus makes this disease one of the most important emerging pandemics facing the human race.

Incidence of Canine Diabetes Mellitus

Diabetes mellitus is a relatively common endocrine disorder in middle-aged to older dogs, with a reported incidence ranging from 0.2 to 1.0 % (18-19, 24). Although dogs of all ages can develop diabetes mellitus, typically affected dogs range in age from 4 to 14 years, with the peak incidence at 7 to 9 years of age (18-19, 24-25). In rare cases, dogs less than < 1 year of age will develop diabetes mellitus. Female dogs (intact or spayed) are two to four times more commonly affected than male dogs (18-19, 26-27). Breeds of dogs where a genetic predisposition for diabetes mellitus has been suggested by familial association and pedigree analysis include the Keeshond, Golden Retriever, Samoyed, Miniature poodle, and the Rottweiler (24, 28-33). Breeds where a genetic predisposition is suspected (but not proven) because of the reported higher than average incidence in the breed, include the Pulik, Cairn terrier and the Miniature Pinscher (34). Breeds with a reportedly low risk for developing diabetes mellitus include the Cocker spaniel, German shepherd, Collie and Boxer (27). Genetic factors and/or variations in breed popularity in different geographic regions may influence the reported incidence of diabetes mellitus in different breeds in different studies.

Incidence of Diabetes mellitus in Cats

Diabetes mellitus is a common feline endocrine disease with a reported incidence of 1 in 100 to 1 in 500, which is similar to the reported incidence in dogs (20, 35). The only breed with a recognized familial predisposition for diabetes mellitus is the Burmese (35-36). Neutered males are 1.5 times more likely to be affected than spayed or intact female cats (20, 35). Although cats of all ages have been reported to develop diabetes mellitus, the majority of affected cats are 6 years of age or older, with the mean age at the time of diagnosis being 10 years of age (20, 25, 35, 37).

Classification of Diabetes Mellitus in People

The current classification scheme developed by the American Diabetes Association and the WHO divides diabetes mellitus into four types: type I, type II, type III and gestational diabetes (also termed type IV diabetes) (38). These forms are distinguished based on etiology, pathogenesis, clinical presentation and treatment. Type I and II are the major forms. Type III and IV are much less common and probably only account for 1% of all cases (15, 38-39). Type I diabetes mellitus accounts for about 5 % to 10 % of all human cases in the USA, while type II accounts for the majority (90 % to 95 %) of cases (38). Familial medical history, clinical presentation and results of immunologic and insulin secretagogue tests are relied upon in human medicine to classify patients as having type I versus type II diabetes mellitus (15, 38-39).

Type I diabetes mellitus results from immunologically-mediated destruction of pancreatic beta cells. This ultimately leads to absolute insulin deficiency (15, 18, 39). The result is a requirement for administration of exogenous insulin for treatment (15, 18, 39). An older less-

used term, which is often incorrectly used synonymously with type I diabetes mellitus is *insulin dependant diabetes mellitus (IDDM)* (15, 18, 37, 39). Insulin dependant diabetes mellitus is defined strictly as a diabetic state in which there is insufficient insulin secretion to prevent ketone production. Therefore, IDDM is equivalent to a severe or end-stage form of type I diabetes mellitus where there is complete extinction of beta-cell function (37-40). Because patients with either advanced type I or IDDM are prone to develop ketosis and possibly ketoacidosis due to insulinopenia, both forms are also referred to as *ketosis-prone diabetes mellitus* (38). Because most cases of type I diabetes mellitus in people are caused by immune-mediated beta-cell destruction, type I diabetes mellitus may also be referred to as *immune-mediated type I diabetes mellitus* (38). Multiple genetic predispositions and poorly defined environmental factors are associated with such immune-mediated destruction (38). Since the age of onset of most cases of type I diabetes mellitus is within the first two decades of life, type I diabetes mellitus also used to be referred to as *juvenile-onset diabetes mellitus* (38). This term has gone out of favor in human medicine because older adults may also develop this form of diabetes mellitus.

Type II diabetes mellitus is caused by either a defect in insulin secretion (dysfunctional beta cells), by resistance to the actions of insulin on insulin-dependent tissues or from a combination of these two mechanisms (15, 18, 38, 41). Resistance to insulin occurs at the level of the target cell where insulin interacts with its receptor. It is thought that peripheral insulin resistance plays a major role in the pathogenesis of type II diabetes mellitus (18-19, 41). In people, type II diabetes has a genetic component that is subject to major influence from environmental factors. The two genetic defects in type II diabetes result in peripheral insulin resistance and hyperinsulinemia, both of which are present in the prediabetic phase (41). In the prediabetic

stages of the disease, a compensatory increase in insulin secretion occurs so that normoglycemia is maintained despite peripheral insulin resistance. Eventually, the beta cell's capacity to increase insulin secretion to compensate for insulin resistance is exhausted, and hyperglycemia and overt signs of type II diabetes occur (41). Low insulin sensitivity (insulin resistance) can be exacerbated by factors such as obesity, physical inactivity and diet (15). This is true for both people and cats (15, 20, 35, 42). With type II diabetes mellitus, there may be altered beta cell insulin secretion, with the total amount of insulin secreted being increased, decreased, or normal in comparison to secretion of insulin by normal beta cells (38, 41). However, because the beta cells still retain the ability to secrete insulin, there is an absence of ketosis; therefore some researchers will refer to type II diabetes mellitus as *ketosis resistant diabetes mellitus* (38). Because most patients with type II diabetes mellitus are not dependant on administration of exogenous insulin to prevent ketosis, an older term for type II diabetes mellitus is *non-insulin dependant diabetes mellitus (NIDDM)* (38). However, this term has also fallen out of favor because insulin therapy can be required on a temporary or permanent basis to treat some patients with type II diabetes mellitus (15, 38-39, 43). Indeed, at least 75% of cats and 25% of people with type II or NIDDM require exogenous insulin to adequately control their diabetes (44). Because type II diabetes mellitus typically develops in adults over the age of 40 years, it has also been referred to as *adult-onset diabetes mellitus* (38). However, the incidence of type II diabetes mellitus in adolescents and young adults, especially among obese sedentary youth, is increasing significantly, this term is now considered outdated (38).

A number of other specific types of diabetes mellitus exist and can be lumped under the category of type III diabetes mellitus (15, 38). Within this group are several monogenetic defects

in beta cell function where insulin secretion is impaired. Secondary diabetes mellitus, also lumped into the type III diabetes mellitus category, includes forms of diabetes attributed to another condition, such as chronic pancreatitis, post-pancreatic surgery, chronic hepatic disease, renal failure or insufficiency and severe infections (38). As well, this group contains diabetes mellitus induced by other endocrinopathies (e.g., hyperadrenocorticism and acromegaly) and diabetes induced iatrogenically from administration of some medications, such as chronic glucocorticoid therapy (38).

Gestational diabetes, sometimes referred to as type IV diabetes mellitus, occurs in individuals whose diabetes is first recognized during pregnancy. In most cases, affected women return to normal glycemic control after parturition (38). Affected women are, however, at a markedly increased risk of developing diabetes mellitus in the future given the right predisposing factors (38).

Classification of Diabetes Mellitus in Companion Animals

At the current time, there are no internationally accepted criteria for the classification of diabetes mellitus in dogs and cats (24). If the criteria established for human beings are applied, the same four types of diabetes mellitus recognized in people have all been recognized in animals (24). As in people, the vast majority of cases of diabetes mellitus in dogs and cats are classified as either type I or type II (18-21, 24, 44) when the human classification system is applied. However, in companion animals it is more accurate and clinically relevant to classify diabetic dogs and cats as IDDM or NIDDM rather than as type I or type II (19-20). This is because, unlike in human medicine, familial history is rarely available and clinical presentation is usually

not helpful in differentiating type I and type II diabetes mellitus, especially in cats. As well, beta cell insulin secretagogue response testing is rarely preformed in veterinary medicine because of cost and because the results can be misleading (18-20, 45-46). Instead, the requirement for exogenous insulin administration and/or the failure to control the disease with diet and/or oral hypoglycemic drugs alone are used to establish whether a dog or cat has IDDM versus NIDDM (19). Virtually all dogs, and a minority of cats, have IDDM when they are diagnosed with diabetes mellitus (18-20, 47). Insulin dependant diabetes mellitus in dogs and cats is characterized by an absolute deficiency of insulin secretion by the pancreatic beta cells; affected animals ultimately require treatment with exogenous insulin (18-20). Non insulin dependant diabetes mellitus, which is the most common form of diabetes mellitus seen in cats, is characterized by a relative or absolute deficiency of insulin secretion by pancreatic beta cells at the time of initial diagnosis (20, 47). Treatment of type II diabetes in cats may or may not require administration of exogenous insulin. Dietary factors, correction of obesity, and use of oral hypoglycemic medications are other therapies that may be important in the management of type II diabetes in cats (20, 47).

Classification of Canine Diabetes Mellitus

Virtually all dogs with diabetes mellitus have IDDM (18-19, 24). Only a minority of dogs suffer from one of the other types of diabetes mellitus (19, 47).

There are no well documented studies demonstrating convincingly that NIDDM is a significant disease entity in dogs (18-19, 24, 47). The early onset form of insulin dependant diabetes reported in Keeshond dogs would be classified as type III diabetes using the human

classification system (47). The same is true for the rare cases of diabetes mellitus coexisting in juvenile dogs with exocrine pancreatic insufficiency and diabetes resulting from end-stage pancreatitis (47). Diabetes mellitus occurring secondary to other endocrinopathies, particularly hyperadrenocorticism and acromegaly, or from administration of glucocorticoids, should technically be classified as type III diabetes mellitus (47).

Gestational diabetes or type IV diabetes has been documented in pregnant dogs and in intact bitches during the diestrus phase of their heat cycle (18-19, 24). Provided the diabetes resolves at the end of the pregnancy or diestrus, it is classified as gestational diabetes; however, if overt diabetes mellitus persists after parturition or diestrus then it would be reclassified as type I or type II diabetes mellitus (18-19, 24).

Classification of Feline Diabetes Mellitus

In cats, both type I and type II diabetes mellitus occur. Even though most researchers in the field of feline diabetes believe that type II diabetes mellitus is more common than type I, histological findings consistent with type I diabetes mellitus have been observed in cats, so type I does occur in cats (20, 48-51). Less than 10-20% of cats have other specific types of diabetes mellitus (44, 48). Type III DM in cats may result from insulin resistance or beta cell exhaustion or destruction from an unrelated disease process such as hyperadrenocorticism or acromegaly (20, 48, 50). Resolution of the primary disease process usually eliminates type III DM in these cats unless the diabetes mellitus is advanced (20, 50).

Etiology of Diabetes Mellitus in Humans, Dogs and Cats

Diabetes mellitus is a heterogenous group of metabolic disorders. In people and animals there are basically five main contributing causes for diabetes mellitus recognized: 1) genetic predisposition, 2) pancreatic injury, 3) hormone-induced beta cell exhaustion, 4) altered target tissue sensitivity to insulin, and 5) dyshormonogenesis (15, 18-20, 38, 52). Table 1 contains a summary of the known causes of diabetes mellitus in cats and dogs (18-20, 52).

Although a number of specific causes of diabetes mellitus have been identified in people, the etiology and pathogenesis of the most common types of diabetes mellitus are still not fully understood (15, 38-39). Broadly, type I diabetes mellitus is characterized by a combination of genetic susceptibility and immunologic destruction of the beta cells triggered by environmental factors leading to a progressive and eventual complete inability of the beta cells to produce insulin (39). Auto-antibodies that lead to beta cell destruction can be directed against several islet components including insulin itself and beta cell antigens (glutamic acid decarboxylase, tyrosine phosphatases) (39). Detection of such serum auto-antibodies against islet components can be commonly detected in people with type I diabetes mellitus at the time of initial diagnosis (39). Type II diabetes mellitus, on the other hand, is characterized by insulin resistance and dysfunctional beta cells (39, 41). The etiology of type II diabetes is undoubtedly multifactorial, with genetic factors and superimposed environmental factors playing a role (39, 41).

The exact cause for the development of diabetes mellitus in most dogs and cats also usually remains unknown, but most cases are likely multifactorial and result from an interaction of two or more factors that predispose the animal to develop diabetes mellitus (18-20, 52). These may include genetic risk factors, immune-mediated isletitis, infection, insulin antagonistic diseases

and drugs, obesity, pancreatitis, and islet specific amyloidosis (18-20, 52).

A genetic predisposition for diabetes mellitus has been suggested in certain dog breeds. In rare cases, a congenital absolute deficiency of beta cells and pancreatic islet hypoplasia or aplasia has been reported in dogs (29, 53-54). Genetic factors are also suspected to play a role in the development of diabetes in some dogs where the histology of the pancreas reveals a reduction in the number and size of pancreatic islets, a decrease in the number of beta cells within pancreatic islets, and beta cell vacuolization and degeneration (18-19, 55). The role of genetics remains to be determined in cats (20, 44, 47).

Primary auto-immune-mediated isletitis, such as occurs in some people with type I diabetes mellitus, has also been described in diabetic dogs (18-19, 24, 47, 53, 56-61). Infiltration of the islets of the pancreas by inflammatory cells has been seen in up to 46 % of pancreatic biopsies from diabetic dogs, and serum markers of beta cell cytotoxicity has been demonstrated (53, 56). The recent finding that up to 50 % of diabetic dogs have circulating serum antibodies against pancreatic beta cells also supports a humoral auto-immune response being involved in the pathogenesis of diabetes in some dogs (57-58).

Evidence of acute or chronic pancreatitis occurs in approximately 33 % to 40 % of dogs with type I diabetes mellitus, but whether pancreatitis is the underlying cause for the clinical diabetes or a consequence of the pancreatic pathology is unclear (18-19, 24, 26, 53, 60-62). Activation of pancreatic enzymes within the acinar tissue of the pancreas may initiate pancreatitis, and the beta cells may be affected by extension of necrosis and inflammation into surrounding tissue (18-19, 24). In canine diabetic cases with accompanying pancreatitis, it is speculated that islet beta-cells are selectively damaged as a result of their increased sensitivity to the effects of inflammatory

mediators as compared to the other islet cells (24). In cats with both type I and type II diabetes mellitus, common pancreatic histological abnormalities include islet specific amyloidosis, beta cell vacuolization and degeneration, and chronic pancreatitis (48). Pancreatic adenocarcinoma has been reported to cause diabetes in cats (48). Pancreatic neoplasia is a less common cause of diabetes in dogs (20).

In some pregnant bitches, decreased insulin sensitivity develops around day 30 to 35 of pregnancy and becomes progressively worse in late pregnancy (18-19, 24, 63). Because the hormone profile of dogs in the diestrus phase of a heat cycle is very similar to that seen in pregnant bitches, insulin insensitivity may also develop and lead to signs of diabetes mellitus in bitches during diestrus (18-19, 24). This form of diabetes mellitus in dogs is very similar to gestational diabetes seen in people (18-19, 24). The reduced insulin sensitivity occurs because of elevated progesterone levels in diestrus bitches, and from the combined effects of elevated progesterone and growth hormone in pregnant bitches (64-65).

Certain endocrine diseases, particularly hyperadrenocorticism and acromegaly, can cause insulin resistance and potentially lead to overt diabetes mellitus in cats and dogs (18-20, 24, 50, 66-67). Hypo- and hyper-thyroidism have also been demonstrated to interfere with diabetic regulation in dogs and cats (68-69). Often diabetes mellitus that is secondary to another endocrinopathy is transient and the animal's glucose homeostasis usually returns to normal once the primary disease is treated (47).

Other systemic diseases or disorders in cats and dogs where insulin resistance occurs and can lead to development of signs of diabetes mellitus include renal insufficiency and renal failure (in cats), severe systemic infections, hyperlipidemia, certain non-endocrine cancers (i.e. lymphoma

and mast cell tumors), and endocrine cancers (i.e., glucagonoma; pheochromocytoma) (18-20, 50, 70-72).

Obesity-induced carbohydrate intolerance, as is seen in humans with type II diabetes, has also been identified as a major risk factor for the development of type II diabetes in cats (35, 42). Obesity causes a reversible insulin resistance resulting from downregulation of the number of insulin receptors, impaired insulin receptor binding affinity for insulin and postreceptor defects in insulin action (73-74). These abnormalities are reversible with correction of the obesity (42, 47, 75-76). Although obesity can lead to insulin resistance in dogs, it is not recognized as risk factor for development of type II diabetes mellitus, unlike in people and cats (47, 72).

Although type II diabetes mellitus is rare in dogs, 30-75% of diabetic cats have this form of diabetes (20, 44, 47). The current understanding of the pathogenesis of type II diabetes mellitus in cats suggests that it differs from the pathogenesis of type I diabetes mellitus only in terms of the severity of the loss of beta cells and the severity and reversibility of the concurrent insulin resistance (20). The more severe the islet pathology and/or the more severe and irreversible the underlying cause of insulin resistance, the more likely it is the cat will have type I (IDDM) diabetes mellitus (20). Transient diabetes mellitus may occur in cats with less severe islet pathology (20). It is theorized that cats who develop transient diabetes mellitus are in a subclinical diabetic state prior to expression of clinical signs, and they become clinical when the pancreas is stressed by exposure to a concurrent insulin-antagonistic drug (e.g., depomedrol, megestrol acetate) or disease (e.g., chronic pancreatitis) (44, 77). The resulting chronic hyperglycemia can reversibly suppress beta cell insulin secretion and induce peripheral insulin resistance by promoting the downregulation of glucose transport systems and causing a defect in

post-transport insulin action (20, 44, 78). This phenomenon is often referred to as beta cell glucose toxicity (46, 78-80). In affected cats, beta cells have an impaired response to stimulation by insulin secretagogues; this mimics the impaired response to insulin secretagogues seen with IDDM (20, 79-80). Temporary treatment of the diabetic state with exogenous insulin improves hyperglycemia and insulin resistance and decreases the suppressive effects of hyperglycemia, allowing beta cell function and insulin secretion to return and resolving the apparent IDDM permanently or temporarily in affected cats (20, 44). The future requirement for insulin in these cats will depend on whether the underlying abnormality affecting the islets can be controlled (20).

Normal Glucose Homeostasis

Maintenance of the plasma glucose concentration is critical to survival because glucose is the predominant fuel used by virtually all cells in the body, including those in the central nervous system (CNS) (81-82). Through intracellular intermediary metabolic pathways, glucose is oxidized to release energy in the form of ATP (81-82). If the blood glucose concentration falls below 60 mg/dl (3.3 mmol/L) CNS function may be impaired (18, 81). To prevent this from happening, intricate homeostatic mechanisms have evolved to maintain the normal blood glucose concentration within a fairly narrow range, keeping fluctuations to a minimum (81-82). These homeostatic mechanisms ensure that in normal dogs and cats the average blood glucose concentration is maintained around 100 mg/dl (5.0 mmol/L), with daily fluctuations of only 10 to 20 % despite variations in glucose influx (postprandially) and efflux (strenuous exercise) (18-20, 83).

Table 1. Potential Factors involved in the Etiopathogenesis of Diabetes Mellitus in Dogs and Cats

Dog	Cat
Genetic predisposition	Genetic predisposition?
Pancreatic injury	Pancreatic injury
Trauma	Trauma
Neoplasia	Neoplasia
Infection	Infection
Autoantibodies - immune mediated insulitis	Autoantibodies - immune mediated insulitis?
Inflammation - pancreatitis	Inflammation - pancreatitis
Drugs	Drugs
Islet amyloidosis?	Islet amyloidosis
Hormone-induced B-cell exhaustion	Hormone-induced B-cell exhaustion
Growth hormone excess (Acromegaly)	Growth hormone excess (Acromegaly)
Thyroid hormone excess of deficiency	Thyroid hormone excess of deficiency
Cortisol excess	Cortisol excess
Endogenous - hyperadrenocorticism	Endogenous - hyperadrenocorticism
Exogenous - administered corticosteroids	Exogenous - administered corticosteroids
Progestins	Progestins
Endogenous - pregnancy, diestrus	Endogenous - pregnancy, diestrus
Exogenous - megestrol acetate administration	Exogenous - megestrol acetate administration
Target tissue insulin insensitivity	Target tissue insulin insensitivity
Decreased number of insulin receptors	Decreased number of insulin receptors
Defective insulin receptors	Defective insulin receptors
Defect in postreceptor effects of insulin	Defect in postreceptor effects of insulin
Dyshormonogenesis of insulin	Dyshormonogenesis of insulin
Concurrent illness interfering with action of insulin	Concurrent illness interfering with action of insulin
Cardiac disease	Cardiac disease
Renal insufficiency	Renal insufficiency
Obesity and hyperlipidemia	Obesity and hyperlipidemia

There are numerous hormones involved in glycemic control, but insulin is the primary hormone responsible for lowering the blood glucose concentration and for promoting energy storage (81, 83). Counterregulatory hormones that oppose the action of insulin include sympathetic (epinephrine and norepinephrine) and adrenocortical (cortisol) hormones, growth hormone produced by the pituitary gland, and glucagon produced by pancreatic alpha-cells (81, 83). While insulin has largely anabolic actions, these counterregulatory hormones, with the exception of growth hormone, have largely catabolic actions (81-83).

Insulin is produced by pancreatic beta-cells. Beta cells are one of the four cell types in the islets of Langerhans that make up the endocrine portion of the pancreas (83). The other cell types comprising the islets of Langerhans and their products include alpha-cells (glucagon), delta-cells (Somatostatin), and f-cells (pancreatic polypeptide) (83). Through paracrine interactions the product of each of these cell types can alter the secretion of the other cell types within the islet (83). Pancreatic islets cells are also abundantly innervated by the autonomic nervous system, which is also involved in helping to regulate the secretion of these hormones (83).

Insulin Synthesis and Secretion

Insulin, like other peptide hormones, is synthesized as a larger protein molecule called pre-proinsulin (84-85). Pre-proinsulin consists of proinsulin and a signal peptide, and it is synthesized by the ribosomes of the rough endoplasmic reticulum (84-85). Within the Golgi apparatus, the signal protein is cleaved off to yield proinsulin. Proinsulin is then stored within intracellular secretory vesicles which bud off the Golgi apparatus (84-85). Within the secretory

vesicles, a connecting peptide (C peptide) is cleaved off the proinsulin peptide by specific peptidases to yield equimolar amounts of insulin and C-peptide (84-85). Both of these peptides are released into the circulation when insulin is secreted by the beta-cell via exocytosis (85).

The final insulin polypeptide secreted by the beta-cells consists of two dipeptides designated the A and B chains, which are linked by two disulphide bonds (84-85). Although there are small differences in the amino acid sequence of insulin from species to species, the biologic activity of insulin from different species is not species specific (84-85).

Insulin secretion from the islet cells into the portal veins is characteristically pulsatile. Superimposed on the basal oscillatory secretory pattern of insulin release is post-meal variation in insulin secretion (85). In response to stimuli such as glucose, insulin secretion is characteristically biphasic, with an initial rapid phase of insulin secretion, followed by a less intense but more sustained release phase (85).

Given the pivotal role of insulin in glucose utilization and metabolism, it is not surprising that glucose has multiple influences on insulin biosynthesis and secretion. Indeed, glucose is considered the major physiologic secretagogue for insulin secretion by beta-cells, but it is not the only secretagogue capable of stimulating insulin synthesis and release (82, 84). In order to stimulate insulin release from beta cells, glucose must first enter the beta-cell and be metabolized because it is the glucose metabolites that stimulate insulin secretion (84). Glucose enters beta cells by facilitated diffusion, utilizing a membrane associated glucose transporter called GLUT2 (84). Entry of glucose into beta cells is not dependant on insulin (83-84). This transporter has a high capacity but low affinity for glucose which permits a graded response to changes in the extracellular glucose concentration (84). Glucose entry into the beta cell ultimately triggers the

influx of Ca^{2+} into the cytoplasm through a second messenger system. The influx of Ca^{2+} into the cytoplasm in turn triggers an effector system involving elements of the cytoskeleton, which brings about the pulsatile release of insulin by exocytosis of insulin-containing secretory granules (39, 84). In addition to the generation of the triggering signal, the glucose-induced insulin secretion also activates an amplification pathway that is essential for optimization of the secretory response to the triggering signal (86). The exact second messenger system(s) involved in this amplification pathway have not yet been identified, but the amplifying pathway is only activated when the triggering pathway has been activated (39, 85). This hierarchy ensures that under normal circumstances insulin is not inappropriately secreted in the presence of low glucose concentrations (39, 85, 86).

Although glucose is the most potent secretagogue for stimulating insulin release, other molecules are capable of stimulated or inhibiting insulin secretion. Many of these molecules are other nutrients, including certain amino acids, free fatty acids (FFA), volatile fatty acids, and ketone bodies; other hormones (e.g., glucagon); and certain drugs (e.g., sulfonylureas) (84-85). Non-nutrient secretagogues of insulin secretion may also play a role and act via cholinergic and adrenergic pathways, or through other enteric and non-enteric peptide hormones and cationic amino acids (39, 84-85). Vagal nerve stimulation of insulin secretion is thought to mediate the cephalic phase of insulin secretion, occurring when food is seen, smelled, or acutely ingested (84-85). Insulin secreted by this mechanism does not occur in the fasting state or when the blood glucose concentration is low, but can help augment insulin secretion in the fed state (85). Adrenergic stimulation of beta cells through α2-adenoreceptors inhibits the release of insulin during stress and exercise (85). A number of peptide hormones also influence insulin secretion,

including several enteric hormones and other nonenteric hormones (84-85). Table 2 reviews the currently known mediators of insulin secretion.

Table 2. Mediators of Insulin Secretion

Stimulus	Nutrient	Hormone	Neural
Stimulatory	Glucose Amino acids Ketones	Growth hormone Glucagon Gastric inhibitory peptide (GIP) Glucagon-like peptide 1 (GLP-1) Secretin Cholecystokinin Vasoactive intestinal peptide (VIP) Gastrin releasing peptide	ß-adrenergic Cholinergic (vagal)
Inhibitory		Adrenocorticosteroids Somatostatin Epinephrine Norepinephrine Neuropeptide Y Calcitonin gene-related peptide (CGRP) Prostaglandin E Insulin Amylin and pancreastatin	α-adrenergic

Kinetics of Insulin Secretion

Insulin secretion depends not only on the concentration of blood glucose that beta cells are exposed to, but also on the rate of change of the blood glucose concentration (86). When the blood glucose concentration rises abruptly, insulin secretion displays biphasic kinetics (86). There is an initial rapid early insulin peak followed by a second slower but sustained insulin peak (86). The rapid early insulin secretion peak occurs within seconds, lasts approximately ten minutes, and is assumed to reflect the release of insulin already synthesized and stored in secretory granules within the beta-cell (85, 86). A resting period lasting several minutes occurs after this initial phase. This is then followed by the second phase of insulin secretion that lasts

the duration of the hyperglycemia and is proportional to the serum glucose concentration (85, 86). This second phase of insulin secretion occurs more gradually, but reaches a sustained peak and is thought to reflect release of a less available intracellular storage pool of insulin, in addition to release of newly synthesized insulin (86). Other factors that will influence insulin secretion include the cephalic phase of insulin stimulation, the nutrient composition of the meal, the rate of gastric emptying, gastrointestinal motility, release of other enteric hormones, and neural input (85). The biphasic secretion of insulin in response to glucose loading is also referred to as inducible, stimulated, or regulated insulin secretion (85-86). About 50% of the daily secretion of insulin is inducible and occurs in response to consumption of food (85-86). The remaining 50% of the total daily insulin secretion occurs under basal conditions and is referred to as constitutive or unregulated insulin secretion (86).

Insulin Receptors and Insulin Binding

Insulin initiates its actions by binding to insulin receptors that are distributed widely throughout tissues of the body, and especially in those tissues classically regarded as insulin-sensitive, such as liver, muscle and adipose tissue (87). When insulin binds to its receptor it results in a conformational change in the receptor that triggers a cascade of enzymatic reactions that mediate the intracellular actions of insulin. Different second messenger systems are involved in the postreceptor effects of insulin (85, 87). One of the principle actions of insulin is to promote glucose uptake by insulin sensitive tissues. Glucose enters such cells in an ATP-independent manner by means of glucose transporter proteins (GLUT), of which at least 5 subtypes have been identified in different tissues (87).

Actions of Insulin at the Cellular Level

The actions of insulin at the cellular level encompass effects on carbohydrate, lipid and amino acid metabolism, and mRNA transcription and translation of other cellular proteins involved in intermediary metabolism (85, 87). Insulin is essential for the intracellular transport of glucose into insulin-dependent tissues such as muscle and adipose tissue; by signaling caloric abundance, insulin also inhibits breakdown of fat and promotes storage of excess glucose as fat or glycogen within adipocytes, hepatocytes and myocytes (85, 87). Lipolysis, gluconeogenesis and glycogenolysis are simultaneously inhibited in adipocytes, hepatocytes and myocytes (85, 87). Insulin also enhances cellular uptake of potassium, magnesium, nucleosides, and inorganic phosphate (87).

Carbohydrate Metabolism

Insulin affects multiple aspects of carbohydrate metabolism (85, 87). Insulin secretion is stimulated by postprandial hyperglycemia and this promotes uptake of glucose by insulin dependent tissues and storage of excess glucose as glycogen within cells of the liver and muscle through the activation of enzymes involved in glycogenesis (87). Intermediary metabolic pathways that promote the release of glucose into the circulation such as glycogenolysis, gluconeogenesis, and ketogenesis are simultaneously inhibited (87). The mechanism by which insulin promotes glucose uptake by different tissues varies (87).

Lipid Metabolism

Insulin stimulates fatty acid, cholesterol and triglyceride synthesis in adipose tissue and the

liver, and promotes formation and storage of triglycerides in these tissues by simultaneously inhibiting lipolysis (85, 87). Oxidation of fatty acids, cholesterol breakdown and triglyceride breakdown are suppressed (94, 104). Phospholipid metabolism is also influenced by insulin (85, 87).

Protein Synthesis

Insulin promotes protein synthesis in a range of tissues (85, 87). Uptake of amino acids is promoted and gluconeogenesis in the liver and kidney is inhibited (85, 87). Insulin also promotes the transcription and translation of specific mRNA into proteins (85, 87). The effects on translation are widespread and are also influenced by other hormones such as insulin-like-growth factor 1 (IGF-1) (85, 87).

Degradation of Insulin

The circulating half-life of insulin is between three to five minutes (87). Insulin is catabolized by the liver and the kidney (85, 87). It is estimated that roughly 50% of secreted insulin is removed by the liver through first pass metabolism (85, 87). C-peptide and any proinsulin that is released are catabolized by the kidney (85, 87).

Hormonal Dysregulation with Insulin Dependant Diabetes Mellitus

Despite the tremendous reserve capacity of the endocrine portion of the pancreas, islet cells have very little capacity to regenerate once injured; when more than 70 to 75 % of them have been destroyed, hyperglycemia and signs of diabetes mellitus result (21, 83). With diabetes

mellitus, the normal adaptations to the fasting and the fed state are deranged (88). Insulin deficiency leads to a relative or absolute hyperglucagonemia due to loss of the restraining influence of insulin on the alpha cells (15, 88). Hyperglucagonemia and a decrease in the insulin/glucagon ratio leads to the following: increased production of glucose by the liver, impaired glucose utilization by insulin-dependent tissues, activation of lipolysis in adipose tissue, enhancement of proteolysis in muscle to supply amino acids for gluconeogenesis, and intensification of the effects of glucagon on the liver (88; 47). Glucagon activates glycogenolysis, gluconeogenesis, and possibly ketosis in the liver (89). Insulin deficiency also enhances the delivery of amino acids and free fatty acids to the liver, which are then used as substrates for glucose and ketone production (89). With the development of diabetic ketoacidosis, other counterregulatory hormones, including epinephrine, norepinephrine, cortisol, growth hormone, angiotensin, and vasopressin, may be released; their hyperglycemic effect is exaggerated by the insulin deficiency (25, 52).

Clinical Features of Diabetes Mellitus in Companion Animals

The classic clinical signs seen with uncomplicated diabetes mellitus include polyuria, polydipsia, polyphagia, and weight loss (18-20, 24-25, 37). All these signs can be understood in terms of the underlying pathophysiologic changes to lipid, carbohydrate, and protein metabolism (18-20, 24-25). Hyperglycemia from impaired glucose utilization and increased production and release of glucose by the liver results in glucosuria and a subsequent osmotic diuresis when the renal threshold for reabsorption of glucose is exceeded (18-20, 25-26, 37). The resulting polyuria causes dehydration and a compensatory polydipsia (18-20, 24-25). Impaired ability to

utilize glucose leads to an increased sense of hunger and activation of the feeding center of the brain; this, in combination with loss of calories from glucosuria, results in the clinical signs of polyphagia and weight loss (18-20, 52). Protein catabolism and the unrestrained increased activity of hormone sensitive lipase in adipocytes also contributes to weight loss, especially in animals that are initially overweight (25).

The onset of clinical signs of diabetes mellitus is typically rapid in dogs, occurring over a period of a few weeks. In cats, especially those with type II or NIDDM, clinical signs may be subtle and progressive over many months to years (37). Acute onset of blindness secondary to bilateral cataract development is another possible presenting complaint in dogs, and there have been occasional reports of dogs presented for weakness and neurologic problems associated with development of a diabetic neuropathy (90-92). Cats may also be presented with signs of diabetic neuropathy such as a plantigrade stance, weakness or inability to jump, or with chronic gastrointestinal signs rather than the classic clinical signs of diabetes (25, 37). Diabetic cataracts are considered a rare finding in cats with diabetes mellitus (93).

Physical examination findings in diabetic animals are often nonspecific (18-20, 24-25, 37, 94). Lethargy, depression, dehydration, unkempt haircoat, and muscle wasting or thin body condition are common findings in cats (25-26, 38, 94). In dogs, dehydration, muscle wasting, and a thin body condition are the most common findings (25, 37). Hepatomegaly can be observed in both diabetic cats and dogs (18-20, 25, 37). Diabetic cataracts are seen in up to 40% of diabetic dogs but are very rare in cats (25). Diabetic cataracts can develop rapidly in dogs, with sudden blindness or diminished vision being the primary reason for initial presentation to a veterinarian (25).

Animals with diabetic ketoacidosis may present for anorexia, weakness, vomiting, and depression (25-26, 95). Physical examination findings may include depression, tachypnea, dehydration, weakness, vomiting, or with signs of shock (collapse, tachycardia, weak pulses, etc.) (26, 94). In one study, 40 % of the diabetic dogs were ketotic at the time of initial presentation to a veterinarian (26).

Diagnosis of Diabetes Mellitus

The diagnosis of diabetes mellitus is relatively straightforward in dogs and cats. Compatible historical and clinical signs and evidence of fasting hyperglycemia with concurrent glucosuria are the cornerstones of the diagnosis (18-20, 25, 37).

Clinical Pathologic Abnormalities

Common clinicopathologic features of uncomplicated diabetes mellitus include fasting hyperglycemia, hypercholesterolemia, increased liver enzymes (alkaline phosphatase, alanine aminotransferase), a neutrophilic leukocytosis, proteinuria, mildly dilute urine specific gravity (typically in the range of 1.025 to 1.035), and glucosuria (18-20, 37). Occasionally, a relatively healthy diabetic dog or cat may have trace or small amounts of ketones in their urine (18-20). Proteinuria may be the result of either a urinary tract infection or result from glomerular damage secondary to disruption of the basement membrane (96). Occult urinary tract infections are common in diabetic dogs (34, 97). Common clinicopathologic findings in patients with diabetic ketoacidosis may include azotemia, ketonemia, significant ketonuria, a leukocytosis, electrolyte abnormalities, bacteriuria, hematuria, pyuria, and possibly elevations in amylase and lipase (18-

20, 37).

Treatment of Diabetes Mellitus in Dogs and Cats

There are four primary aims of therapy for dogs and cats with diabetes mellitus. First, treatment is aimed at resolution of clinical signs (18-20, 24, 44, 94). Second, treatment is aimed at avoidance of insulin-induced hypoglycemia (18-20, 24, 94). Third, treatment should prevent or ameliorate chronic complications of diabetes mellitus. Fourth, treatment is aimed at allowing the pet to resume a normal lifestyle and exercise level (18-20, 24, 94). All this must be accomplished using a treatment regimen that minimizes disruption to the owner's lifestyle, but maximizes the clinical response of the pet to the provided treatment. Administration of exogenous insulin, dietary management, use of adjunctive oral hypoglycemic medications, and treatment and correction of underlying conditions predisposing to or precipitating the disease are the mainstays of therapy (18-20, 24, 44, 94). The management of every diabetic animal must be individualized (18-20, 24, 44, 94). This is especially true when insulin therapy is required. Because of the impact of sex hormones on diabetic control, it is recommended that all diabetic dogs be spayed or neutered in order to avoid unnecessary complications with insulin resistance (18-20).

Insulin Therapy

For dogs and cats with IDDM, the main component of therapy for diabetes mellitus involves regular injections of exogenous insulin given once or twice daily by the owner (18-20, 24, 44, 94). Even diabetic dogs with residual beta cell function, and cats with transient type II diabetes,

usually have inadequate insulin secretory capacity to allow successful management with only oral hypoglycemic drugs and diet (24). A variety of insulin preparations are commercially available (18-20, 98). Regular insulin is the most potent type of insulin and has the shortest duration of action; it is typically only used to treat dogs and cats on a short-term basis for the management of diabetic ketoacidosis (18-20, 98). Intermediate to long-acting preparations, including ultralente, lente, protamine zinc (PZI), and neutral protamine Hagedorn (NPH) insulin, are more suited for long-term management of outpatient diabetic dogs and cats (18-20, 98). Premixed combinations of short- and long-acting insulins are also available and are occasionally used to treat diabetic cats and dogs (24, 94). Lente insulin, a premixture of semilente and ultralente, and various combinations of regular and NPH insulin are some examples of premixed commercial insulin preparations (24, 94). Good glycemic control can be achieved with most insulin preparations but some have a more predictable effect and so are easier to use. As a general rule, the longer the duration of action of an insulin preparation, the greater the inter- and intra-dog and cat variability in the response to the insulin that can be expected (24, 94).

Other than the duration of action of insulin, the species of origin of the exogenous insulin can sometimes also be a factor for consideration (18-20; 24, 94, 98). Porcine insulin has an amino acid sequence identical to canine insulin, so it should not induce anti-insulin antibodies even with long term use (99-101). Bovine insulin, however, differs from canine insulin by two amino acids and anti-insulin antibodies have been detected in dogs treated with pure bovine insulin or combinations of bovine/porcine insulin (100-102). Currently, recombinant human insulin, which differs by only one amino acid from canine insulin, is the most common species of exogenous insulin available (102). The clinical significance of anti-insulin antibodies is that they

may make it difficult to achieve good glycemic control in some diabetic dogs (18-20, 24, 95, 102).

Most human recombinant insulin preparations are sold at a concentrations of 100 U/ml and the typical starting dose for non-ketotic diabetic dogs is 0.25 – 0.5 U/kg (18-20, 24, 94, 98). Caninsulin ® (a porcine insulin), and PZI insulin (bovine/porcine), both marketed as veterinary products, are less concentrated (40 U/ml) insulin preparations (18-19, 94, 98). These more dilute preparations are useful for more accurately dosing smaller dogs that require fairly low doses of insulin (24, 94). It is also possible to dilute some types of more concentrated insulin to facilitate more accurate dosing in smaller patients (98).

In most dogs, insulin is administered subcutaneously twice daily, but in a small minority of dogs once-daily dosing is possible (18-19, 94, 98). Rotating the site of insulin injection is recommended to avoid problems with insulin absorption due to development of scar tissue (18-20, 98). Owners need to be instructed on the proper administration technique and on how to properly store and handle insulin (18-20, 98).

The major complication of insulin therapy is severe hypoglycemia (18-20, 24, 37, 50, 94, 98). This results from insulin overdose and can cause irreversible brain damage and death (18-20, 98). Avoidance of insulin-induced hypoglycemia is one of the primary aims of therapy and usually requires a conservative approach to insulin dosing (18-20, 98).

Oral Hypoglycemic Medications

There are five classes of oral hypoglycemic drugs approved for the treatment of type II diabetes mellitus in people. These include sulfonylureas, meglitinides, biguanides,

thiazolidinediones and alpha-glucosidase inhibitors. In addition there are a number of other nutraceuticals, trace minerals, and herbal supplements that are used as adjunctive treatments (18-20, 103-104). Most oral hypoglycemic agents act by improving insulin sensitivity, increasing beta cell insulin secretory response to glucose, or by decreasing hepatic glucose production (103). Other oral hypoglycemic drugs do not affect insulin secretion or tissue sensitivity to insulin but work by minimizing postprandial glucose absorption.

Sulfonylurea drugs, including glipizide, glyburide, and glibenclamide, which act by amplifying insulin secretion from beta-cells, are the most commonly used oral hypoglycemic medication in cats (103-105). Since dogs mostly get type I or IDDM, oral hypoglycemic agents have a very limited role in treatment and should only ever be used as an adjunctive to insulin therapy and never as a sole therapy (18-19, 24, 94). Because most diabetic dogs do not have sufficient beta-cell function to allow these drugs to be effective, they will not be discussed further (18-20, 24).

Other drugs that increase the sensitivity of insulin-sensitive tissues to insulin (e.g., biguanides and thiazolidinediones), which are widely used in people with NIDDM, have a very limited role to play in treatment of diabetes in dogs and cats (106). However, for dogs that have poorly controlled diabetes despite insulin therapy, or in dogs that have evidence of insulin resistance due to an uncorrectable underlying disease, then use of some of these oral hypoglycemic agents may be worthwhile (18-20, 24). Because cats, unlike dogs, commonly have type II diabetes, use of these drugs is more common and applicable in cats than in dogs (18-20, 24, 94).

Acarbose, an alpha-glucosidase inhibitor, competitively inhibits α-amylase and α-

glucosidases in the intestine, delaying absorption of glucose and blunting the postprandial hyperglycemia (18-22, 107-108). This has been used as an adjunctive treatment in diabetic dogs receiving insulin (18-19, 24, 94, 107-108) and has been shown to be effective (107-108).

Chromium is a dietary mineral supplement thought to potentiate insulin's action on peripheral tissues so it is sometimes used as an adjunctive therapy to improve glycemic control in insulin-treated dogs and people (24, 94, 109). However, in one study chromium picolinate was not found to improve glycemic control in insulin-treated diabetic dogs (110).

Dietary Therapy and Feeding Schedule

The diet fed to a diabetic cat or dog will vary depending on the case (18-20, 70, 111). Because multiple studies indicate that high-fiber diets are associated with improved glycemic control in dogs, such diets are commonly recommended, especially for obese dogs (112-116). Several mechanisms have been proposed to explain how fiber improves glycemic control (111, 117). A delay in gastric emptying, a delay in intestinal glucose absorption resulting from an effect on the diffusion of glucose through the intestinal brush border, and a fiber-induced effect on the release of regulatory gastrointestinal tract hormones into the circulation, are the most likely mechanisms (135, 117). Since derangements in fat metabolism are common in diabetic dogs and feeding diets high in fat can lead to insulin resistance, it is strongly recommended that diets fed to diabetic dogs should also be low in fat (18-20, 111).

For dogs that are thin or emaciated when first diagnosed with diabetes mellitus, high-fiber diets should not be fed (18-19, 111). Instead, a diet that has a higher caloric density and is generally lower in fiber is recommended (18-19, 24, 111). Once a normal body weight is

attained, it may be possible to switch such dogs over to a diet with higher fiber content. If dogs refuse to consume a high-fiber diet, then they should be fed a good quality maintenance diet (18-19, 24, 111). Good to excellent glycemic control can usually be achieved with maintenance diets, so it is not essential to feed a high-fiber diet if a dog refuses to eat it (18-19, 24, 94). Also, if a diabetic dog has other concurrent diseases that require different nutritional management, then these requirements may need to take precedence or the dietary therapy for all disorders can be blended (18-19, 24, 94). In contrast to dogs, the current recommendation for diabetic cats is to feed diabetic cats a high protein diet to take advantage of their obligate carnivore nature and relative carbohydrate intolerance (37).

The feeding schedule for a diabetic animal should be designed to enhance the actions of insulin and minimize postprandial hyperglycemia (18-19, 24, 94, 111). The goal is to have glucose slowly absorbed when insulin levels are maximal, thereby minimizing postprandial hypoglycemia (18-20, 94, 111). Ideally, diabetic dogs should eat just before the anticipated time of peak insulin activity. This usually requires that they are fed within four hours of administration of lente insulin, and within 1-8 hours after administration of NPH insulin (18-19). Unfortunately, this is rarely practical in most cases and so, to simplify management, dogs are usually fed immediately before they receive their insulin injection (18-19, 24, 94). Typically, dogs receiving insulin twice daily are fed two equal-sized meals at the time of each insulin injection (18-19, 24, 94, 111). For dogs receiving insulin only once a day, half of the daily caloric intake is fed at the time of insulin administration and the remaining amount is fed 8-10 hours later (18-19, 24, 94, 111).

Exercise Schedule

Exercise plays an important role in maintaining glycemic control in diabetic dogs. Exercise promotes weight loss and helps to eliminate obesity-induced insulin resistance (18-19, 24, 94). Exercise also helps to mobilize insulin from its injection site by increasing blood flow to the area (18-19, 24, 94). The daily routine of diabetic dogs should include exercise, ideally at a consistent time each day (18-19, 24, 94). Strenuous and sporadic exercise can result in hypoglycemia and should be avoided (18-19, 24, 94). For working, field trial, and hunting dogs, the insulin dose should be decreased by 50% on days of anticipated increased exercise (18-19, 24, 94).

Monitoring Response to Therapy of Diabetes Mellitus: Glycemic Indices

The primary aim of long-term therapy for diabetic pets is to achieve resolution of their clinical signs (18-20, 24, 70, 94, 98). This allows the pet to return to their normal activity level, while allowing them to maintain their optimal body weight and resolve their polyuria, polydipsia, and polyphagia (18-20, 24, 70, 94, 98). A number of parameters are all used to help assess the level of diabetic regulation of the diabetic dog or cat. These include the following: assessment of the resolution of the classic clinical signs of diabetes mellitus with initiation of treatment, and subsequent monitoring for the return of these clinical signs despite treatment, monitoring of urine glucose and ketone levels by owners and/or at follow-up hospital visits, monitoring trends in serial blood glucose curves, and measurement of long term indices of glycemic control, such as body weight, glycosylated hemoglobin concentrations, and serum fructosamine concentration (18-20, 24, 70, 94, 98, 118).

Home Monitoring of Glycemic Control: Owner's Subjective Observations

In a newly diagnosed diabetic animal, resolution or persistence of diabetic clinical signs are an important indicator used to assess glycemic control (18-20, 24, 70, 98, 118-119). Likewise, return of the clinical signs of diabetes in a previously well-regulated diabetic animal is also an important indicator of diminished glycemic control (18-20). Therefore, it is imperative that owners monitor their pet's water intake, attitude, appetite, and urination frequency and volume (18-20, 24, 70, 94, 98, 118-119). This is particularly true for cats where stress hyperglycemia may interfere with in-hospital blood glucose curve monitoring, making the results of serial blood glucose curves unreliable (20, 70). Owners are encouraged to keep a daily diary where they record their pet's appetite, general demeanor, the amount and times of feeding, amount and time of insulin administration, and if feasible, the quantity of their pet's water intake (18-20, 24, 94). Persistence or return of polyuria and polydipsia in the absence of another underlying disease that can cause such signs is an indication that the pet's diabetes mellitus is not well controlled (118). The owner's log book or general impressions of their pet's diabetic control should be reviewed at each follow-up visit. One study looking at subjective owner indicators of poor diabetic control (i.e., persistent polydipsia (> 60 ml/kg/day) and polyuria, lethargy, and muscle weakness) in dogs with IDDM found the owner's assessment to be the most helpful indicator for classifying control of glycemia as good or poor (119). Weight loss in a non-obese diabetic dog or cat, persistence of ≥ 3+ glucosuria, and detection of ketonuria are other parameters that may also be valid indicators of poor control (24, 94, 118-119).

In-Hospital Monitoring of Glycemic Control: Serial Blood Glucose Curves

For most feline and canine diabetic patients, information obtained from serial blood glucose curves is used to monitor glycemic control and to help decide whether the dose, type, and frequency of insulin administration is appropriate in a particular individual cat or dog (18-20, 24, 941, 118). The first blood glucose curve is usually evaluated 7-14 days after initiating insulin therapy, and curves are repeated every 7-10 days until the patient's diabetes is considered well regulated (18-20, 24, 94). Any time a change is made in the patient's insulin dose or frequency, a curve should be performed 7-10 days later (18-20, 24, 94). Performing a glucose curve earlier than this is unwise, as it takes time for a patient to equilibrate with any change in the dose or frequency of administration of insulin (18-20, 24, 94, 118).

A standard protocol for performing a blood glucose curve involves admitting the dog to the hospital prior to administration of their morning insulin injection and obtaining a baseline blood glucose reading (18-19, 94). After this, food is provided and the insulin dose is administered once the dog eats their breakfast meal (18-19, 94). For dogs that are unwilling to eat in the hospital the morning preinsulin blood glucose reading can be omitted and the dog can be brought into the hospital after eating (18-19, 24, 94). Blood glucose concentrations are measured every 1 to 2 hours for a 12 or 24 hour period until their next insulin dose is due (18-19, 24, 94, 118). Only a drop of blood taken from a peripheral vein or ear vein is required (18-20, 24, 70, 94). The pet's glucose concentration is measured using a properly calibrated portable glucometer (18-19, 24, 94). In general, most hand-held whole blood glucometers used in dogs and cats give readings that are 10-15 mg/dl lower than a true laboratory serum glucose value (118, 120). This should be accounted for to avoid an incorrect diagnosis of hypoglycemia, or the misperception

that the glycemic control is better or worse than it actually is (24, 94). The blood glucose values obtained can then be plotted on standard graph paper (121). Important aspects of the curve to evaluate include the overall shape of the curve, the blood glucose nadir, the preinsulin blood glucose concentration(s), and the duration of action of the insulin (24, 94, 118). While the pet is hospitalized for the glucose curve, it is imperative to minimize stress and to maintain the pet's normal feeding and exercise routine (24, 94).

When analyzing glucose curves it is important to keep in mind that their use has important limitations. Studies have shown that there is a tremendous amount of day to day inter- and intra-dog variability between blood glucose curves performed on individual dogs receiving an identical insulin dose and meal (122). Potential reasons for this variability include unavoidable variations in the dose of insulin administered, differences in the rate of absorption from the SC injection site, inherent errors in the glucometer used, and inter- and intra-dog variability in counterregulatory mechanisms (18-19, 24, 122). Because of this, results of a serial blood glucose curves should always be considered in conjunction with assessment of patient history, physical examination findings, and changes in body weight prior to making any changes in the dose, type, or frequency of administration of the pet's insulin (24, 119).

Glucose curves should hopefully allow the clinician in charge of managing the pet's diabetes mellitus to answer four fundamental questions. First, is the insulin type effective in the patient? If a reasonable dose of insulin appears to have no effect (blood glucose values stay higher than 20-30 mmol/L with little blood glucose lowering effect), insulin resistance or insulin ineffectiveness should be considered (18-19, 24). High initial blood glucose measurements with a suboptimal response to what should be an adequate dose of insulin might also result from a

Somogyi phenomenon, and this must always remain a consideration (18-20, 24, 70, 123). The Somogyi phenomenon results from a normal physiologic response to hypoglycemia induced by an excessive insulin dose (18-20, 123). This will occur when the blood glucose concentration declines to less than 3.3 mmol/L or when the glucose concentration drops rapidly regardless of the ultimate glucose nadir (123). Second, is the dose of insulin optimal? This is determined by looking at the pre-insulin glucose and glucose nadir concentrations. Ideally, the blood glucose nadir should fall between 6-10 mmol/L for diabetic cats and dogs. If the nadir blood glucose concentration is in the hypoglycemic range (< 5 mmol/L), or the dog has shown signs of hypoglycemia at home or in the hospital, the insulin dose should be reduced by 20 to 50% (24). If the nadir blood glucose concentration is in the range of 5-8 mmol/L and both of the preinsulin blood glucose values are > 10 mmol/L, no change in the insulin regimen is needed provided the pet's clinical signs at home reflect good control (24). If the nadir blood glucose concentration is greater than 8 mmol/L and the preinsulin blood glucose values are greater than 10 mmol/L, the dog's insulin dose should be increased by 20 % (24). Third, is the duration of insulin adequate? Ideally, the duration of action of any insulin should be such that the patient's blood glucose is kept in the optimal range of 5.5 – 14 mmol/L for the time period between insulin injections (19, 24). For dogs receiving insulin twice-daily, then the ideal duration of insulin effectiveness is approximately 12 hours (19, 24). For dogs receiving insulin once-daily, the ideal duration of insulin effectiveness is approximately 24 hours. Fourth, are there any patient variables that can be identified that might affect glycemic control and, if so, can they be corrected? This basically involves identifying if stress hyperglycemia is a problem, or if the patient has any concurrent diseases that can cause insulin resistance (19, 24). Initial or follow-up blood work, the results of

one or more blood glucose curves, and historical and physical examination findings are important in assessing for the existence of such conditions (19, 24, 124).

Adjustments in insulin dose are usually dictated by the type of insulin, the glucose nadir, and its timing following administration of insulin (18-20, 24, 98). Changes in the type of insulin to be administered will be dictated by the duration of effect of the exogenous insulin in an individual dog or cat (18-20, 24, 98).

Home Monitoring of Blood Glucose and Urine Glucose by the Owner

An alternative to in-hospital generated glucose curves is to have owners generate blood glucose curves at home using the ear or lip prick technique and a portable home glucose monitoring device (125-127). The advantage of performing a glucose curve in the pet's home environment is that it may offer a means of avoiding the problems of inappetence and stress hyperglycemia, and the curve generated may be a more accurate reflection of the actual glucose metabolism in the animal's normal environment (123, 125-125). The disadvantage of this is that owners have to learn the technique and some owners may start making changes in the pet's insulin dose based on the results without consulting their veterinarian. Such activity needs to be strongly discouraged (18-20).

Ideally, diabetic animals should have negative glucosuria for the majority of the day, but not for the entire day. When glucosuria is detected, 1-2+ is acceptable, but persistently marked glucosuria (3+ to 4+) likely indicates poor glycemic control (18-20, 24, 123, 125-127). For dogs and cats with persistently negative glucosuria, this may signal the need to decrease the pet's insulin dosage due to the likelihood of concurrent hypoglycemia occurring (24, 125-127). If

ketones in the urine are being monitored, then clients should be instructed to call their veterinarian if their cat or dog has more than trace ketones in their urine on any single assessment (125-127). This may allow early detection and treatment for diabetic ketoacidosis (125-127).

Monitoring Long-term Glycemic Control

The ability to measure glycosylated hemoglobin (GHb) and serum fructosamine concentrations has enhanced our ability to monitor long-term glycemic control in diabetic cats and dogs (18-20, 24, 118, 123, 128-131). Glycosylated protein concentrations are a marker of mean blood glucose concentrations during the circulating lifespan of the respective protein (18-20, 24, 118, 123, 128-136). Changes to these parameters do not occur with only transient elevations in the blood glucose concentration (18-20, 24, 118, 123, 128-136). In cats and dogs, serum fructosamine generally reflects glycemic control over the previous 7-21 days, while glycosylated hemoglobin reflects glycemic control over the previous 2-4 months in cats and dogs, respectively (18-20, 24, 118, 123, 128-130, 132-134, 137).

Serum Fructosamine

Serum fructosamine is formed through the non-enzymatic, insulin-independent, irreversible glycosylation of serum proteins (18-20). The serum fructosamine concentration depends on the serum protein concentration and on the plasma glucose concentration (131, 138). Severe hypoalbuminemia, hyperlipidemia and hyperthyroidism are three laboratory findings that may interfere with measurement of serum fructosamine (135).

Serum fructosamine is determined using a colorimetric assay (18-19). The reference range

for normal dogs is 310 - 370 umol/L (18-19). Several studies have documented significantly elevated serum fructosamine concentrations in diabetic dogs compared to healthy dogs (129, 135 138-142). Different analytical assays account for the variability in results seen between different studies (18-19).

Use of serum fructosamine values for helping to assess glycemic regulation may take on an even more central role for dogs where serial blood glucose curves are unreliable. This would include aggressive, excitable, or highly stressed dogs where stress-induced hyperglycemia interferes with glucose curve evaluation (18-20). Reference ranges have been established for categorizing glycemic control as excellent, good, fair, or poor, based on the serum fructosamine value seen in a diabetic dog and cat (see table 3) (18-20, 123, 129, 134, 136).

Glycosylated Hemoglobin

Glycosylated hemoglobin forms from the slow, non-enzymatic, irreversible, insulin-independent binding of glucose to hemoglobin in red blood cells (18-19, 123, 129). The formation of glycosylated hemoglobin is directly related to the serum glucose concentration, as well as to the erythrocyte life span, which is approximately 120 days in dogs (137). Provided there is a normal turnover of erythrocytes, GHb provides an accurate index of the average glucose concentration over the preceding 120 and 70 days in dogs and cats, respectively. Any condition that affects erythrocyte lifespan will affect the measured glycosylated hemoglobin (18-19, 137). Anemia and polycythemia will falsely increase and decrease glycosylated hemoglobin respectively (18-19, 137).

Measurement of glycosylated hemoglobin can be done by a number of different

methodologies. This accounts for the variability in the reference ranges quoted by different studies. Values in normoglycemic dogs vary from 1.7% to 4.9% (18-19, 128, 130). The lack of a universal reference range, along with the expense, limited availability of the test, and the possibility of falsely elevated levels can be problematic when interpreting this test (123).

Values in diabetic dogs may be normal if the onset of diabetes is recent but typically are between 6 and 15.5 % depending on the level of glycemic control achieved (see table 3) (18-19). Table 3 provides general guidelines for collection, sample handling, and interpretation of the results as an indicator of glycemic control (18-20).

Complications of Diabetes Mellitus

Complications associated with diabetes mellitus in humans, especially late onset or chronic complications, are the main reason for invalidity and early mortality (143-144). Many of these devastating chronic complications (e.g., secondary cardiovascular disease, diabetic nephropathy and neuropathy) require 10-20 years to develop in people, and many are potentially reversible if diagnosed in the early stages (143). Treatment and prevention of chronic complications includes not only specific treatment for each disorder but, most importantly, this involves aggressive measures to improve and maintain good glycemic regulation (18-20, 24, 143, 145-147).

Table 3. Sample Handling, methodology, and values for Serum Fructosamine and Blood total Glycosylated Hemoglobin for Normal and Diabetic Dogs.

	Fructosamine	Glycosylated Hemoglobin
Blood Sample	2 mls serum	2 mls EDTA blood
Sample handling	Freeze until assayed	Refrigerate until assayed
Methodology	Automated colorimetric assay	Affinity chromatography
Factors affecting result	Hypoproteinemia Hyperlipidemia Azotemia Inappropriate handling	Inappropriate handling Anemia - decrease Polycythemia - decrease
Normal Range	310 - 370 umol/L	3 - 4.3 %
Interpretation of range in diabetic dogs		
Excellent control	350 - 400 umol/L	4 - 5%
Good control	400 - 450 umol/L	5 - 6%
Fair control	450 - 500 umol/L	6 - 7 %
Poor control	> 500 umol/L	> 7%
Prolonged hypoglycemia	< 300 umol/L	< 4 %

Epidemiological studies and clinical trials strongly support the notion that hyperglycemia is the principle cause of these complications (143, 145-146). Intensive therapy to maintain tight glycemic control in the short and long term has been shown to effectively delay the onset and slow the progression of diabetic retinopathy, nephropathy, and neuropathy (143, 145-147). Postulated pathogenic mechanisms responsible for diabetic complications can be grouped into the following three categories: glucose-related, including abnormalities in polyol metabolism and excessive glycosylation of circulating and membrane-bound protein; vascular mechanisms, including endothelial injury and injury to support cells of the retina and the renal glomeruli; and other mechanisms, including abnormalities in platelet function and growth factors, and influences from genetic factors (148). Hyperglycemia-induced oxidative stress is the chief underlying

mechanism of hyperglycemia-mediated vascular damage (149). Vascular damage also includes damage from systemic hypertension. Further discussion of the chronic complications will focus only on those seen in dogs.

Diabetic dogs rarely suffer from some of the more devastating complications seen in diabetic people because diabetic dogs simply do not live long enough with the condition for these to develop (18-20). Acute diabetic complications seen in dogs include diabetic ketoacidosis, insulin-induced hypoglycemia, and non-ketotic hyperosmolar syndrome (18-20). Chronic diabetic complications include diabetic cataracts, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, diabetes-induced lens-induced uveitis, and systemic hypertension (18-20).

Cataracts

Cataract formation is one of the most common and important long-term complications of diabetes mellitus in the dog. Cataracts are a very rare complication of diabetes in cats (18-20, 150). One large study concluded that cataracts will develop within five to six months of diagnosis in the majority of diabetic dogs and within sixteen months approximately 80% of dogs will have significant cataract formation (151). Cataract formation is an irreversible process once it begins, and in some diabetic dogs diabetic cataracts develop very rapidly (18-19, 150). Lens associated uveitis or blindness are the end results of severe diabetic cataracts (19-20, 150). Poorly controlled diabetes resulting in wide fluctuations in blood glucose concentrations seems to be an important risk factor for rapid development of cataracts (18-19, 150). Good glycemic control with minimal fluctuations in blood glucose concentrations delays the onset of cataracts (18-19, 150).

Lens-Induced Uveitis and Diabetic Retinopathy

During diabetic cataract formation, lens proteins that are normally sequestered from the animal's immune system are exposed causing uveitis (150). Lens-induced uveitis needs to be controlled in order to reduce the pain associated with this condition. Diabetic retinopathy refers to the retinal changes that result from retinal vascular damage from prolonged hyperglycemia (150). Diabetic retinopathy is very uncommon in dogs but there is a close association between development of diabetic retinopathy and suboptimal glycemic control (152-155).

Diabetic Neuropathy

Diabetic neuropathy is a common complication in diabetic cats (156-158). Although diabetic neuropathy is less common in dogs with diabetes mellitus, reports are well described in the literature (91-92, 156, 159). Diabetic neuropathy in dogs is primarily a distal polyneuropathy characterized by segmental demyelination and remyelination (18-19, 156). Electrophysiologic testing may be used to help confirm the existence of a diabetic neuropathy (156-157, 160-161). Currently there is no specific approved treatment for diabetic neuropathies in cats or dogs (18-20, 156). Aggressive glycemic regulation with insulin may improve nerve conduction and reverse the weakness and the plantigrade posture seen with this condition, but the response is variable (18-20, 156). Generally, the longer the duration of time the neuropathy has been present and the more severe the neuropathy, the less likely improved glycemic control will reverse the clinical signs (18-20, 156).

Diabetic Nephropathy

Although diabetic nephropathy has been occasionally reported in dogs, it is considered an uncommon complication of diabetes (162-165). Consistent findings include membranous glomerulonephritis with fusion of the glomerular foot processes, thickening of the glomerular and tubular basement membranes, the presence of subendothelial deposits, increase in mesangial matrix material, glomerular fibrosis, and sclerosis (163, 165). Clinical signs will depend on the severity of the renal damage, but chronic renal failure may be the devastating end result.

Systemic Arterial Hypertension

In a recent study looking at the prevalence of systemic hypertension in 50 dogs with IDDM, 46 % of the dogs were hypertensive (systolic blood pressure > 160 mm Hg or diastolic > 100 mmHg) (96). Duration of diabetes mellitus and presence of proteinuria were significant predictors of hypertension in this group of dogs (96). In human diabetic patients the incidence of systemic hypertension is estimated to be 40-80% (166).Control of glycemia appears to influence the severity of hypertension in human diabetic patients; however in diabetic dogs, although the incidence of hypertension is correlated to the duration of diabetes, there is no correlation between control of glycemia and detection of systemic hypertension (96, 166).

Clinicopathologic Complications

Hematologic complications are common in cats and dogs with diabetes mellitus (167). These include abnormalities in the function of all types of peripheral blood cells (18-20, 167). Animals rarely present because of these abnormalities; however, these may contribute to the

overall costs associated with management and increased debility of the pet because of their potential consequences (18-20, 167). Diabetes may result in anemia associated with chronic disease or from Heinz body formation due to oxidative damage associated with chronic hyperglycemia (167). Diabetic pets also have increased susceptibility to infections, especially of the skin and urinary tract, due to impaired leukocyte chemotaxis, phagocytosis, and intracellular bactericidal killing ability (167). Hyperlipidemia associated with the diabetic state also increases the pet's risk for developing pancreatitis and atheroschlerosis (18-20, 167). Hypercoagulability from the effects of hyperglycemia causing increased platelet aggregation, increased thrombin activation, and increased levels of fibrinogen and other coagulation factors can also be a problem (167-168). Hypercoagulability leads to an increased risk of thromboembolism and cardiovascular disease in diabetic people, but these problems are not documented in diabetic dogs and cats (167).

Some hematologic changes, such as glycosylation of hemoglobin and albumin are used as markers of glycemic control (18-20, 24, 118, 123, 128-136).

Complications of Insulin Therapy: Hypoglycemia

This is one of the most common and important complications of insulin therapy because it may be life-threatening and occur with little or no warning signs (18-20). Hypoglycemic animals may be symptomatic or asymptomatic (18-20, 169). Asymptomatic hypoglycemia is typically identified during evaluation of a serial blood glucose curve or may be suggested by a normal serum fructosamine concentration in a diabetic patient (18-20). However, asymptomatic hypoglycemia may also go unrecognized because of hypoglycemia-induced glucose

counterregulation (Somogyi phenomenon) (18-20, 169). With symptomatic hypoglycemia, clinical signs may include lethargy, weakness, head tilting, ataxia, seizures, and coma (18-20, 81). Symptomatic hypoglycemia may occur due to iatrogenic reasons or from non-iatrogenic reasons (18-20, 169). An insulin overdose, doubling up on an insulin dose because of failure to inject all of the first dose, and persistent dosing in the face of inappetence are common iatrogenic causes of hypoglycemia (169). Iatrogenic hypoglycemia may also occur when dogs are switched from once a day insulin therapy to twice a day insulin therapy because of overlap in the action of insulin therapy (18-20, 25). When adjunctive treatments are prescribed for patients with IDDM, the combined glucose-lowering effect of insulin therapy and these therapies may also result in hypoglycemia. Common causes of non-iatrogenic hypoglycemia in a previously well controlled diabetic usually involve a physiologic change in the patient's insulin requirements (18-20, 169). Correction of a concurrent disease causing insulin resistance may also result in a decline in the pet's insulin requirements. If this is not accounted for in the dosing regimen, then hypoglycemia may result (169).

Recurrence or Persistence of Clinical Signs

Recurrence or persistence of the clinical signs associated with diabetes mellitus is a common complication of insulin therapy in dogs and cats, and is suggestive of either insulin ineffectiveness or insulin resistance problems (18-20, 71, 170-171).

Insulin ineffectiveness is usually a problem with the biologic activity of the insulin being used (18-20, 71). Causes of insulin ineffectiveness can include: use of an inappropriate insulin type, under-dosing (total dose is < 1.5 U/kg) or over-dosing of insulin, problems with the species

of insulin being used, an inappropriate frequency of insulin administration, problems with improper insulin storage and handling (inactive insulin), problems with insulin administration (improper technique, or subcutaneous degradation or malabsorption of insulin), overriding effects of stress (stress hyperglycemia), or from an allergic type reaction to the insulin or from the presence of circulating anti-insulin antibodies (18-20, 25, 71). Such problems should be investigated and ruled out before a diagnostic work up for causes of insulin resistance is undertaken in a patient with evidence of poor glycemic control (18-20, 71).

Circulating anti-insulin antibodies can reduce insulin effectiveness, cause erratic fluctuations in the blood glucose concentration that may not be correlated with insulin administration and, in severe cases, result in complete insulin resistance (18-20, 71). Although formation of anti-insulin antibodies is an uncommon cause of poor glycemic control in diabetic dogs and cats, it should be considered if other causes of poor glycemic control have been effectively ruled out.

An allergy to insulin has been documented as a cause of poor glycemic regulation in human diabetics (39), but although suspected to occur in a very small fraction of diabetic cats and dogs, to date this has not been definitively confirmed (18-20, 39, 171).

Insulin resistance should be suspected in any dog or cat that remains markedly hyperglycemic throughout the day despite insulin doses of > 1.5 IU/kg per injection (18-20, 71, 171-172). Insulin resistance should also be suspected if a large dose of insulin > 2.2 IU/kg per injection is necessary to maintain adequate glycemic control (18-20, 71, 171-172). All the causes of insulin ineffectiveness mentioned in the earlier section need to be rule out first. Insulin resistance can result from a pre-receptor, receptor, or a post-receptor problem (18-20, 71, 171). The major causes of insulin resistance are briefly outlined below. Common causes of insulin

resistance that need to be considered include drugs (concurrent corticosteroid or progesterone administration), concurrent diseases known to cause insulin resistance (hyperadrenocorticism, acromegaly, bacterial infections), and other conditions where hormonal interference with insulin may occur (obesity, diestrus, pregnancy, chronic stress) (18-19, 24, 70, 94, 173). Less common causes of insulin resistance include development of auto-antibodies that neutralize exogenous insulin, and other systemic diseases that are either rare or have variable effects on insulin activity (renal and hepatic disease, neoplasia, hyperthyroidism, hypothyroidism, pheochromocytoma) (18-19, 24, 70, 94, 174).

Introduction to Complementary and Alternative Medicine

Complementary/alternative therapies, including herbal medicines like ginseng, are increasingly used by the general population. In the U.S.A., it is estimated that roughly 40% of people are taking at least one type of alternative therapy (175). The increased popularity is confirmed by the 400% increase in the sales of herbal remedies in the US between 1990 and 1997, and by the total sales of alternative medicine in Canada which was estimated to be just under $4 billion Canadian dollars in 1998 (4-5).

One of the diseases where use of alternative medicines has gained popularity is diabetes mellitus (9, 176). In one Canadian study, 33% of diabetic patients surveyed admitted to taking an alternative medicine in addition to their other prescribed diabetic medications (2). By some estimates, up to 25 % of all diabetic patients are taking at least one or more alternative medicines in addition to their prescribed diabetic treatments (4). Canadian diabetic patients alone are reported to spend over $432 million dollars on nonprescription over-the-counter and alternative

medications (2). In some cases, diabetic patients taking alternative medications report spending as much money on alternative non-prescription supplements as they spend on their prescription diabetic medications (2). Use of these alternative medications for treating diabetes mellitus has undoubtedly stemmed from the recognized importance of maintaining good glycemic control in order to prevent or delay the onset and progression of chronic diabetic complications (177). Several factors have contributed to the increased use of alternative medications with proposed antihyperglycemic activities: the desire of patients to be proactive, the high incidence of adverse side effects associated with some prescription diabetic medications, and the limited efficacy of some of the more traditional diabetic medications, especially those used to treat type II diabetes (2, 4). Another factor that has facilitated the increased use of alternative medications by diabetic patients is the inherent difficulty associated with making and sustaining the recommended dietary and life-style changes (i.e., dietary constraints and regular exercise) required for patients living with diabetes (2, 4). Another factor contributing to the surge in consumption of herbal remedies for treating diabetes mellitus and other chronic health conditions is the notion that because herbal products are natural, they must be safe and effective (2,4). Also, patients faced with a serious health condition often want to replace their sense of helplessness with a feeling of empowerment and self determination (2, 4). The final factor that undoubtedly plays a role in the popularity of herbal remedies is that because they are classified as supplements and not drugs, there are minimal regulatory requirements by the American Food and Drug Administration, which has allowed manufacturers of these products to make unsubstantiated claims about their health benefits (2, 175, 178-179).

Unregulated intake, the serious risk of adverse reactions from contaminants in these poorly

regulated supplements, and the risk of adverse reactions when complementary and alternative medications are taken in combination with some prescribed medications are serious issues associated with the use of herbal remedies (178-179). Because of these potential dangers, there has been a strong push by the medical community for randomized controlled clinical trials to evaluate the efficacy of complementary and alternative treatments. Add to this the inadequate regulatory standards imposed on the manufacturers of these products, the failure of most patients to disclose their use of these alternative medicines to their physicians, and the fact that most graduating physicians receive no formal education about alternative medicines, it is surprising that the incidence of adverse effects reported for patients taking these complementary and alternative medications is not higher (178).

Introduction to the Herb Ginseng

Ginseng is currently one of the most widely used herbal remedies (180). The Chinese refer to ginseng as the "King of Herbs", crediting it as a panacea with preventive, curative and aphrodisiac properties (181). Ginseng actually comprises a number of different species including Chinese or Korean (*Panax ginseng*), Japanese (*Panax japonicus*), American (*Panax quinquefolius*), and Siberian ginseng (*Eleutherococcus senticosus*) (182-183). *Panax ginseng CA Meyer* is the source plant for Chinese, Korean, and Japanese brands of ginseng; *Panax quinquefolius* is the source plant for American ginseng (179, 183). Commercial ginseng products are derived from the root of ginseng and are of one of two kinds, white or red, depending on the process used to prepare it for market (183). White ginseng is the dried root of ginseng, while red ginseng is derived from the steamed root (183). Most ginseng products used in North America

are white ginseng (183). Some sources report greater medicinal efficacy for ginseng species with roots that are greater than 3 years of age compared to products made from younger roots (184). The pharmacological properties of ginseng, including its anti-hyperglycemic effects, are attributed to triterpene glycosides called ginsenosides (183, 185). The ginsenosides are named according to their mobility on thin layer chromatography plates (184). To date, 31 different ginsenosides have been isolated and identified in ginseng products, but six of the ginsenosides account for 90 % of the total content in most species (181, 184). The profile of ginsenosides as determined by high performance liquid chromatography-tandem mass spectrometry varies between the different species; this profile can be used similar to a human finger print to identify the different species of ginseng (185). In general, the experimentally shown effects of ginseng have been observed using the whole root extract; few single ginsenosides have been individually investigated (183). Recent studies have also shown that the leaves and berries of the ginseng plant may also have some anti-hyperglycemic effects (7, 8, 186-187).

Panax species of ginseng are often touted for their "cure-all" adaptogenic properties. Modern therapeutic claims for which ginseng include a boost in immune function, improvement of cognitive function, improvement of glycemic control (anti-diabetogenic effects), anti-inflammatory, anti-oxidant, anti-carcinogenic and anti-viral effects, and promotion of cardiovascular health (181-182, 188-190). The antioxidant effect of ginseng is attributed to its stimulation of enhanced nitric oxide synthesis by the corpus cavernosum in the brain and by endothelial cells in the lung, heart and kidney (191-193). Oxidative damage from hyperglycemia is one of the important mechanisms responsible for the chronic complications of diabetes mellitus (194-197), and there is preliminary evidence that the anti-oxidant properties of ginseng

can be used to protect against the oxidant damage from hyperglycemia in diabetes mellitus (198-199). Indeed, a recent *in vitro* study suggested that it is the antioxidant properties of ginseng that are likely responsible for ginseng's inhibitory effect on the formation of glycosylated hemoglobin. Since glycosylation of proteins is known to play a role in the pathogenesis of many chronic diabetic complications, this may be one benefit of ginseng in diabetic patients (200).

The ability of ginseng to inhibit platelet thromboxane production and thereby inhibit platelet aggregation has made it a popular treatment for treating various cardiovascular disorders (201). Since cardiovascular complications are common in human diabetics due to the adverse macro- and microvascular effects of hyperglycemia, ginseng may provide added benefits over and above its anti-hyperglycemic and antioxidant effects for diabetic patients. Ginseng is also marketed for its ability to improve overall quality of life (178, 189). Claims that it helps to maintain energy levels, that it can increase mental and physical abilities (aphrodisiac properties), and that it improves mood and promote general health and well-being are widely reported (182, 189).

Although ginseng is used to treat many conditions, there is a paucity of evidence to support its use (182). There is also a lack of quality control between available commercial brands of ginseng, and many of the therapeutic claims for ginseng are either based on anecdotal reports, from studies done in mice and rats, or from uncontrolled nonrandomized studies in people (182). Many of these studies tend to either overestimate the beneficial effect of ginseng or their results are equivocal (182). The reality is that there is little credible scientific evidence to support the use of ginseng for most of these therapeutic claims at this time (182). Fortunately, provided a high quality product is consumed, ginseng seems to be relatively safe. However, adverse effects have been reported. A "ginseng abuse syndrome" has been described in some people who

chronically consume large doses (3 g or more daily) (182, 202). Such patients may experience hypertension, nausea, headache, insomnia, nervousness, and diarrhea (182, 202). Other adverse reactions reported include diarrhea and tiredness (182). In rare cases, signs of acute systemic illness, such as headache, nausea, vomiting, and chest pains have been reported (182). Vaginal bleeding and hyperactivity have also been attributed to ginseng (182). Further, adverse drug interactions in patients taking ginseng have been reported (182). In particular, ginseng may inhibit the anticoagulant effects of warfarin (203) and interact with some monoamine oxidase inhibitors (182).

Ginseng and Diabetes

There is growing evidence from *in vitro* work, animal models and several human trials that various species of ginseng, including American ginseng *(Panex quinquefolius)*, improve glycemic regulation. The evidence to support the antihyperglycemic properties of ginseng will be reviewed.

Evidence of the Role of Ginseng in Glycemic Control: *In vitro* and Animal Models

Recent *in vitro* work using HIT-T15 cell cultures exposed to an extract of American ginseng demonstrated that it is capable of increasing insulin secretion in a dose dependant manor when compared to a buffer control solution (204). The HIT-T15 cells have ATP-sensitive K+ channels (SUR 1 receptors) similar to those in pancreatic beta cells and are capable of secreting insulin (204). When rat pancreas was perfused with 0.2 mg/ml ginseng extract in another study, insulin release was stimulated (205). This result also supports ginseng having anti-hyperglycemic

effects and suggests that one of the mechanisms by which it does this is by promoting insulin secretion (205).

From animal experimental models, there is considerable data to support the anti-hyperglycemic activity of different ginseng species. When dried root of Asian ginseng was injected simultaneously with intravenous glucose in genetically diabetic mice, the ginseng was found to decrease blood glucose concentrations when compared to intravenous glucose alone (206). A water extract of Asian ginseng, given orally at doses of 200 and 400 mg/kg of body weight (BW), was also shown to decrease blood glucose values in normal mice by 18% and 28%, respectively, when compared to control mice (207). The effect in this study was shown to be dose dependent, with no glucose-lowering effect seen when ginseng was administered at a lower dose of 50 mg/kg BW (207). The same doses of the extract of Asian ginseng given orally at 200 and 400 mg/kg BW were also shown to lower blood glucose concentrations in mice with epinephrine-induced hyperglycemia by 23% and 36%, respectively, compared to control mice with epinephrine-induced hyperglycemia (207). In another study, methanol treated extracts of Chinese, Korean, Siberian, Sanchi ginseng, and American ginseng were administered by stomach tube to normal resting mice, and a 5-15 % decrease in their serum blood glucose occurred when compared to placebo treated mice (208). Intraperitoneal injection of an extract of Asian ginseng also was shown to decrease blood glucose in resting mice by 8 % to 15% two to eight hours after injection when compared to control mice (209). Other studies using established extracts of Asian ginseng have also shown blood glucose lowering effects. A water extract of Asian ginseng called DPG-1, given intraperitoneally, was shown to decrease epinephrine-induced hyperglycemia in normal mice when compared to tolazoline, a thiazolidinedione oral

hypoglycaemic drug (210). Intravenous administration of two other Asian ginseng extracts, PG-3-2 and EPG-3-2, both water-based low molecular weight extracts, also resulted in a dose-dependant reduction in intravenous blood glucose tolerance curves in genetically diabetic mice compared to control mice (210). American ginseng berry extract has also been shown to have anti-hyperglycemic effects in diabetic ob/ob mice (186). These ob/ob mice exhibit profound obesity, insulin resistance, and hyperglycemia similar to people with type II diabetes mellitus, making them a suitable animal model for type II diabetes (186). In this study, obese diabetic ob/ob mice and their lean littermates received daily intraperitoneal injections of American ginseng berry extract and its major constituent ginsenoside Re for 12 days while control group of ob/ob mice received a placebo (186). The mean fasting blood glucose concentration of ob/ob mice was significantly higher compared to lean control mice on day 0 (186). On day 5, the mean fasting blood glucose had decreased significantly in the treated ob/ob mice compared to vehicle treated controls (186). By day 12, the obese ob/ob mice treated with the ginseng berry extract were normoglycemic and their mean blood glucose was not significantly different compared to that of the lean control mice, but remained significantly lower than vehicle treated ob/ob obese mice (186). In addition, the overall glucose excursion during a 2-hr intraperitoneal glucose tolerance test decreased by 46% in the obese ob/ob mice treated with American ginseng berry extract when compared to control vehicle treated obese ob/ob mice (186). The improvement in blood glucose levels in the American ginseng berry extract treated ob/ob mice was associated with a significant reduction in serum insulin concentrations in the fed and fasting state, and a hyperglycemic-euglycemic clamp study revealed more than a two-fold increase in the rate of insulin-stimulated glucose disposal in the treated ob/ob mice when compared to control vehicle

treated ob/ob mice (8). Significant increases in body temperature and weight loss were also seen in the American ginseng berry extract treated obese ob/ob mice compared to their placebo treated counterparts (8). The increased weight loss and elevated body temperature was attributed to increased energy expenditure (8). Serum cholesterol levels were also significantly reduced in the treated obese ob/ob mice compared to obese control ob/ob mice (8). Although similar antihyperglycemic effects were seen by these investigators with the administration of ginsenoside Re on its own, there was not a similar anti-obesity effect seen (8). This suggests that constituents in the ginseng berry extract other than ginsenoside Re were responsible for the weight loss in the ob/ob mice treated with the American ginseng berry extract (8). In another study investigating the anti-hyperglycemic effects of Panax ginseng root extract and ginseng berry extract at identical doses in ob/ob mice, both where shown to have antihyperglycemic properties, but the berry extract had more potent anti-hyperglycemic activity and only the berry extract showed marked anti-obesity effects (7). Leaf extracts of American ginseng have also been shown to possess anti-hyperglycemic properties compared to placebo when administered to ob/ob mice intraperitoneally (187). Leaf extracts have also been reported to have anti-diabetic effects in an alloxan-induced diabetic model (187). In another study where white ginseng radix and the rootlet were administered orally to KKAy mice for 4 weeks, the fasting blood glucose levels in both treatment groups were lower compared to the control groups (211). KKAy mice were used as a hypoinsulinemic nonobese type II diabetes model. To elucidate the mechanism(s) responsible for the hypoglycaemia for the white ginseng radix and rootlet, this group of investigators looked at hepatic hexokinase and glucose-6-phosphatase activities and glucose absorption from the small intestine, (211). Their results suggested that radix can improve

hyperglycemia in KKAy mice, possibly by blocking intestinal glucose absorption and by inhibiting hepatic glucose-6-phosphatase, while the rootlet improves glycemic control by inhibiting intestinal glucose absorption (211). Wild ginseng, anecdotally reported to be more pharmacologically potent than cultivated ginseng, has also been shown to have significant anti-hyperglycemic and anti-obesity effects in mice feed a high-fat diet compared to a placebo (212). In this experiment, mice that received wild ginseng ethanol extract (WGEE) and a high fat diet had a dose-dependant reduction in weight gain, fasting blood glucose, triglyceride, and free fatty acid levels compared to control mice (212). The WGEE-treated mice receiving doses of 250 and 500 mg/kg had an improved insulin resistance index of 55 % and 61% compared to high fat diet control mice, respectively (212).

Work with fractions of ginseng has also shown blood glucose lowering ability. When protopanaxatriol ginsenoside, Rg1, the most prevalent saponin of ginseng, was fed by stomach tube to mice, it decreased their serum blood glucose concentration by 16% compared to placebo-treated mice (208). Another protopanaxatriol ginsenoside, Rb2, only found in low concentrations in ginseng, decreased blood glucose concentrations after only 6 days of administration, when given by intraperitoneal injection to streptozotocin-induced diabetic rats (209). It has also been demonstrated that all of the panaxans, when administered by intraperitoneal injections at doses of 10 to 300 mg/kg, have marked but differential blood glucose-lowering effects in both normal and alloxan-induced hyperglycemic mice (213-218).

Evidence for the Role of Ginseng in Glycemic Control from Human Studies

Most of the clinical trials investigating the anti-hyperglycemic effects of ginseng species in

people have utilized American ginseng, and most studies have examined the short term effect of the herb on healthy patients and patients with type II diabetes (10, 13-14, 203, 219-220). Three short-term trials in healthy volunteers found that ginseng administration decreases postprandial blood glucose concentrations (14, 219-220). However, all of these trials were small and conducted by the same investigator group. Despite this, each of the trials in this series were single or double blind, randomized, and placebo-controlled. These trials evaluated the efficacy of American ginseng on lowering the postprandial blood glucose in patients, and the effect of dosing and the time of administration with respect to eating in both nondiabetic healthy volunteers and patients with type II diabetes mellitus (10, 13-14, 203, 219-220). In these studies, the same batch of American ginseng was given to patients at doses ranging from 1 to 9 g orally per day (9-10, 203, 219-220). The time of administration of the ginseng in these studies varied from 0 to 120 minutes before a 25 g oral glucose tolerance test (9-10, 203, 284-285). The results showed that American ginseng reduces postprandial blood glucose from 9.1% to 38% in both diabetic and non-diabetic patients (9-10, 203, 219-220). Doses of 1 and 9 g were shown to be equally effective at achieving these reductions, suggesting that 1 g is a sufficient dose in people (9-10, 203, 219-220). Time of administration of the American ginseng prior to the oral glucose challenge test did not affect the blood glucose-lowering effects in diabetic patients (9-10, 203, 219-220). However, in nondiabetic patients, American ginseng had to be administered at least 40 minutes prior to glucose challenge for a beneficial postprandial blood glucose lowering effect to be seen (9-10, 203, 219-220). No adverse effects from taking the American ginseng were reported in this series of studies, which involved a total of 51 patients (10, 203, 219-220). In another separate study, it was demonstrated that patients with normal glucose tolerance given 3, 6

and 9 g of American ginseng all had lower postprandial glucose concentrations compared to a placebo (221). This study was double blind, placebo-controlled, and the crossover design helped to reduce bias from uncontrolled variables (221). In this study, there was no progressive influence on postprandial glycemia with the 6 and 9 g doses as compared to the 3 g dose of American ginseng (221). There was also no additional decrease in postprandial glycemia with an increase in the time of administration from 40 to 80 to 120 minutes prior to challenge with an oral glucose tolerance test (221).

Two longer-term trials where American ginseng was administered for 8 weeks to people with type II diabetes mellitus have also been performed. Both studies reported decreases in fasting blood glucose and glycosylated hemoglobin (6, 12). One study demonstrated that administration of 100 mg/day and 200 mg/day of ginseng for a period of 8 weeks to patients with type II diabetes mellitus resulted in a significant lowering of the mean fasting blood glucose concentration and improved overall glycemic control as assessed by serial glycosylated hemoglobin A1c levels when compared to a placebo (6). However, the type of ginseng used in this study was not specified, and the results of this study were ambiguous due to significant weight loss differences between the treatment groups (6). In another 8-week double-blind, placebo-controlled crossover trial in patients with type II diabetes, the extract of ginseng used was produced to have a ginsenoside profile similar to the American ginseng used in the acute studies done by the same group of investigators (12). In this study, 24 patients with type II diabetes received either 1 g of ginseng or a placebo orally forty minutes before eating three times daily for 8 weeks. Seventeen of the patients in this study were also taking other oral hypoglycemic agents, while the remaining 7 were being treated by dietary therapy alone (12).

This was followed by a 4 week washout period after which patients were then crossed over to the alternate treatment for an additional 8 weeks (12). Fasting blood glucose, serum insulin levels, and glycosylated hemoglobin were the parameters of glycemic control evaluated. Modest but significant decreases in the fasting blood glucose (12.8%) and glycosylated hemoglobin (4.5%) values were seen in the patients receiving ginseng compared to the placebo (12). No adverse effects from long-term administration of ginseng were seen in any of the patients (12). Patients taking American ginseng plus oral hypoglycemic drugs did have lower blood glucose levels than patients taking hypoglycaemic drugs and a placebo. Hence, it is possible that American ginseng may act synergistically with other oral hypoglycemic agents. Because of American ginseng's ability to attenuate postprandial and fasting hyperglycemia, it has been recommended that it be taken with meals and patients always be warned that taking it with other prescribed oral hypoglycemic medications may precipitate hypoglycemia (179).

Other Benefits of Ginseng Administration in Diabetic Human Patients

Patients with diabetes mellitus have a higher incidence of hypertension that increases their risk for mortality associated with cardiovascular disease. One very dated report found that hypertension developed in 14 adult people taking ginseng root (202), but other more recent studies have found either a neutral or an anti-hypertensive effect of ginseng administration. A recent randomised, double-blinded, controlled trial investigated the short-term effect of American ginseng on blood pressure in 16 hypertensive individuals, 13 of whom were also taking other anti-hypertensive medications (222). Six batches of American ginseng root that varied in quality and ginsenoside content, representing the spectrum of this ginseng on the

market, were used. None of the American ginseng preparations differed from the placebo in their effect on overall mean blood pressure change (222). Taken together, these researchers concluded that American ginseng exerts a neutral effect on blood pressure in hypertensive individuals (222). In another randomised, placebo-controlled, double blind crossover trial in 52 hypertensive individuals, the effect of long-term (12 weeks) administration of American ginseng intake on 24-hour blood pressure was evaluated (223). Cystatin C levels as a marker of renal function were also evaluated. After a 4-week placebo run-in, 52 patients were randomly assigned to receive either 3 g of ginseng or placebo for 12 weeks (223). This was followed by an 8-week washout and subsequent 12-week period in which the opposite treatment was administered. At run-in and at weeks 0 and 12 of each treatment period, participants were fitted with an ambulatory blood pressure monitor to assess 24-hour blood pressure. The findings from this study showed that long-term administration of ginseng had no effect on 24-hour blood pressure or renal function in hypertensive individuals (223).

Another longer-term, double blind, placebo-controlled cross over design study involved 24 patients with well controlled normotensive type II diabetes who were also being treated with oral hypoglycaemic agents (n=18) or dietary therapy alone (n=6)(224). These patients were randomly assigned to receive either 3 g of American ginseng or placebo orally for 8 weeks, separated by an 8-week washout period (224). Nine of the subjects were also receiving a hypotensive medication. During the course of the study, no changes in body weight or dietary intake were seen in any of the patients. American ginseng treatment resulted in a reduction in the mean systolic blood pressure from 137 to 126 mmHg, while placebo treatment showed no effect. Additionally, the mean diastolic blood pressure was reduced from 83 to 78 mmHg following

treatment with American ginseng, but remained unchanged following placebo treatment. The authors concluded that chronic administration of American ginseng to patients with type II diabetes improved blood pressure control (224).

Proposed Blood-Glucose Lowering Action of Ginseng

The mechanism(s) by which American ginseng lowers blood glucose remain unknown. However, data from animal models support three possible mechanisms: 1) modulation of glucose disposal (9, 207, 209), 2) promotion of insulin secretion (9, 205, 225), and 3) altered digestion of carbohydrates (9, 226). Most evidence supports the first two mechanisms (9).

Modulation of glucose disposal may occur through an increase in glucose 2 transporter (GLUT2) in the liver and by an increase in the activity of the rate limiting glycolytic enzymes phosphofructokinase and pyruvate kinase, with a concurrent decrease in the activity of the rate limiting gluconeogenic enzyme glucose-6-phosphatase in the liver (207). Such enzymatic effects have been demonstrated *in vitro* in normal rat liver cells and in liver cells from streptozotocin induced diabetic rats exposed to ginseng extract (207, 213). Results from the acute American ginseng studies done in people also support the ability of American ginseng to modulate glucose disposal and/or to promote insulin secretion as the primary mechanisms underlying its hypoglycemic action (9). In the five acute human studies, the glucose-lowering effect occurred after the first thirty minutes following a oral glucose tolerance test (OGTT). If American ginseng was able to slow digestion, a decrease in the blood glucose values in the first 30 minutes following challenge would have been expected, as is seen with the effects of other agents that slow carbohydrate digestion such as soluble fiber and acarbose (219, 227-228). However, *in*

vitro studies using isolated rat and human duodenal mucosa showed that 1 g of Asian ginseng inhibited both glucose- and maltose-stimulated short-circuit currents, and this may lead to a decrease in digestion and or absorption of these sugars (276).

In a rat model, it has been shown that nitric oxide (NOx) stimulates both insulin and non-insulin-stimulated glucose uptake by cells and potentiates glucose-dependant secretion of insulin by rat beta cells (229-230). Evidence indicates that several ginseng species are capable of increasing NOx synthesis and this may be playing a role in the hypoglycemic effect seen with ginseng. Nitric oxide synthesis in response to ginseng administration occurs in the endothelium of the lung, heart, kidney, and in the corpus cavernosum in rats (191).

In one of the acute studies involving 8 human patients with type II diabetes, serum insulin and NOx concentrations were measured in patients receiving 6g of American ginseng 40 minutes before or together with a oral glucose tolerance test (OGTT), and a trend toward higher insulin secretion and NOx levels was seen in patients receiving ginseng when compared to controls (231). However, the results were not statistically significant. Again, significant reductions in blood glucose were observed when American ginseng was given 40 minutes before but not together with the OGTT, with the reduction occurring only after the first 60 minutes of the test (231). Increased plasma concentrations of NOx have also been detected in a double blind, placebo-controlled crossover design study involving 24 human patients with type II diabetes mellitus taking ginseng (192). This study suggested that American ginseng might have insulin secretagogue properties and that its blood glucose-lowering effects might be tied to the modulation of NOx (9, 192, 231). Improved pancreatic endothelial function may help promote insulin secretion and therefore benefit glycemic regulation (192). However, not all studies agree

that ginseng administration promotes release of NOx. In a study involving streptozotocin-induced diabetic rats, administration of ginseng radix was found to suppress the expression of the enzyme nitric oxide synthase (NOS) in the rat hippocampus (193). Ginseng (0.5 to 1.0 mg/ml) has been shown to stimulate insulin biosynthesis *in vitro* in different preparations of mice pancreatic islet cells and in rat pancreas (205, 225). Rotshteyn et al also recently used *in vitro* assays with HIT-T15 cells to demonstrate that American ginseng has sulfonylurea-like activity (204). Insulin secretion was significantly higher in cells exposed to American ginseng compared to cells exposed to buffer control solution, and the effect was dose dependent (204). In addition, American ginseng has been shown to increase glucose-stimulated insulin secretion *in vivo* in alloxan-induced diabetic mice when doses from 10-50 mg/kg were injected intraperitoneally (205). Although it did not reach statistical significance, American ginseng resulted in a 25 % increase in fasting insulin concentration in human patients after eight weeks of supplementation (13).

It is possible that ginseng may promote insulin secretion by mediation of cholinergic stimulation or adrenergic blockade of beta cells (9). Certain ginsenoside (Rg1, Re) components have increased choline acetyltransferase mRNA protein and activity in rat brains; this suggests possible enhancement of acetylcholine secretion (9, 232-233). In addition, total ginsenosides and some individual ginsenosides, including Rb1, Rc, Re, Rf, Rg (234), Rg2 (235), Rg3 (235, 236), and Rh2 (236) have been shown to decrease catecholamine secretion (234, 236). Cholinergic stimulation or adrenergic blockade can increase beta cell glucose uptake (237-238) and might increase glucose-stimulated insulin secretion in rat islet cells (339-240). In Wistar rats ginsenoside Rh2 decreased plasma glucose concentrations in a dose-dependent manner with a

concurrent increase in plasma insulin and C-peptide levels (241). These effects of Rh2 were reversed by atropine but not by the ganglionic nicotinic antagonists pentolinium or hexamethonium (307). Disruption of synaptically available acetylcholine (ACh) using an inhibitor of choline uptake (hemicholinium-3) or an inhibitor of vesicular ACh transport (vesamicol) abolished the actions of Rh2 (241). In addition, physostigmine, at a concentration sufficient to inhibit acetylcholinesterase, enhanced the actions of the ginsenoside Rh2 (241). Blockade of the increase in plasma insulin and C peptide concentrations, as well as the plasma glucose-lowering action of Rh2 by 4-diphenylacetoxy-N-methylpiperdine methiodide (4-DAMP), indicates the participation of muscarinic M3 receptors (241). The results of this study suggest that ginsenoside Rh2 has the ability to increase insulin secretion as a result of the release of ACh from nerve terminals with subsequent stimulation of muscarinic M3 receptors (241).

In another *in vivo* study investigating the hypoglycemic mechanism of ginseng glycopeptide (GGP) in mice, the levels of insulin, lactate dehydrogenase, lactic acid, and oxygen consumption, as well as blood glucose and liver glycogen were measured after administration of the GGP (242). Adenylate cyclase activity and cAMP level were also measured to study the effects of GGP on blood glucose and liver glycogen metabolism, and to determine whether the effects were mediated through a cAMP dependent second messenger system (242). It was concluded that the hypoglycemic activity of ginseng glycopeptide may be attributed to the enhancement of aerobic glycolysis through stimulation of beta-adrenoreceptors and through the increase of various rate-limiting enzyme activities involved in the tricarboxylic acid cycle (308).

In conclusion, preliminary data from *in vitro* work, and from *in vivo* work in animal models and people suggests that the glucose-lowering effect of American ginseng may be due to several

different mechanisms. These mechanisms include: 1) modulation of glucose disposal (207, 209), 2) promotion of insulin secretion (205, 225), and 3) altered digestion of carbohydrates (226). Additional work needs to be done to further investigate these and other mechanisms.

Ginseng Quality Control Issues

Because of poor standardization of ginseng, it is not known whether the observed blood glucose lowering effects observed in the studies in animal models and people apply to all species of ginseng or even to all American ginseng products (182, 243-244). In one study where 25 commercially available ginseng products were analyzed by high performance liquid chromatography-tandem mass spectrometry, the concentrations of marker ginsenosides detected were found to be lower than the labeled concentration in half of the 25 products sampled (243). Ginsenoside concentrations in commercial ginseng products have been shown to vary as much as 15-fold in capsules and 36-fold in liquid preparations (243).

Medicinal preparations of ginseng usually use the herb's root, and some sources report greater anti-hyperglycemic effects with roots that are greater than 3 years old (183, 245). Because of this, ginseng is not supposed to be harvested until it is 5 years old, but increased demand for medicinal plants has lead to harvesting of immature plants, which may account for the lower than expected ginsenoside concentration in some products (183, 245). If plants younger that 3-5 years of age are being harvested, then this may be partially responsible for the poor standardization in individual commercial products as well as for the variation between different commercial ginseng products (243). In another study where a watch-dog consumer protection laboratory tested 21 commercial ginseng products for quality and purity, only 9

products passed ConsumerLab.com criteria (246). Unacceptable pesticide and heavy metal contamination were found in some tested products, and several of the products had less than the required concentration of ginsenosides (246). In addition, there have also been reports that up to 32 % of Chinese herbal medicines contain undeclared pharmaceuticals and potentially toxic concentrations of heavy metal contaminants (247). The American Federal Drug Administration also has reported that one ginseng product marketed as a diabetes remedy contained a sulfonylurea drug (248).

In addition to the age of the ginseng, the part of the plant harvested and the method of processing (steamed versus dried) may also influence the anti-hyperglycemic properties. The origin and physical characteristics of the root may also influence the medicinal value of the product (243). Ginsenosides concentrations in Panax species are considerably higher in the flowers and leaves than in the root, but it is usually the root that is used for medicinal purposes (245). If there is contamination from other parts of the plant during harvesting or processing, then this may affect the ginsenoside concentrations measured.

Because of the poor standardization of ginseng products, it is not known whether the observed glucose-lowering effects shown for one species or product would apply to all species of ginseng, to all American ginseng products, or even to different batches of the same American ginseng product. Because of this fact, when a study is conducted looking at the effects of ginseng or any other herbal remedy, it is important that the same batch of ginseng be used for all study subjects in order to help minimize experimental error from this factor.

Summary

Diabetes mellitus is a serious metabolic disease that has a significant impact on the health quality of life and life expectancy of affected people and pets. In addition treatment of this disease and its acute and chronic complications is represents an enormous burden to the health care system. Conventional therapies employed for the treatment of diabetes (e.g., insulin injections, oral hypoglycemic medications, life-style management) may be insufficient or patient compliance poor. In addition to adverse effects associated with conventional therapies (i.e., episodes of hypoglycemia), these treatments are not always satisfactory at achieving good glycemic control and in avoiding late stage diabetic complications when used alone. This has lead to increased use of complementary and alternative medications such as medicinal herbs with anti-hyperglycemic activity. This trend will likely also occur in veterinary diabetic patients. Predictably the increased use of complementary and alternative medicines is likely to be associated with an increase in the incidence of interactions with other more traditionally prescribed drugs and treatments. In addition to this, the recently highlighted lack of quality control, product standardization, and potential for harmful contamination of such herbal remedies makes it very important that mainstream veterinarians start to learn more about alternative medicines. For all these reasons, it is very important that more blinded, placebo-controlled studies investigating the use of ginseng and other herbal remedies for the treatment of diabetes be done, so that medical decisions to use such alternative therapies can be based on sound evidence-based medicine rather than just anecdotal reports and dubious claims. Data from experimental trials in rodent diabetic models, as well as some acute and chronic double-blind, placebo controlled cross-over trials in human diabetic patients, indicate that ginseng does have anti-

hyperglycemic activity (6-10, 12, 186-187, 203-221). This pilot study was undertaken to determine if American ginseng is an efficacious and safe adjunct therapy for dogs with type I diabetes mellitus.

Materials and Methods

Subject Selection

Eight client-owned dogs with well controlled type I diabetes mellitus were recruited from the Atlantic Veterinary College (AVC) or from referring veterinary clinics in Prince Edward Island and Nova Scotia. A copy of the letter sent to referring veterinarians in an attempt to recruit eligible dogs into the study can be found in Appendix A. Dogs eligible for enrolment in the study were all in good health, were receiving insulin therapy, and their glycemic control was assessed by the primary investigator as good prior to enrolment in the study. Good control was assessed based on the owner's reports of resolution of the typical clinical signs associated with uncontrolled diabetes (polyuria, polydipsia and polyphagia), stable body weight, and reasonable results from the most recent 12-hour glucose curve (done within the last 2-3 weeks) performed prior to enrolling each of the dogs in the study. For dogs 2, 6, and 7, some adjustments in their insulin dose or frequency was required prior to enrolment in the study. Dog 2 was originally receiving her insulin once daily, but due to inadequate control this was changed to twice daily administration prior to enrolling her in the study. For dog 6, her enrolment into the study had to be delayed by 3 weeks during which her dose of insulin was increased slightly to improve her glycemic regulation, and an occult urinary tract infection was treated. Dog 7 required a reduction in her insulin dose because of documented clinical episodes of hypoglycemia prior to enrolment

in the study. All of these dogs had been on their new dose of insulin for at least 10 days prior to beginning the study to ensure they had had sufficient time to equilibrate to their new insulin dose.

All the dogs enrolled in the study were also judged to be free of any concurrent diseases known to affect glycemic control based on the results of the initial physical examination, initial laboratory work, and assessment of their glycemic control based on their most recent blood glucose curves. For the duration of the study, none of the dogs received on any other medication, with the exception of antibiotics (Dog 6), buffered aspirin (Dog 3) or another non-steroidal anti-inflammatory medication for arthritis (Dog 4 and 6 were receiving Mobicox) and phenobarbital for presumed idiopathic epilepsy (Dog 7). Dog 8 also was undergoing acupuncture treatments intermittently during the study as an adjuvant treatment for osteoarthritis.

The duration of time since the initial diagnosis of diabetes mellitus in the dogs varied from 2 months to 4.5 years, with 5 out of the 8 dogs having been diagnosed with diabetes mellitus within the 12 months prior to enrolment in the study. For the duration of the study, each dog was maintained on their regular diet. Once enrolled in the study, no changes were made in the management of their diabetes mellitus unless absolutely necessary. Changes in the dose of insulin were, however, required for 2 of the 8 dogs (dog 2 and 6) during the study. In addition, the owners were instructed not to alter the dog's daily exercise routine during the course of the study.

Dogs 2 and 6 were also tested for hypothyroidism prior to enrolling them into the study, because moderate to marked elevations in serum cholesterol were detected on their initial serum biochemistry profiles. These dogs had T4 and TSH concentrations within the normal reference interval, ruling out hypothyroidism as a contributing factor for their hypercholesterolemia. Since

none of the dogs showed evidence of insulin resistance or other clinical signs compatible with hyperadrenocorticism, further work-up to definitively rule out hyperadrenocorticism as a contributing cause for their hypercholesterolemia was not done. In these two dogs, their hypercholesterolemia was therefore attributed to their diabetes mellitus.

As an incentive to comply with the study protocol, owners were given $200 when they completed the study.

Experimental Design

A double blind, placebo-controlled crossover design was used with each dog serving as their own control. At the beginning of the study, the owner of each dog completed a questionnaire and signed a consent form agreeing to the terms of enrolment. Appendix A contains a copy of the consent form and the initial questionnaire. Each dog underwent a physical examination and the following parameters were evaluated: a complete blood count (CBC), serum biochemistry profile, urinalysis, urine culture, serum fructosamine, glycosylated hemoglobin and systemic blood pressure measurement. Appendix B contains the day 0 blood work and normal reference intervals for the tests done. Normal reference intervals for systemic arterial blood pressure measurement in dogs and guidelines for assessment of the severity of hypertension are also provided in Appendix B. A 12-hour fed glucose curve was then performed with blood glucose measurements taken every hour for a total of 13 readings. Appendix C contains the results of all the 12-hour glucose curves for all dogs, including the initial curves done on the day of enrolment. The same portable glucose meter (Precision Xtra Medisense Products Mississauga, Ontario, Canada) was used for all the glucose curves done on all dogs throughout the study. In addition,

the same batch of coded glucose strips designed for the glucometer were used for all the glucose values done during the course of generating the serial glucose curves on all the dogs throughout the study. This consistency was designed to eliminate any variability in results from such parameters.

At the end of this first evaluation, the eight dogs were assigned a number of 1-8 based on the chronological order in which they were enrolled into the study. Each dog was then randomly assigned to receive either American ginseng (study drug A) or the placebo (study drug B) as their first treatment by an unbiased person who was not the principle investigator. Details are given in Table 4. Dogs who got Study drug A first received 500-1000 mg of American ginseng, depending on their body weight, orally twice daily with food for 8 weeks, followed by 4-week washout period and then 8 weeks of same dose of a placebo. Dogs who received study drug B first received 500-1000 mg of cornstarch (placebo), depending on their body weight, orally twice daily with food for 8 weeks, followed by 4-week washout and then 8 weeks of the same dose of the study drug. Dogs less than 22 kg received 500 mg of American ginseng or placebo, while dogs over 22 kg in body weight received 1000 mg of American ginseng or placebo. The dose in mg and mg/kg that each dog received is provided in Table 5.

The placebo capsules were all prepared ahead of time by the principle investigator. Cornflour from Speerville Flour mill (Speerville, NB) was used as the placebo. The North American ginseng product used was manufactured by Tropic Canada Ltd (Penticton, BC). The same source of cornstarch and the same batch of American ginseng (Lot # L91006A) were used for all dogs throughout the study to eliminate bias or variability in the results from these sources. Identical gelatine capsules Coni-Snap #0 Natural (Wiler-PCCA, London, ON) were used to

administer both the placebo and ginseng. The capsules were dispensed to each owner by an unbiased third party. The principal investigator remained blinded to the treatment each individual dog was receiving throughout the study.

Table 4. Random Assignment of Dogs to Group A (Ginseng) versus Group B (Placebo)

Dog Number	Treatment Group Dog Randomly Assigned to Receive First A = Ginseng B = Placebo
1	B
2	A
3	B
4	B
5	B
6	A
7	A
8	A

Table 5. Dose of American Ginseng and Placebo in mg and in mg/kg for each study dog

Dog #	Dose in mg	Body weight in kg	Dose of American ginseng and Placebo in mg/kg
1	500	16.7	30
2	1000	31.6	32
3	1000	45.7	22
4	500	12.5	40
5	500	12.9	39
6	500	7.8	64
7	500	21.2	24
8	1000	26.4	38

On days 28 and 56 of each treatment period, each dog underwent a repeat physical examination and all the parameters measured at the beginning of the study, including a 12-hour fed glucose curve, were re-evaluated. The only exception was the glycosylated hemoglobin concentration, which was only measured on day 1 and day 56 of each study period. For each

individual glucose curve the mean blood glucose was determined from the average of the total number of readings. The postprandial blood glucose concentration for each glucose curve was the glucose measurement one hour after feeding and administration of insulin. The fasting blood glucose was the glucose measurement taken immediately before feeding and insulin administration for each glucose curve. The midpoint blood glucose was calculated as the average of the glucose concentration at hour 6 of the 12 hour glucose curve.

Analytical Methods

The blood and urine analyses were performed by the Diagnostic Laboratory at the AVC. The biochemistry profile analyses were determined using a wet chemistry analyzer (Hitachi 917, Roche Diagnostics, Laval, QC, Canada). The CBC analyses were determined using an automated cell counter (Cell-Dyn 3500 Abbot, Abbot Laboratories, Abbott, IL, USA) with manual differentials. The serum fructosamine analyses were done by the endocrinology service of the AVC using a colorimetric assay (Hitachi 917, Roche Diagnostics, Laval, QC, Canada). The glycosylated hemoglobin analyses were performed by the Diagnostic Laboratory at the University of California, Davis, using a quantitative methodology (Glyco-afin GHb, Isolab, Acron Ohio, USA). The normal ranges utilized for all the test parameters were established for adult dogs by the diagnostic laboratories in which the tests were performed. Blood pressure measurements were obtained using an oscillometric recording device (Dinamap Vital Signs Monitor 1846 SX, Critikon, Inc., Tampa Florida). Between 6 and 10 recordings of the systolic, mean and diastolic blood pressure were recorded for each dog at each visit. An average of the mean, diastolic and systolic readings was calculated for each dog at each visit.

Statistical Analysis

All variables were evaluated by analysis of variance (ANOVA) using a linear model that incorporated the crossover design (drug effect) and accounted for the inter-animal variation and the effect of the insulin type. Since all parameters at T= 0 for both treatment arms of the experimental design would be expected to be very similar for each dog, and because it was not known whether 4 weeks of ginseng therapy would be sufficient to see a difference in the glycemic control for individual dogs, the data was analysed in two ways using the ANOVA. Table 6 below outlines the 2 different ways in which the data was analysed. The statistical program used to run the ANOVA analyses was JMP SAS Version 5.1 (Campus Drive Cary, NC 27513), and GraphPad Prism (2005, GraphPad Software, Inc.) was used to plot all the graphs of the data.

All the results are expressed as the mean (+/-) standard deviation (SD) and a P value < 0.05 was considered significant. All the residuals were checked manually and determined to be acceptable with no obvious outliers.

Table 6. Two ways the data was analysed using an ANOVA.

Analysis	For each variable it was determined whether there was a statistical difference between values at the stated times while on ginseng compared to the placebo
1	Day 56 m 0 ginseng versus Day 56 m 0 placebo = compares the mean value of the parameter of interest on day 56 minus the mean on day 0 for each arm of the experiment (ginseng versus placebo).
2	[(56 + 28)/ 2 - 0] ginseng versus [(56+ 28)/ 2 - 0] placebo = compares the meanvalue of the parameter of interest for the average of day 28 and day 56 minus that onday 0 for each arm of the experiment (ginseng versus placebo).

Results

Initial Questionnaire

Appendix C contains tabular summaries of data from the initial questionnaire. This questionnaire was primarily used to help identify any adverse effects associated with administration of ginseng, of which there were none seen.

The dogs in this study ranged in age from 5 to 13 years old; the average age was 9 years of age. None of the dogs were sexually intact and they consisted of 5 spayed females and 3 neutered males. The average body weight was 20 kg with a range of 7.8 to 47.1 kg. Three of the dogs were considered large breed dogs with a body weight over 22 kg; the other five were considered small breed dogs with a body weight of less than 22 kg. Three of the dogs were pure-bred; the remainder were mixed-breeds. The pure-bred dogs included one Rottweiler and two Miniature schnauzers. The cross-bred dogs included two German shepherd crosses, one terrier cross, one Shetland sheepdog cross, and one poodle cross.

The average dose of insulin per dog at the start of the study was 0.75 U/kg, with only one dog receiving a dose greater than 1 U/kg (dog 6 who was receiving 1.54 U/kg). All eight dogs were receiving an intermediate duration insulin: 3 dogs were receiving NPH insulin, 5 were receiving lente insulin. Of the dogs that were being treated with lente insulin, one dog (Dog 4) was receiving a human recombinant insulin (Humulin –L) (Eli Lilly Canada Inc., Toronto, ON), and the other four dogs were receiving a porcine-origin veterinary insulin (Caninsulin) (Intervet Canada Ltd. Whitby, ON). During the study, all of the dogs were fed their regular diets, which were different for each dog. With the exception of one dog (dog 3), the daily amount of food fed for each dog also did not change during the course of the study. All the dogs except for one dog

(Dog 7) were consuming a recommended high-fiber diet or a senior dog food. Dog 7 was fed a grocery store brand of dry and canned dog food. All owners except those of Dog 7 rated their dog's appetite as excellent at the initial examination. The owners of Dog 7 only rated their dog's appetite as fair.

Three out of 8 owners rated their dog's energy level at the initial examination as moderate to excellent. The owners of the other 5 dogs rated their dog's energy level as fair. At the initial examination, 5 out of 8 of the owners rated their dog's mental agility as excellent; the remaining 3 owners rated their dog's mental agility as good. At the initial examination, all owners rated their dog's diabetic control as either good (5) or excellent (3). Table 7 contains detailed information on owner ratings.

All of the dogs enrolled except dog 6 had evidence of diabetic cataracts. Dog 6 had phthisis bulbi bilaterally, presumably from previous long standing severe pheacoclastic uveitis. Dogs 1, 2, 4 and 5 only had mild diabetic cataracts while dogs 3, 7, and 8 had moderate to severe diabetic cataracts. The severity of the cataracts did not seem to be related to the length of time dogs had been diabetic or to overall assessment of glycemic control. Dog 8 developed uveitis secondary to her diabetic cataracts and corneal lipid dystrophy during the study which required treatment with a topical ophthalmic nonsteroidal anti-inflammatory medication (flurbiprofen, SkyePharma Canada, Inc, Quebec, Canada). Dogs 2, 3 and 6 all had moderate hypercholesterolemia at T=0 and this persisted throughout the study. Dog 3 and 8 had bilateral corneal lipid dystrophy presumed to be secondary to lipid abnormalities associated with their diabetes. Hypothyroidism was ruled out as a contributing cause of the hypercholesterolemia in these dogs. Several of the dogs in this study had been diagnosed with other complications of diabetes mellitus either before

entering the study or during the study. Dog 3 had previously had an episode of DKA 8 months prior to being enrolled in the study. Dogs 5, 6, 7, and 8 had all been diagnosed with urinary tract infections in conjunction with their diabetes prior to enrolment in the study. During the study dog 6 developed an occult urinary tract and skin infection and dog 7 developed an anal gland abscess.

During the study, no adverse side effects were reported when the dogs were receiving the American ginseng or placebo treatments. Dog 1 had a single episode of diarrhea, but this was attributed to dietary indiscretion rather than to the drug.

Table 7. Owner and Principle Investigator's Assessment of each Dog's Glycemic control at the initial examination.

Dog #	Duration of time since diagnosed with diabetes	Owner's assessment of the study dog's diabetic control at the initial examination	Investigator's assessment of the study dog's diabetic control at the initial examination
1	6 months	Good	Excellent
2	12 months	Good	Excellent
3	8 months	Excellent	Good
4	3 months	Good	Excellent
5	4.5 years	Excellent	Excellent
6	7 months	Good-excellent	Good
7	6 years	Good	Good
8	3 months	Excellent	Good

During the study, while Dog 3 was in the washout phase of the study, she developed a head tilt and swollen hocks. Arthrocentesis of the hocks was consistent with chronic degenerative joint disease. Her mentation, as well as her other cranial nerve functions, were assessed as normal. These clinical signs have never been reported in people or in other experimental animal models receiving American ginseng. The acute onset and compatible clinical findings were most

consistent with a presumptive diagnosis of idiopathic vestibular disease. Because of this, the dog was not withdrawn from the study. The dog's diabetic control continued to be good and her head tilt gradually resolved over a 3-4 week period, as would be expected in the majority of dogs suffering from idiopathic vestibular disease. Because the dog's activity level was acutely decreased following development of her head tilt, her insulin dose and food intake both had to be decreased to accommodate for her decreased activity level from her concurrent vestibular signs and osteoarthritis.

During the study, owners noticed no major changes to their dog's appetite, energy level, mental agility, urination or water consumption for ginseng versus placebo treatments. Some owners did report a possible increase in their dog's activity level while on the ginseng, but in all cases the timing also coincided with better weather. This was judged to be as likely, or more likely, responsible for the increase in activity level. Appendix C contains a summary of the follow-up questionnaire data on days 0, 28 and 56 of each treatment period.

The compliance by owners during the study in terms of administering the placebo and the American ginseng treatments was good to excellent. Owners of dogs 1, 3, 4, 7 and 8 failed to give all the prescribed placebo or ginseng capsules, but for all these dogs except one (Dog 4), only one to two doses had been missed over the entire study period. Dog 4 did not receive 3 doses of the ginseng and 8 doses of the placebo.

All the dogs remained healthy throughout the study. Clinical signs related to poor glycemic control were not observed in any of the dogs for either the placebo or ginseng treatments.

Hematological Parameters

Mean results ± SD for changes in all the hematologic variables are shown in Table 8. No significant differences were seen in any of the hematological parameters for the ginseng versus the placebo treatments. Table 9 shows the P values for each ANOVA analysis comparing 1) the means for Day 56 minus Day 0 for American ginseng versus placebo treatments and 2) the means for the average of Day 56 and Day 28 minus day 0 for ginseng versus placebo treatments, for all the hematologic variables.

When the two ANOVA analyses were done to evaluate if the drug order (ginseng versus placebo) or the insulin type had any significant effect alone, or if there was any interaction between insulin type and drug order, no significant differences were found for any of the hematologic variables. These data are summarized in Table 10.

Serum Biochemistry Profile Analysis

Mean results for all the serum biochemical profile variables for ginseng and placebo treatments are shown in Table 11. No significant differences were seen between the American ginseng and placebo treatments for all of the variables, except for the serum blood glucose concentration looking at the average of days 28 and 56 minus day 0 for ginseng versus placebo, where dogs receiving placebo had a statistically significant higher serum blood glucose concentration than dogs receiving American ginseng (Table 12). A closer inspection of the data, however, revealed that this is likely only significant because for 6/8 dogs the glucose value at day 28 while receiving the placebo was the highest glucose value seen at any time point during the study. The mean and standard deviation for the serum blood glucose concentration of all dogs on

day 56 while receiving placebo was very comparable to the mean and standard deviation for the serum blood glucose concentration seen on days 28 and 56 when dogs were receiving American ginseng. Table 13 contains a summary of these data. Given this, the statistically significant result for the average of the serum blood glucose on days 28 and 56 minus on day 0 for ginseng versus placebo is not likely biologically significant. The two ANOVA analyses done to determine if the drug order or the insulin type had any significant effect on the results, and to see if there was any interaction between the insulin type and the drug order, failed to show any significant differences (Table 14).

None of the dogs in this study had evidence of hypoproteinemia or azotemia which could have interfered with measurement of serum fructosamine. However, lipemia may have interfered with measurement of serum fructosamine in dogs 2, 3 4, and 6. None of the dogs in this study were anemic or had erythrocytosis which could have interfered with measurement of glycosylated hemoglobin.

Table 8. Changes in hematologic parameters for the 8 dogs with spontaneous diabetes mellitus during the two experimental treatment periods (Ginseng versus Placebo). Data represents the mean ± SD for the two ANOVA analysis of day 56 minus day 0 Ginseng versus 56 minus day 0 Placebo and [(56+28)/2-0] Ginseng versus [(56+28)/2-0] Placebo.

Variable	56-0Ginseng	56-0Placebo	[(56+28)/2-0]Ginseng	[(56+28)/2-0]Placebo
Red blood cells (RBC) X 10^{12}/L	0.041 ± 0.22	-0.44 ± 0.41	0.05 ± 0.08	-0.34 ± 0.13
Hematocrit (HCT) L/L	0.003 ± 0.02	-0.026 ± 0.03	0.004 ± 0.006	-0.021 ± 0.009
Hemoglobin (HGB) g/L	0.75 ± 9.35	-8.75 ± 7.46	0.438 ± 3.10	-7.31 ± 2.38
White Blood Cells (WBC) X 10^9/L	0.075 ± 1.0	0.85 ± 0.92	0.29 ± 0.39	0.84 ± 0.34
Segmented Neutrophils X 10^9/L	-0.16 ± 0.79	0.89 ± 1.06	0.08 ± 0.33	0.95 ± 0.38
Monocytes X 10^9/L	0.11± 0.32	0.08 ± 0.38	0.06 ± 0.12	0.02 ±0.09
Lymphocytes X 10^9/L	-0.05 ± 0.35	-0.02 ± 0.59	0.04 ± 0.14	-0.06 ± 0.21
Eosinophils X 10^9/L	0.14 ± 0.15	-0.08 ± 0.17	0.07 ± 0.07	-0.07 ± 0.07
Band Neutrophils X 10^9/L	0.02 ± 0.07	0 ± 0	0.03 ± 0.02	0.01 ± 0.008
Platelets X 10^9/L	-65.38 ± 79.68	-39.25 ± 65.58	-49.44 ± 28.31	-36.19 ± 24.40

Table 9. P values for ANOVA analyses comparing 1) the means for Day 56 minus Day 0 for Ginseng versus Placebo treatments and 2) the means for the average of Day 56 and Day 28 minus day 0 for ginseng versus placebo treatments for all hematologic variables.

Variable	P Value 56m0 Ginseng versus 56m0 Placebo	P Value [(56+28)/2-0]Ginseng versus [(56+28)/2-0]Placebo
Red blood cells (RBC)	0.07	0.09
Hematocrit (HCT)	0.20	0.18
Hemoglobin (HGB)	0.08	0.13
White Blood Cells (WBC)	0.47	0.79
Segmented Neutrophils	0.24	0.50
Monocytes	0.95	0.43
Lymphocytes	0.87	0.88
Eosinophils	0.14	0.40
Band Neutrophils	0.88	0.79
Platelets	0.38	0.50

Table 10. P values for All Hematologic Parameters for the Two ANOVA Investigating whether there was any effect of drug order or insulin type, or interaction between the insulin type and drug order.

Variable	P Value 56m0 Ginseng versus 56m0 Placebo	P Value [(56+28)/2-0]Ginseng versus [(56+28)/2-0]Placebo
Red blood cells (RBC)	0.74	0.80
Hematocrit (HCT)	0.69	0.68
Hemoglobin (HGB)	0.58	0.67
White Blood Cells (WBC)	0.44	0.07
Segmented Neutrophils	0.60	0.08
Monocytes	0.78	0.63
Lymphocytes	0.32	0.34
Eosinophils	0.81	0.84
Band Neutrophils	0.56	0.52
Platelets	0.11	0.23

Table 11. Results of serum biochemical profile parameters in 8 dogs with spontaneous diabetes mellitus during the two experimental periods (Ginseng versus Placebo). Data represents the mean ± SD for two ANOVA analysis of 56-0 Ginseng versus 56-0 Placebo and [(56+28)/2-0] Ginseng versus [(56+28)/2-0] Placebo.

Variable	56-0 Ginseng	56-0 Placebo	[(56+28)/2-0]Ginseng	[(56+28)/2-0]Placebo
Sodium mmol/L	2.375 ± 3.34	1.125 ± 5.36	2.19 ± 0.96	-0.69 ± 1.64
Potassium mmol/L	-0.0625 ± 0.53	0.075 ± 0.28	-0.013 ± 0.16	0.24 ± 0.13
Chloride mmol/L	10.75 ± 26.98	-0.125 ± 5.60	11.19 ± 9.52	-2.5 ± 1.66
Calcium mmol/L	-0.016 ± 0.11	0.051 ± 0.11	-0.003 ± 0.041	0.03± 0.029
Phosphorus mmol/L	1.48 ± 0.21	1.32 ± 0.19	0.10 ± 0.078	0.12 ± 0.11
Urea mmol/L	0.025 ± 0.79	0.2375 ± 0.90	-0.01 ± 0.167	0.33 ± 0.296
Creatinine umol/L	-5.5 ± 18.17	-0.75 ± 18.38	-7.69 ± 4.51	-2.34 ± 6.65
Lipase U/L	0.38 ± 34.06	-12.13 ± 44.48	2.94 ± 12.51	-28.25 ± 19.10
Amylase U/L	-43.625 ± 106.24	-38.625 ± 72.15	-47.94 ± 31.19	-43.44 ± 27.44
ALT U/L	-8.625 ± 76.95	-10.75 ± 43.22	-6.44 ± 23.89	-5.81 ± 11.69
Alk Phos U/L	-15.25 ± 304.79	-58.125 ± 433.42	18.31 ± 74.43	-31.75 ± 87.12
AST U/L	-3.3375 ± 33.26	3.625 ± 18.32	-3.56 ± 8.99	1.31 ± 4.79
GGT U/L	0.625 ± 4.44	-3.25 ± 11.50	1.94 ± 1.60	-1.34 ± 2.25
SDH U/L	3 ± 15.54	5.75 ± 14.48	-1.83 ± 4.87	4.88 ± 3.47
Cholesterol mmol/L	-1.42 ± 4.34	-0.833 ± 2.01	-0.88 ± 0.74	-0.06 ± 0.81
Glucose mmol/L	-0.56 ± 5.75	-1.42 ± 7.60	-0.89 ± 1.90	6.58 ± 2.48
Total Bilirubin umol/L	0 ± 1.069	-0.125 ± 0.64	0 ± 0.28	-0.13 ± 0.13
Creatine Kinase U/L	43.88 ± 124.128	178.38 ± 415.82	13.31 ± 33.32	105.88 ± 92.09
Total protein g/L	0.5 ± 3.07	-1.38 ± 3.89	0.19 ± 1.01	-0.75 ± 1.15
Albumin g/L	0.13 ± 1.64	-0.13 ± 0.64	0.19 ± 0.42	-0.31 ± 0.23
Globulin g/L	0.38 ± 2.83	-1.25 ± 3.54	0 ± 1	-0.44 ± 1.05
Albumin/globulin ratio	-0.01 ± 0.083	0.03 ± 0.084	-0.002 ± 0.03	0.001 ± 0.02

Table12. P values for ANOVA analysis comparing 1) the means for Day 56 minus Day 0 for Ginseng versus Placebo treatments and 2) the means for the average of day 56 and 28 minus day 0 for ginseng versus placebo treatments for all serum biochemical variables.

Variable	P Value 56m0 Ginseng versus 56m0 Placebo	P Value [(56+28)/2-0]Ginseng versus [(56+28)/2-0]Placebo
Sodium	0.84	0.55
Potassium	0.52	0.46
Chloride	0.48	0.40
Calcium	0.52	0.73
Phosphorus	0.27	0.41
Urea	0.50	0.66
Creatinine	0.71	0.41
Lipase	0.73	0.65
Amylase	0.96	0.96
ALT	0.67	0.46
Alk Phos	0.19	0.10
AST	0.73	0.67
GGT	0.20	0.20
SDH	0.72	0.70
Cholesterol	0.49	0.15
Glucose	0.37	**0.03**
Total Bilirubin	0.96	0.89
Creatine Kinase	0.40	0.38
Total protein	0.38	0.36
Albumin	0.23	0.32
Globulin	0.60	0.65
Albumin/globulin ratio	0.76	0.95

* Bold indicates statistical significance

Table 13. Mean ± SD for the mean blood glucose at each experimental time point for all 8 dogs with spontaneous diabetes mellitus for Ginseng versus Placebo treatments.

Variable	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng
Mean Blood Glucose mmol/L	12.04 ± 2.37	15.69 ± 3.92	10.66 ± 4.53	10.5675± 2.29	9.47 ± 2.10	11.24 ± 3.46

Table14. P values for All Serum Biochemical Parameters for the Two ANOVA Investigating whether there was any effect of drug order and insulin type, or interaction between the insulin type and drug order.

Variable	P Value 56m0 Ginseng versus 56m0Placebo	P Value [(56+28)/2-0]Ginseng versus [(56+28)/2-0]Placebo
Sodium	0.21	0.06
Potassium	0.12	0.08
Chloride	0.57	0.63
Calcium	0.84	0.86
Phosphorus	0.57	0.93
Urea	0.13	0.35
Creatinine	0.55	0.30
Lipase	0.07	0.49
Amylase	0.91	0.93
ALT	0.90	0.75
Alk Phos	0.98	0.95
AST	0.94	0.87
GGT	0.55	0.59
SDH	0.11	0.13
Cholesterol	0.91	0.88
Glucose	0.08	0.25
Total Bilirubin	0.14	0.08
Creatine Kinase	0.17	0.13
Total protein	0.57	0.37
Albumin	0.08	0.22
Globulin	0.50	0.37
Albumin/globulin ratio	0.37	0.35

Urinalysis Parameters

Mean results ± SD for the urine specific gravity for day 56 minus day 0 for American ginseng versus placebo were 0 ± 0.013 and 0 ± 0 respectively. Mean results for the urine specific gravity for the average of days 56 and 28 minus day 0 for American ginseng versus placebo were -0.065 ± 0.07 and 0 ± 0.003 respectively. No significant difference was seen in mean urine specific gravity for dogs receiving ginseng versus placebo treatments for each of the two analyses. The P value comparing the means for urine specific gravity for ginseng versus placebo on day 56 minus day 0 was 0.78. The P value comparing the means for urine specific gravity for ginseng versus placebo for the average of day 56 and 28 minus day 0 for American ginseng versus placebo treatments was 0.22. The two ANOVA analyses done to determine if the drug order or the insulin type had any significant effect on these results, and to see if there was any interaction between the insulin type and the drug order, also failed to show any significant differences for ginseng versus placebo treatments (P value for day 56 minus day 0 American ginseng versus placebo was 0.84; P value for day the average of 56 plus 28 minus day 0 for American ginseng versus placebo treatments was 0.42.)

The other urine parameters were not evaluated statistically because they were not numerical values. Glucosuria was a common finding for all diabetic dogs while receiving ginseng or placebo, and there was not a general trend for urine glucose values to be lower for dogs receiving American ginseng versus the placebo. Appendix B contains a summary of the urinalysis findings for all dogs at all experimental time points.

Only one dog (dog 6) developed a urinary tract infection during the study, despite the fairly persistent glucosuria seen in all dogs throughout the study. Dog 6 had a positive urine culture on

day 28 while taking the placebo and *Eschericia coli* was cultured. Amoxicillin was administered for 14 days to treat this urinary tract infection, and all follow up cultures were negative for bacterial growth.

All 8 dogs had evidence of proteinuria at a minimum of one experimental time point, and most dogs had proteinuria documented at multiple time points. There was no relationship between the subjective degree of proteinuria, measured by the urine dipstick, with either the drug administered (ginseng versus placebo) or the duration of diabetes for the individual dogs. Dogs receiving NPH insulin, however, tended to have lower proteinuria values than dogs receiving Lente insulin. However, there were fewer dogs receiving NPH insulin than Lente insulin which could be a confounding factor. As well, the total number of dogs in each group was so small that this precludes any meaningful conclusions.

Glycemic Parameters

Mean results for all the glycemic parameters are shown in Table 15. No significant differences were seen between the ginseng and placebo treatments for any of the glycemic parameters (See Table 16). The two-way ANOVA analyses done to determine if the drug order or the insulin type had any significant effect, and to see if there was any interaction between the insulin type and the drug order also failed to show any significant differences (Table 17). The results of all the 12-hour glucose curves for each dog at all experimental time points (Figures 1-48) show that there was a tremendous amount of intra- and inter-dog variability in the results, regardless of the type of insulin or the drug treatment (ginseng versus placebo) each dog was receiving.

The mean values for the glycemic variables for all 8 dogs at each experimental time point for American ginseng versus placebo treatments are shown in figures 49 through 56. Figures 57 through 64 show the mean values for all dogs of the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments. Although not statistically significant, there is a trend towards ginseng lowering the mean, fasting, and mid-point blood glucose concentrations, as well as the mean AUC for the 12-hour glucose curves. Table 18 provides a summary of this information.

Table 15. Results of glycemic parameters in 8 dogs with spontaneous diabetes mellitus during the two experimental periods (Ginseng versus Placebo). Data represents the mean ± SD for two ANOVA analysis of 56-0 Ginseng versus 56-0 Placebo and [(56+28)/2-0] Ginseng versus [(56+28)/2-0] Placebo.

Variable	56-0 Ginseng	56-0 Placebo	[(56+28)/2-0] Ginseng	[(56+28)/2-0] Placebo
Insulin/kg BW IU/kg	-0.0138 ± 0.035	0.048 ± 0.07	-0.011 ± 0.012	0.03 ± 0.02
Postprandial Blood Glucosemmol/L	0.73 ± 5.24	-2.513 ± 5.36	1.45 ± 1.24	0.18 ± 1.50
Mean Blood Glucose mmol/L	0.67 ± 2.90	-1.3775 ± 4.30	-0.22 ± 0.77	1.14 ± 1.49
Mid point Blood Glucose mmol/L	0.075 ± 2.31	-0.894 ± 2.76	-0.69 ± 0.85	2.30 ± 1.38
Fasting Blood Glucose mmol/L	-0.613 ± 6.61	-0.68 ± 5.16	-1.11 ± 1.71	2.07 ± 1.71
Serum Fructosamine umol/L	17.25 ± 104.61	22.88 ± 130.79	7.5 ± 26.76	42.06 ± 35.13
Glycosylatedhemoglobin %	-0.375 ± 1.18	-0.413 ± 0.95	Not possible *	Not possible *
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	12.24 ± 35.42	-14.36 ± 38.89	1.96 ± 9.59	12.7 ± 15.69

* Not possible as there were no glycosylated hemoglobin values measured on day 28 of either treatment period.

Table 16. P values for each glycemic variable for each of the 2 different ANOVA analyses.

Variable	P Value 56m0 Ginseng versus 56m0 Placebo	P Value [(56+28)/2-1]Ginseng versus [(56+28)/2-0]Placebo
Insulin/kg BW IU/kg	0.10	0.11
Postprandial Blood Glucose	0.36	0.18
Mean Blood Glucose	0.54	0.36
Mid point Blood Glucose	0.63	0.17
Fasting Blood Glucose	0.32	0.33
Serum Fructosamine	0.91	0.81
Glycosylated hemoglobin	0.40	Not possible
Area under 12 hr Glucose Curve (AUC 12 hr)	0.35	0.39

* Not possible as there were no glycosylated hemoglobin values measured on day 28 of either treatment period.

Table17. P values for all glycemic parameters for the two ANOVA analyses where the effect of drug order (ginseng or placebo first) and insulin type were investigated.

Variable	P Value 56 m 0 Ginseng versus 56 m 0 Placebo	P Value [(56+28)/2-0]Ginseng versus [(56+28)/2-0]Placebo
Insulin/kg BW	0.41	0.07
Postprandial Blood Glucose	0.59	0.75
Mean Blood Glucose	0.61	0.50
Mid point Blood Glucose	0.27	0.38
Fasting Blood Glucose	0.06	0.07
Serum Fructosamine	0.98	0.81
Glycosylated haemoglobin	0.29	Not possible
Area under 12 hr Glucose Curve (AUC 12 hr)	0.49	0.24

Table 18. Mean ± SD of the average of days 28 and 56 for all glycemic variables in 8 dogs with spontaneous diabetes mellitus for ginseng versus placebo treatments.

Variable	Ginseng	Placebo
Insulin/kg BW IU/kg	0.74 ± 0.12	0.76 ± 0.14
Postprandial Blood Glucosemmol/L	16.41 ± 0.96	16.21 ± 1.42
Mean Blood Glucose mmol/L	10.35 ± 0.87	13.18 ± 1.44
Mid point Blood Glucose mmol/L	8.55 ± 0.84	11.89 ± 1.70
Fasting Blood Glucose mmol/L	10.75 ± 1.56	15.28 ± 1.43
Serum Fructosamine umol/L	479.13 ± 12.03	492.19 ± 28.50
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	123.46 ± 9.78	161.98± 15.83

Dog 1 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Figure 1. Blood Glucose Curve For Dog 1 Day 0 Placebo

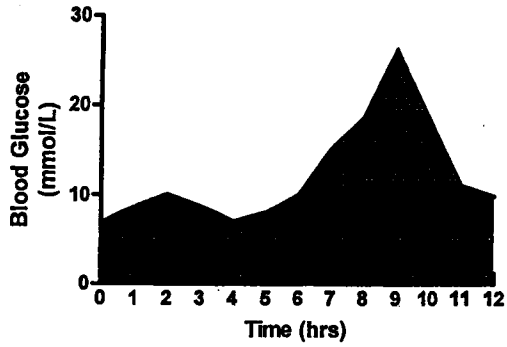


Figure 2. Blood Glucose Curve Dog 1 Day 28 Placebo

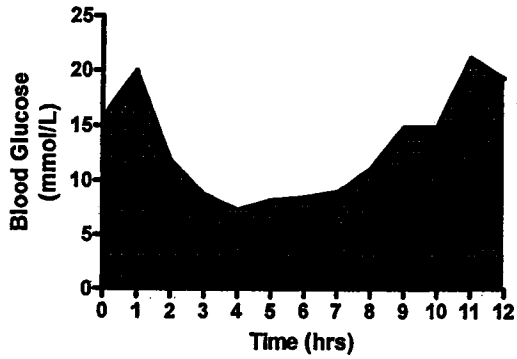


Figure 3. Blood Glucose Curve Dog 1 Day 56 Placebo

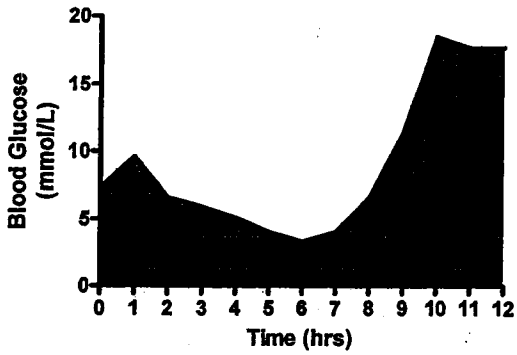


Figure 4. Blood Glucose Curve Dog 1 Day 0 Ginseng Treatment

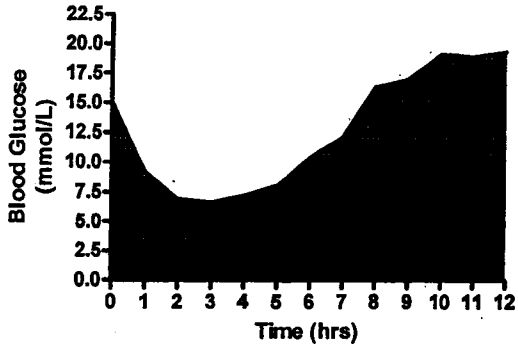


Figure 5. Blood Glucose Curve Dog 1 Day 28 Ginseng Treatment

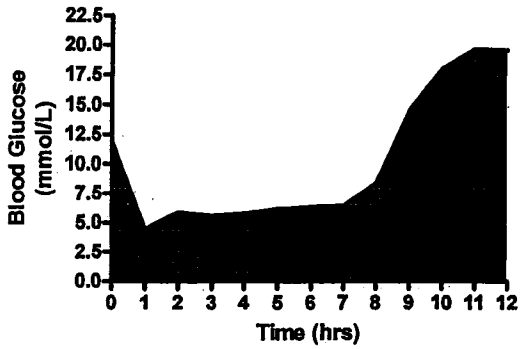
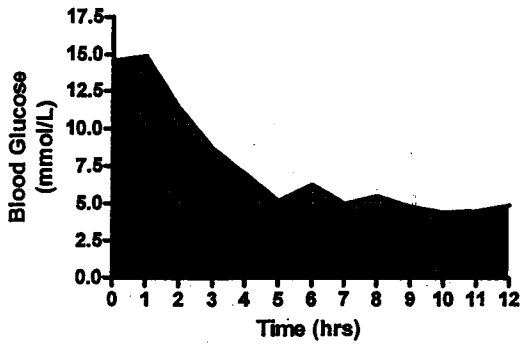


Figure 6. Blood Glucose Curve Dog 1 Day 56 Ginseng Treatment



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 2 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 7 Blood Glucose Curve Dog 2
Day 0 Placebo

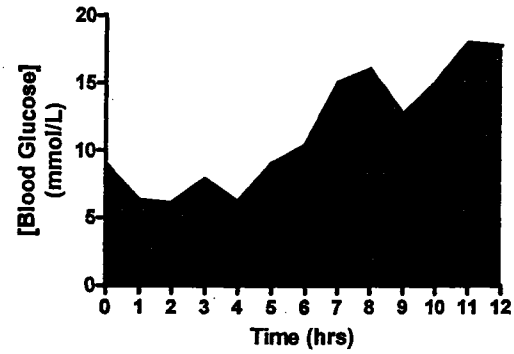


Fig. 10 Blood Glucose Curve Dog 2
Day 0 Ginseng

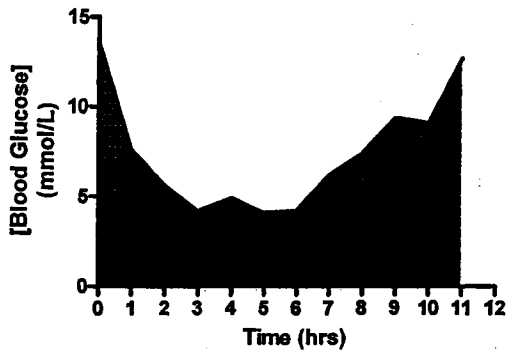


Fig. 8 Blood Glucose Curve Dog 2
Day 28 Placebo

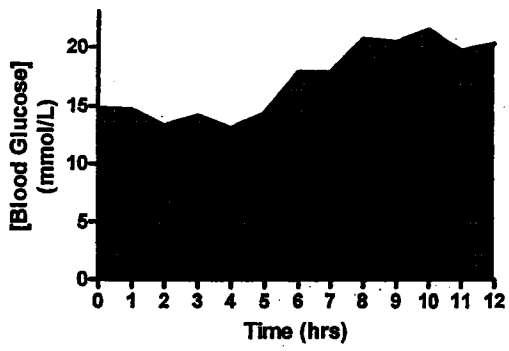


Fig. 11 Blood Glucose Curve Dog 2
Day 28 Ginseng

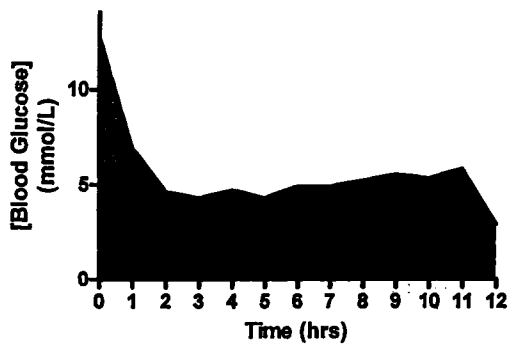


Fig. 9 Blood Glucose Curve Dog 2
Day 56 Placebo

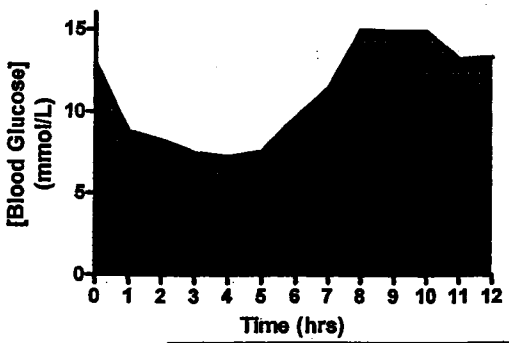
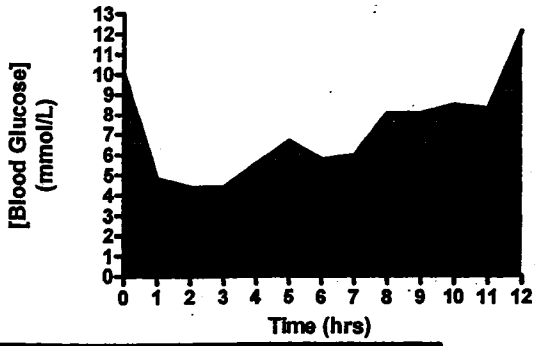


Fig. 12 Blood Glucose Curve Dog 2
Day 56 Placebo



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 3 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 13 Blood Glucose Curve Dog 3 Day 0 Placebo

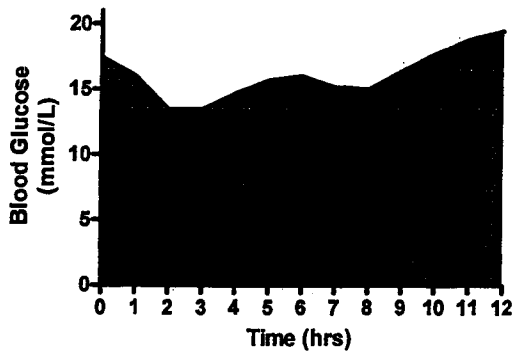


Fig. 16 Blood Glucose Curve Dog 3 Day 0 Ginseng

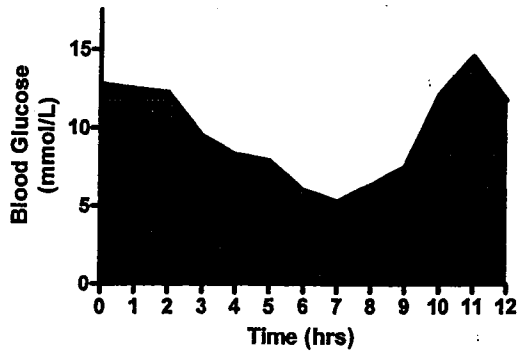


Fig. 14 Blood Glucose Curve Dog 3 Day 28 Placebo

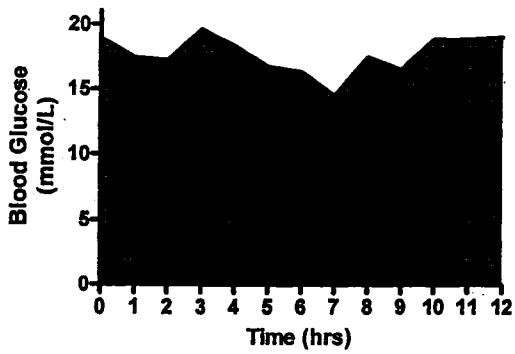


Fig. 17 Blood Glucose Curve Dog 3 Day 28 Ginseng

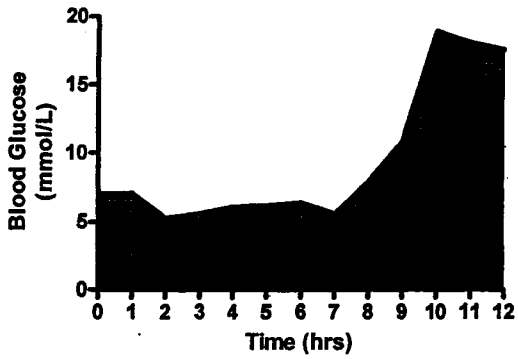


Fig. 15 Blood Glucose Curve Dog 3 Day 56 Placebo

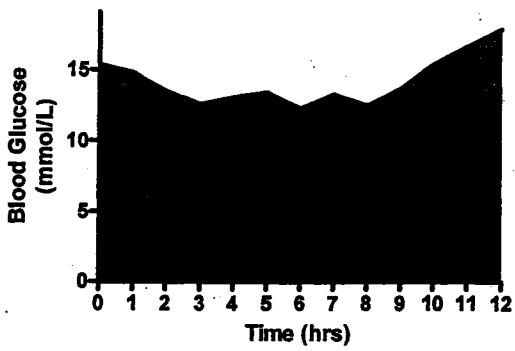
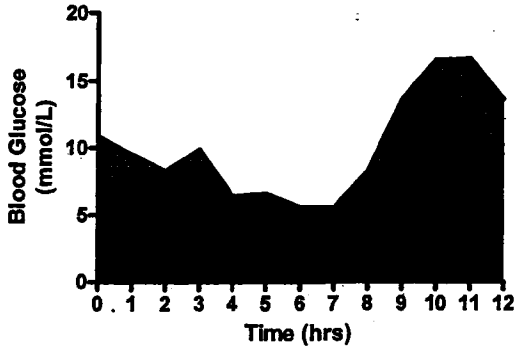


Fig. 18 Blood Glucose Curve Dog 3 Day 56 Ginseng



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 4 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 19 Blood Glucose Curve Dog 4 Day 0 Placebo

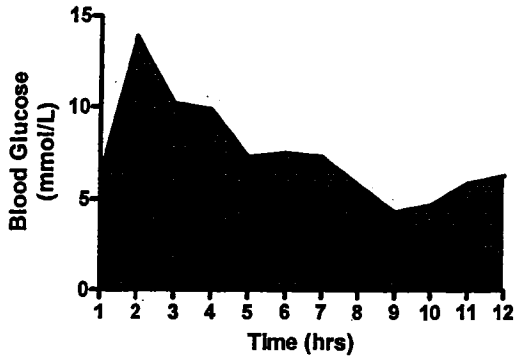


Fig. 22 Blood Glucose Curve Dog 4 Day 0 Ginseng Treatment

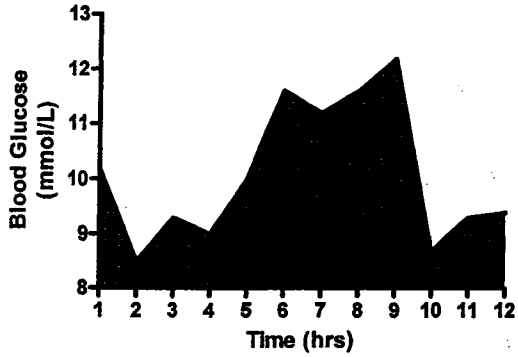


Fig. 20 Blood Glucose Curve Dog 4 Day 28 Placebo

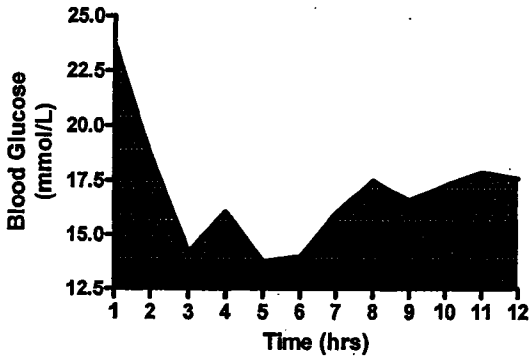


Fig. 23 Blood Glucose Curve Dog 4 Day 28 Ginseng Treatment

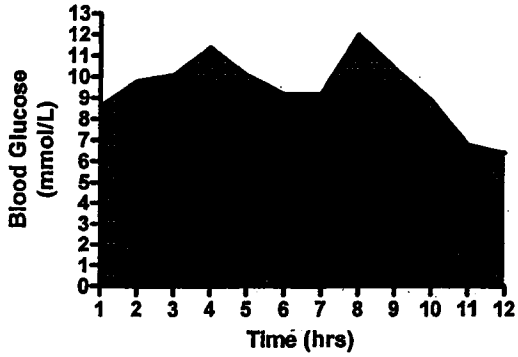


Fig. 21 Blood Glucose Curve Dog 4 Day 56 Placebo

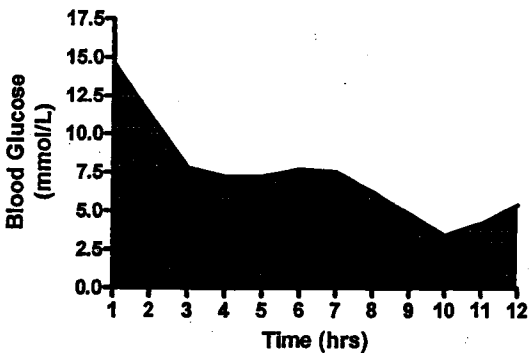
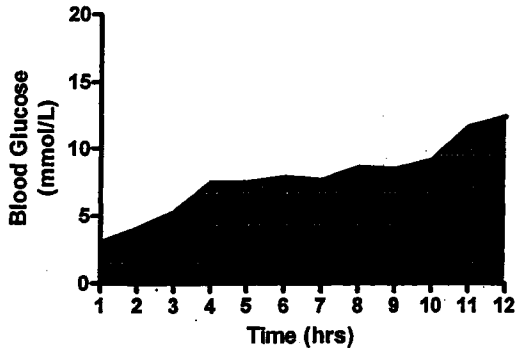


Fig. 24 Blood Glucose Curve Dog 4 Day 56 Ginseng Treatment



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 5 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 25 Blood Glucose Curve Dog 5 Day 0 Placebo

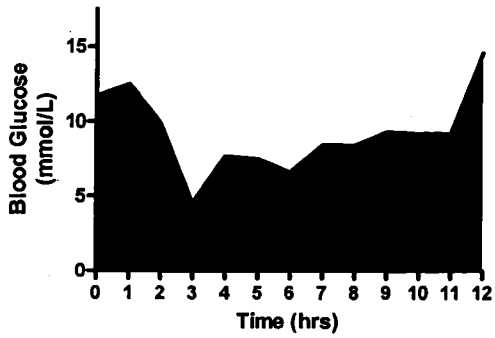


Fig. 28 Blood Glucose Curve Dog 5 Day 0 Ginseng

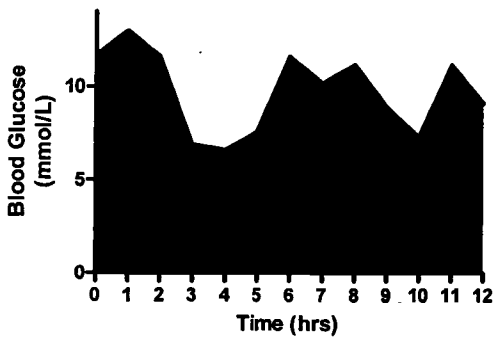


Fig. 26 Blood Glucose Curve Dog 5 Day 28 Placebo

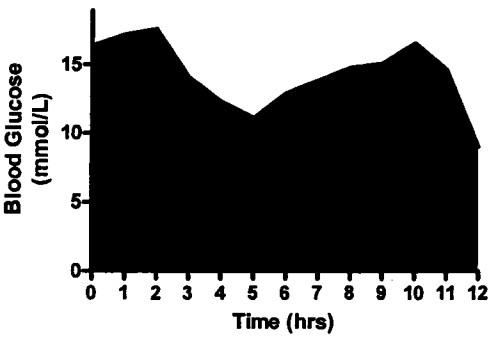


Fig. 29 Blood Glucose Curve Dog 5 Day 28 Ginseng

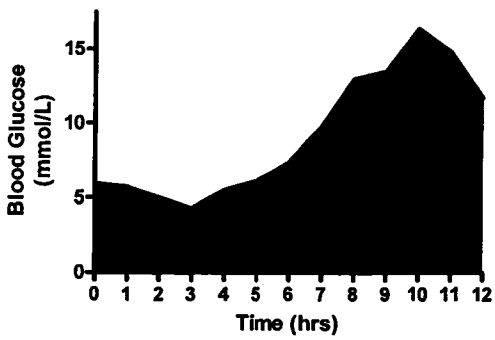


Fig. 27 Blood Glucose Curve Dog 5 Day 56 Placebo

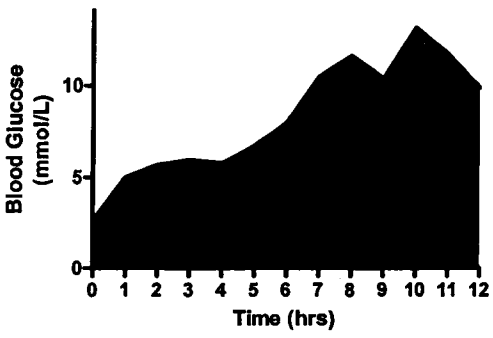
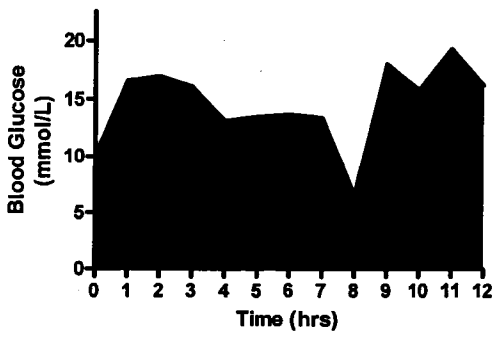


Fig. 30 Blood Glucose Curve Dog 5 Day 56 Ginseng



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 6 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 31 Blood Glucose Curve Dog 6 Day 0 Placebo

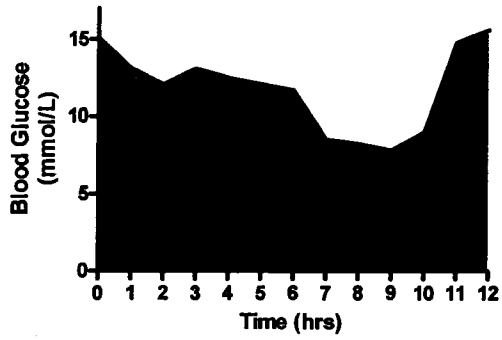


Fig. 34 Blood Glucose Curve Dog 6 Day 0 Ginseng

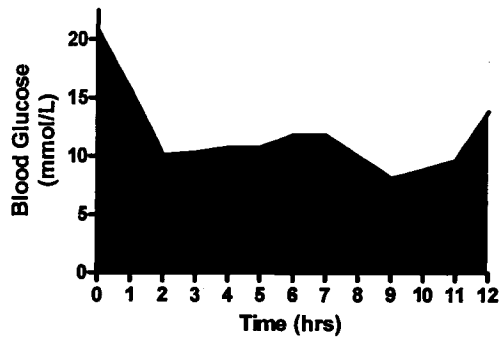


Fig. 32Blood Glucose Curve Dog 6 Day 28 Placebo

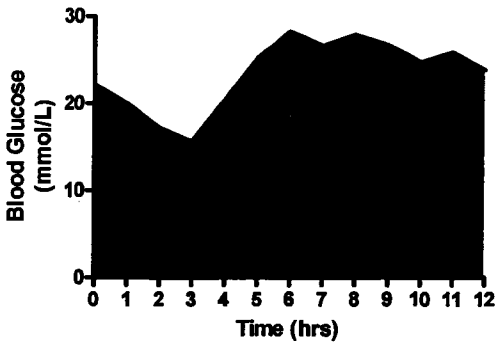


Fig. 35 Blood Glucose Curve Dog 6 Day 28 Ginseng

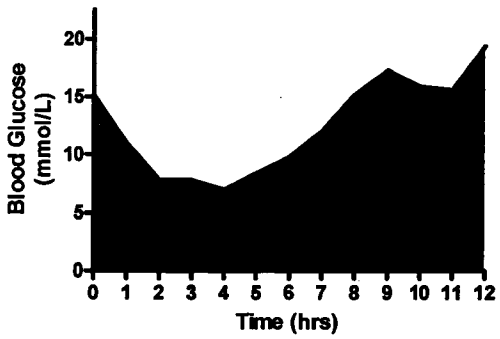


Fig. 33 Blood Glucose Curve Dog 6 Day 56 Placebo

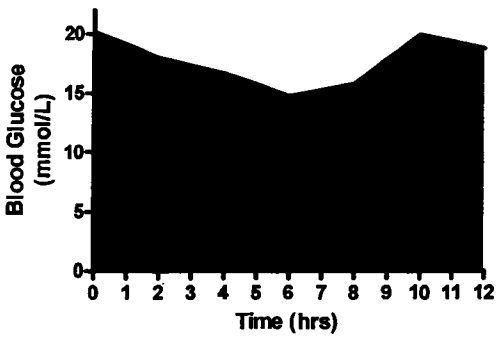
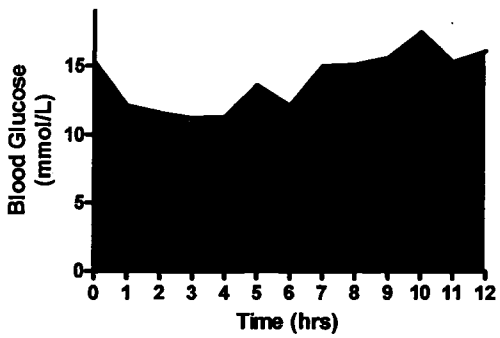


Fig. 36 Blood Glucose Curve Dog 6 Day 56 Ginseng



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 7 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 37 Blood Glucose Curve Dog 7 Day 0 Placebo

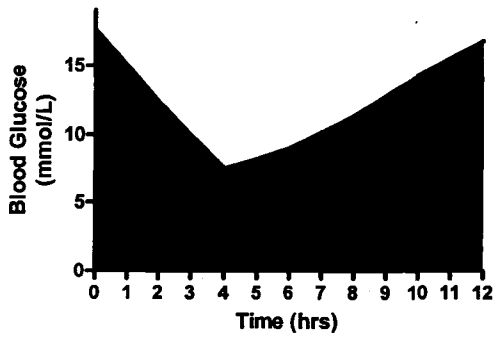


Fig. 40 Blood Glucose Curve Dog 7 Day 0 Ginseng

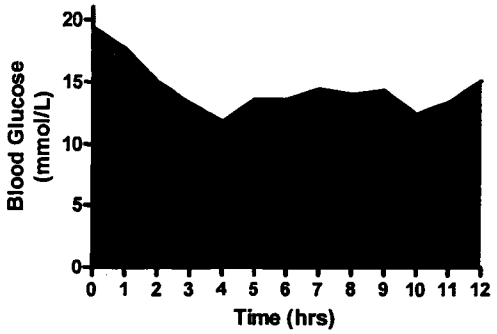


Fig. 38 Blood Glucose Curve Dog 7 Day 28 Placebo

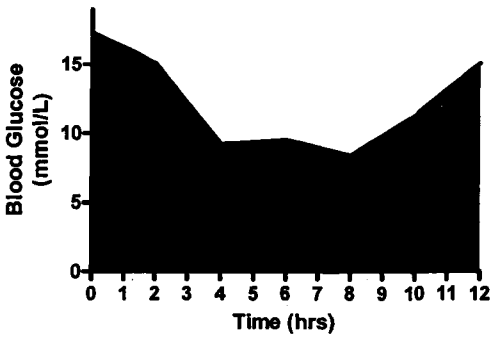


Fig. 41 Blood Glucose Curve Dog 7 Day 28 Ginseng

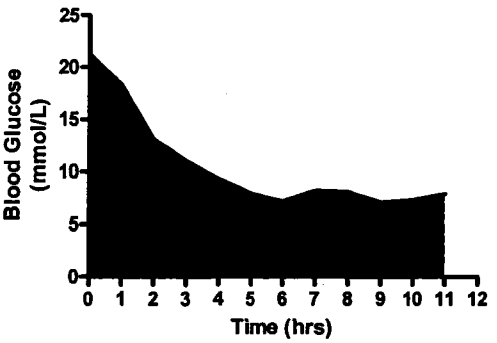


Fig. 39 Blood Glucose Curve Dog 7 Day 56 Placebo

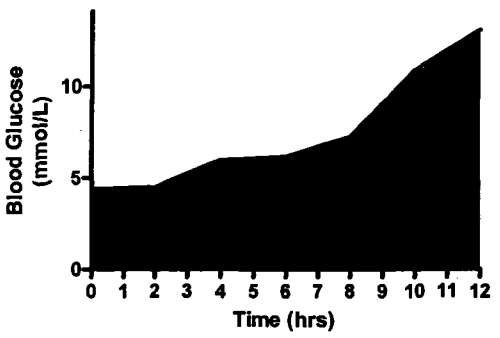
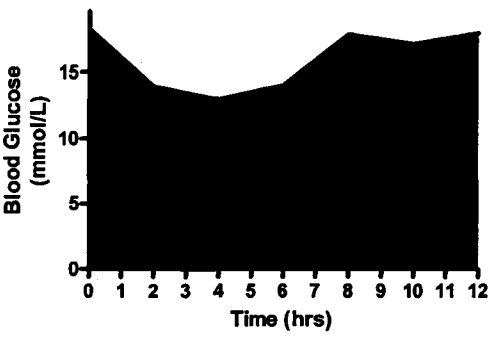


Fig. 42 Blood Glucose Curve Dog 7 Day 56 Ginseng



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Dog 8 Glucose Curves for Days 0, 28 and 56 for Ginseng versus Placebo Treatments

Fig. 43 Blood Glucose Curve Dog 8 Day 0 Placebo

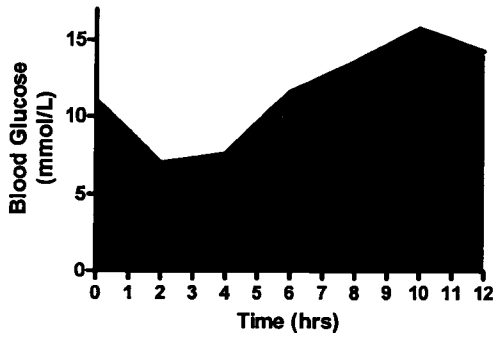


Fig. 44 Blood Glucose Curve Dog 8 Day 28 Placebo

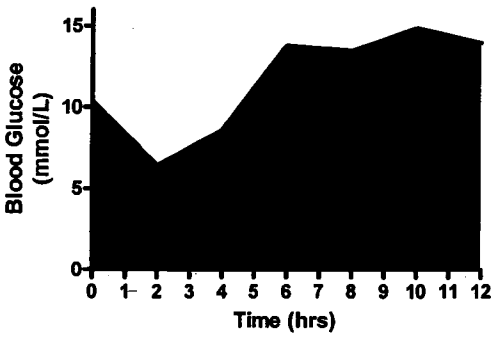


Fig. 45 Blood Glucose Curve Daog 8 Day 56 Placebo

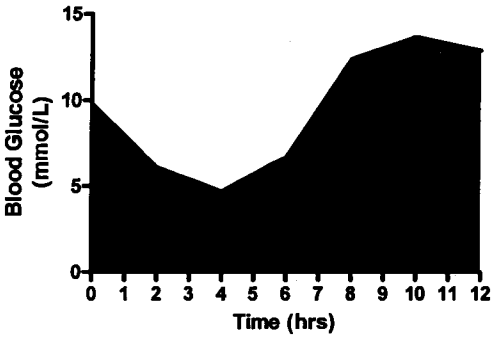


Fig. 46 Blood Glucose Curve Dog 8 Day 0 Ginseng

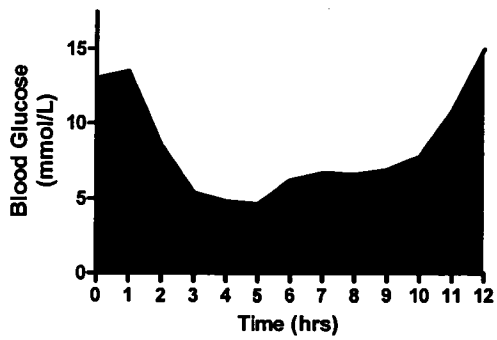


Fig. 47 Blood Glucose Curve Dog 8 Day 28 Ginseng

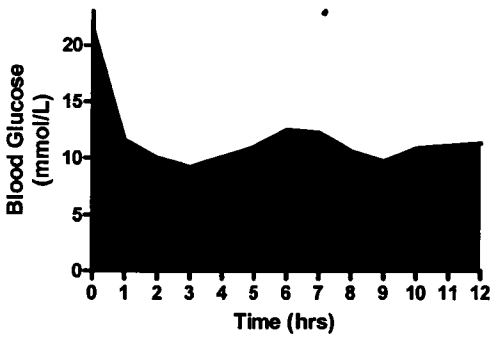
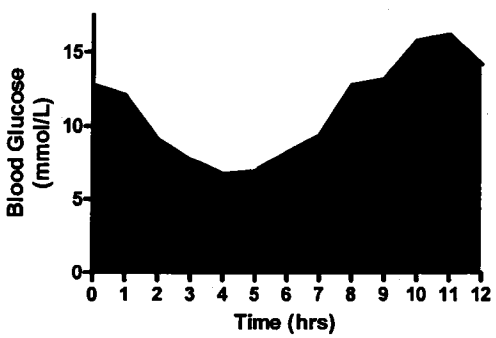


Fig. 48 Blood Glucose Curve Dog 8 Day 56 Ginseng



** For Figures 1-48 Time 0 = time of insulin injection and feeding

Means for All Glycemic Parameters For 8 Dogs with Spontaneous Diabetes Mellitus On Ginseng Versus Placebo Treatments

Fig. 49 Mean Blood Glucose Values for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

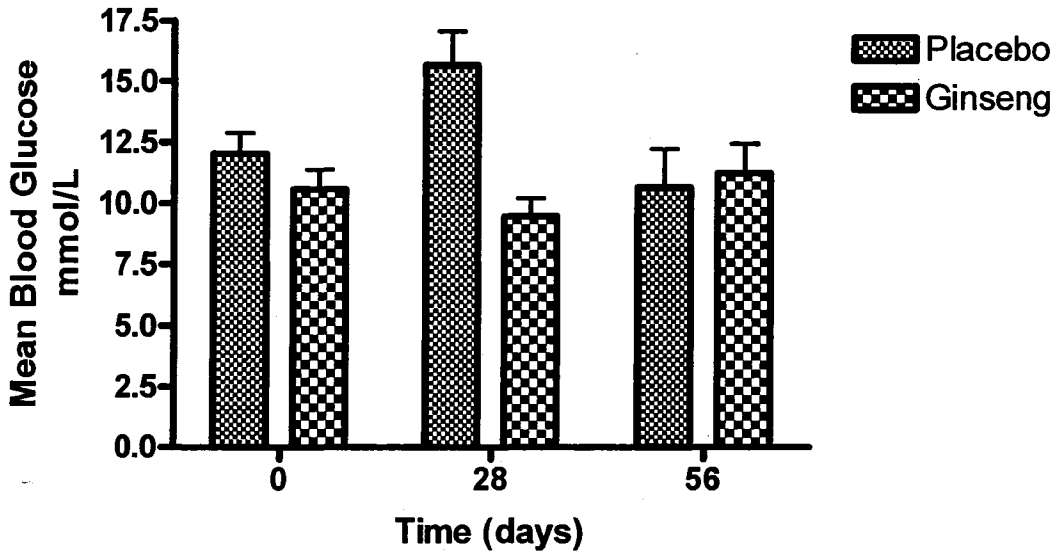


Fig. 50 Mean Fasting Blood Glucose Values for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

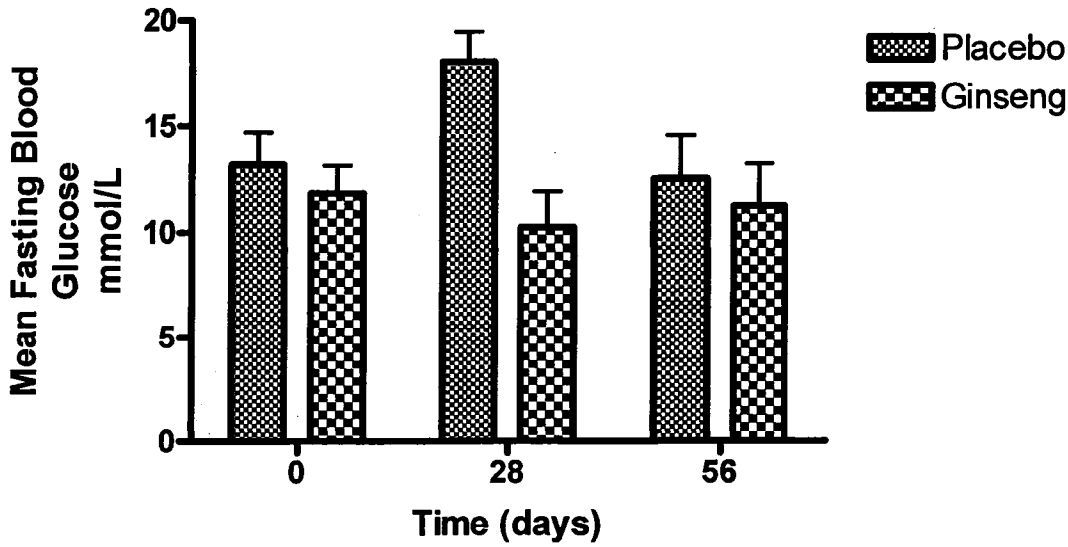


Fig. 51 Mean Postprandial Blood Glucose Values for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

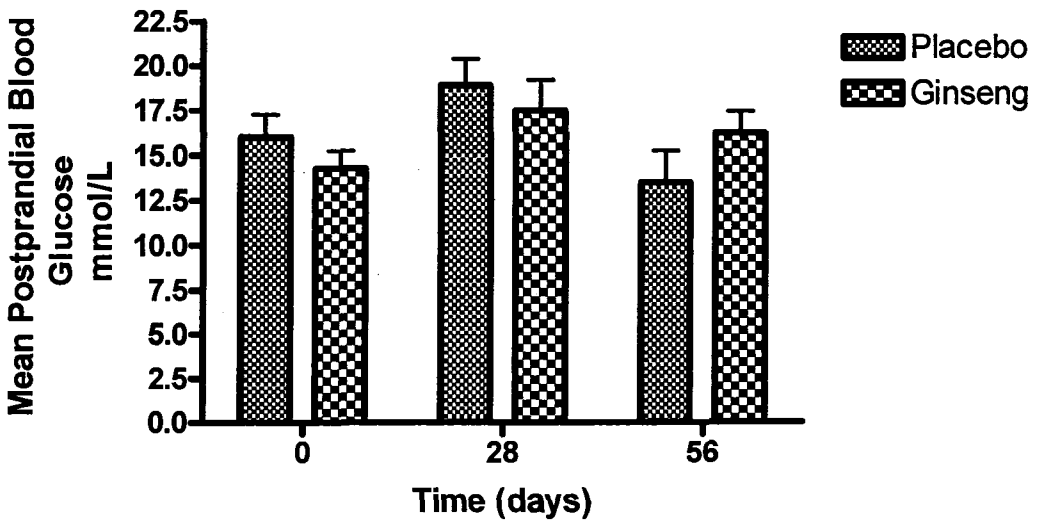


Fig. 52 Mean Midpoint Blood Glucose Values for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

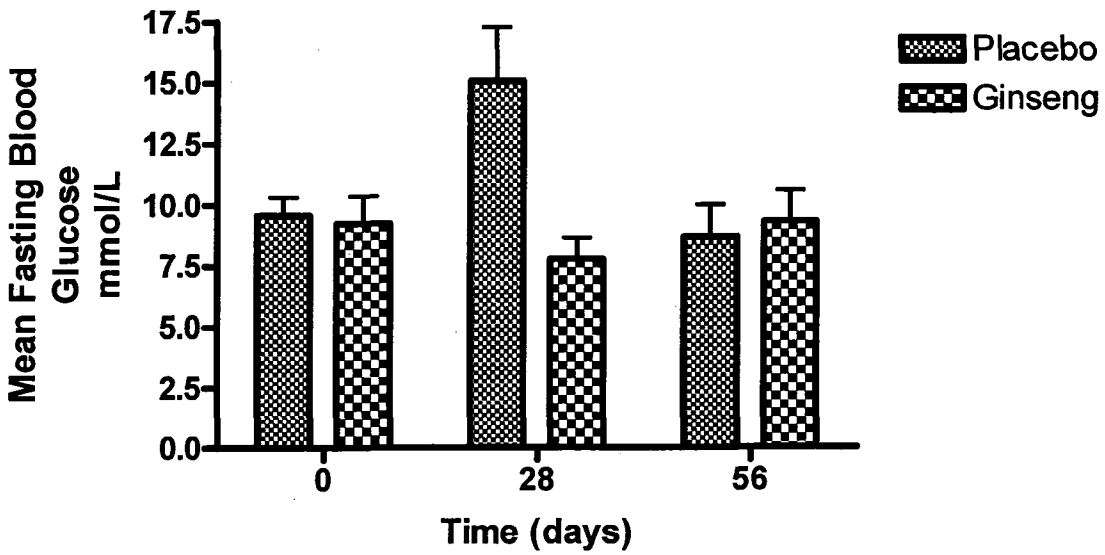


Fig. 53 Mean Serum Fructosamine Values for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

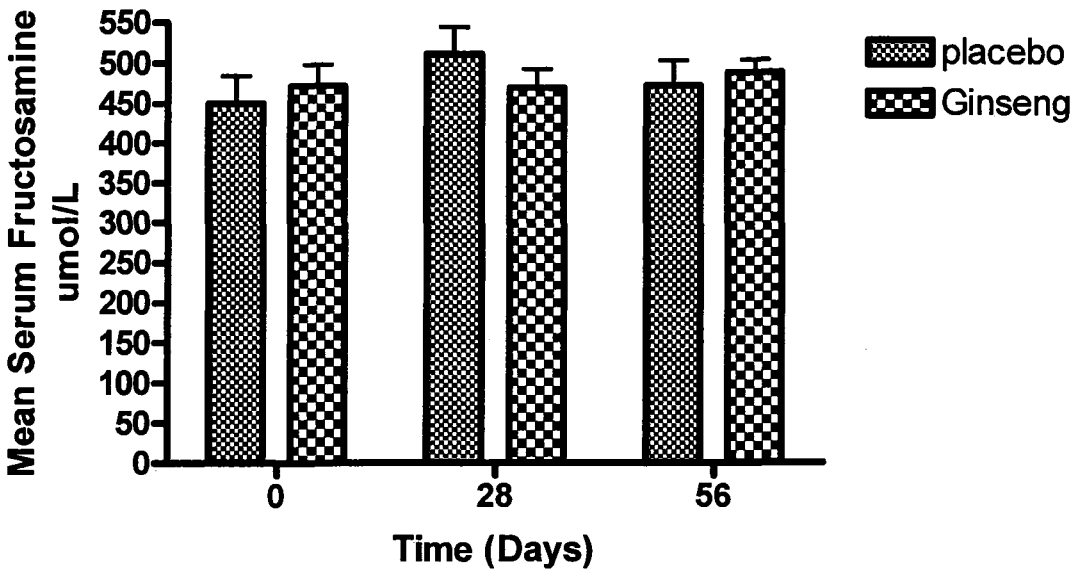


Fig. 54 Mean Glycosylated Hemoglobin Values for All Dogs on Days 0 and 56 for Ginseng versus Placebo

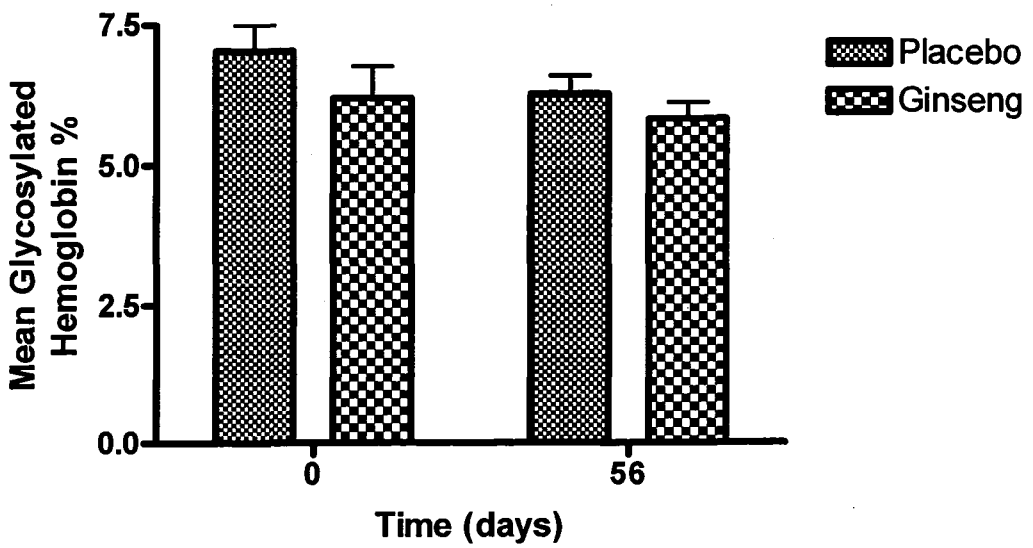


Fig. 55 Mean Insulin dose per kg Body Weight for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo

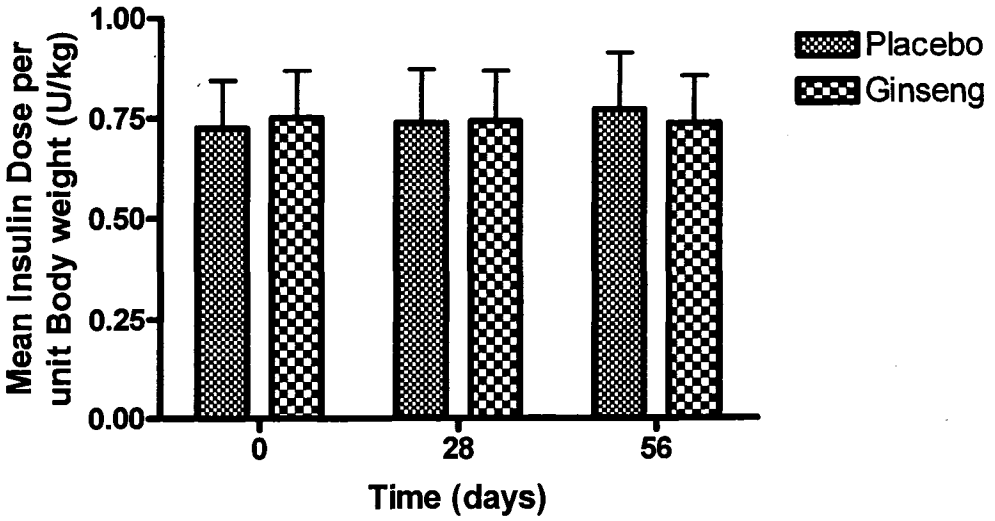
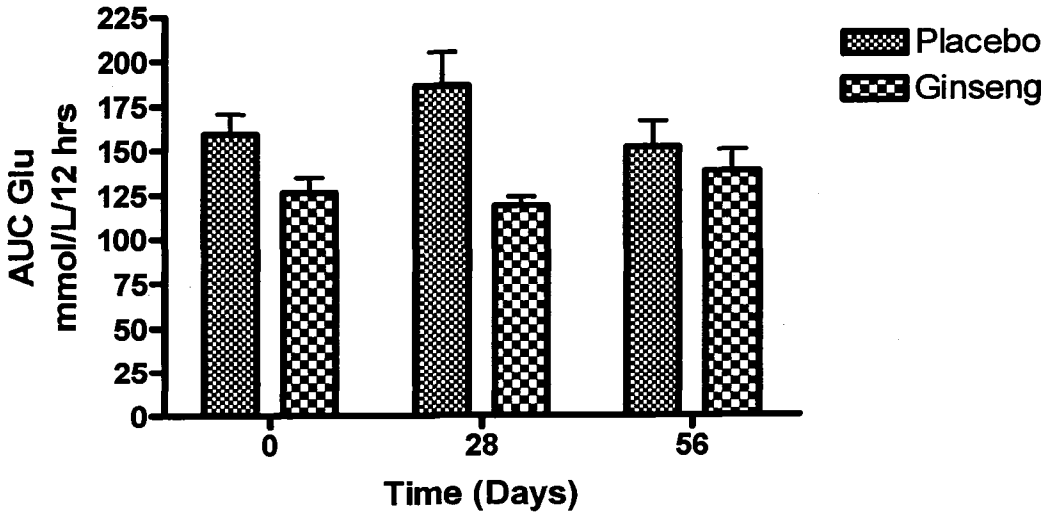


Fig. 56 Mean of the Area Under Curve for the 12 hour Glucose Curve (AUC Glu) for All Dogs on Days 0, 28 and 56 for Ginseng versus Placebo



Glycemic Parameters for 8 dogs with Spontaneous Diabetes Mellltus given American Ginseng versus Piacebo. Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.

Fig. 57 Mean Blood Glucose to assess glycemic control in 8 dogs with spontaneous diabetes mellitus given American Ginseng versus Placebo . Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments .

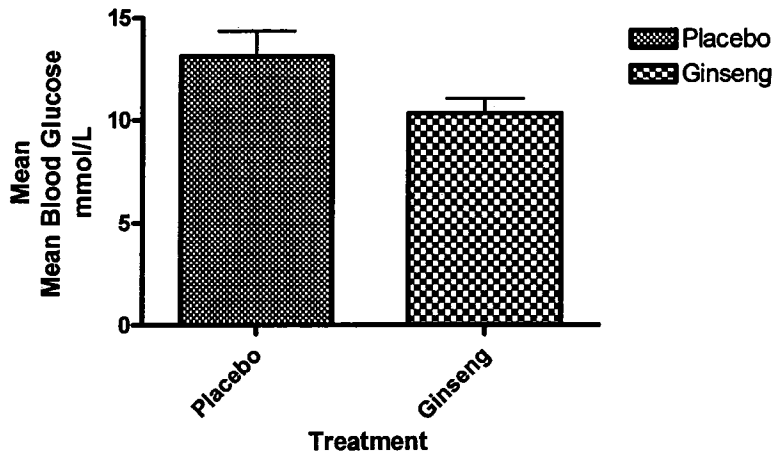


Fig. 58 Mean Midpoint Blood Glucose to assess glycemic control in 8 dogs with spontaneous diabetes mellitus given American Ginseng versus Placebo . Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.

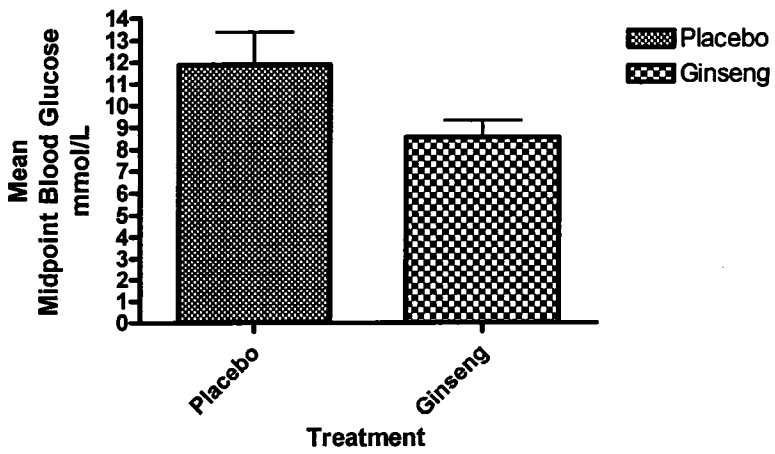
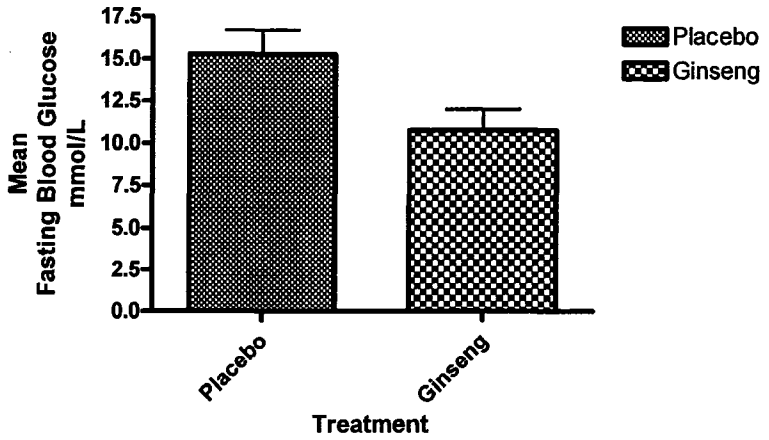


Fig. 59 Mean Fasting Blood Glucose to assess glycemic control In 8 dogs with spontaneous diabetes mellltus given American Ginseng versus Placebo. Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.



Flg. 60 Mean Postprandlal Blood Glucose to assess glycemic control in 8 dogs with spontaneous diabetes mellltus given American Glnseng versus Placebo. Data represents the mean ± SD for the average of days 28 and 56 for all glycemlc variables for ginseng versus placebo treatments.

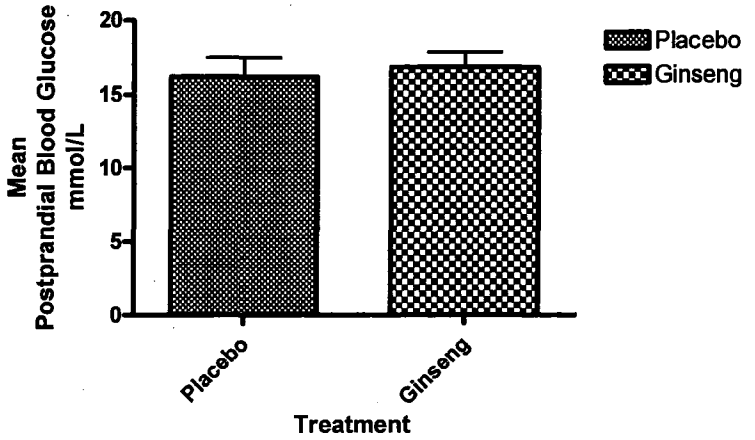


Fig. 61 Mean Insulin dose per kg Body Weight to assess glycemic control in 8 dogs with spontaneous diabetes mellitus given American Ginseng versus Placebo . Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.

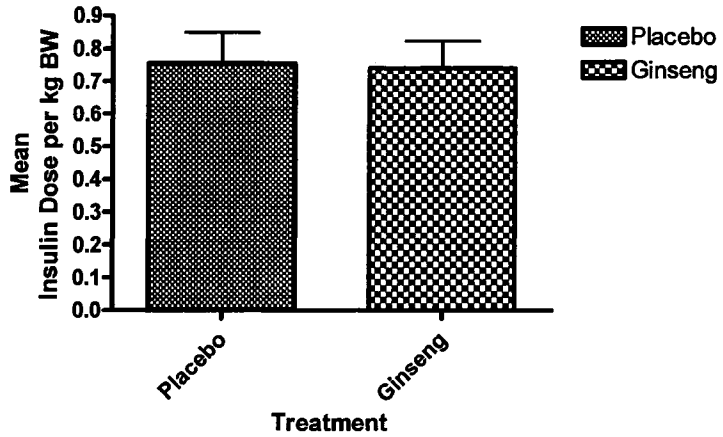


Fig. 62 Mean of the Area Under Curve for the 12 hour Glucose Curve (AUC Glu) to assess glycemic control in 8 dogs with spontaneous diabetes mellitus given American Ginseng versu s Placebo. Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.

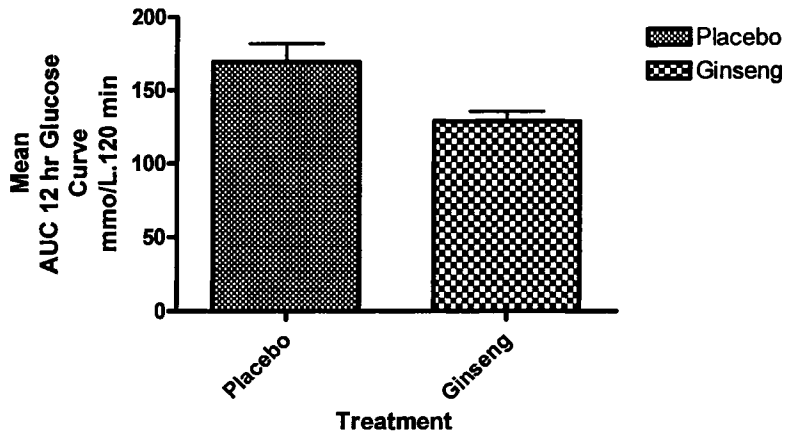
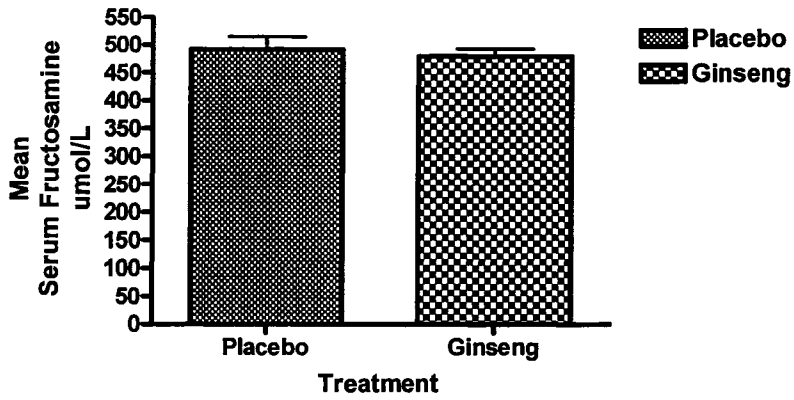


Fig. 63 Serum Fructosamine Concentration to assess glycemic control in 8 dogs with spontaneous diabetes mellitus given American Ginseng versus Placebo. Data represents the mean ± SD for the average of days 28 and 56 for all glycemic variables for ginseng versus placebo treatments.



Systemic Arterial Blood Pressure Parameters

Mean results for the systemic arterial blood pressure parameters are shown in Table 20. No significant differences were seen in any of the systemic arterial blood pressure parameters (P all > 0.05) for the ginseng versus the placebo treatments (Table 21).

The two ANOVA analyses done to determine if the drug order or the insulin type had any significant effect or if there was any interaction between insulin type and order also failed to show any significant differences found for any of the systemic blood pressure parameters (Table 21).

Evaluation of the mean ± SD values for the average of days 28 and 56 for each of the arterial blood pressure parameters investigated for ginseng and placebo treatments (Table 22) shows there were no differences in these means and no trends. Figures 64 to 66 show the mean values

for the arterial blood pressure parameters for all 8 dogs at each experimental time point for American ginseng versus placebo treatments. Figures 67 to 69 show the mean values for all dogs of the average of days 28 and 56 minus day 0 for all systemic arterial blood pressure parameters for ginseng versus placebo treatments.

Although on occasion dogs in this study were hypertensive, none of the dogs was found to be consistently hypertensive or had evidence of other end organ damage of systemic arterial hypertension (e.g., ocular hemorrhage, evidence or renal and cardiac disease).

Table 20. Results of systemic arterial blood pressure parameters in 8 dogs with spontaneous diabetes mellitus during the two experimental periods (ginseng versus placebo). Data represents the mean ± SD for two ANOVA analysis of 56-0 Ginseng versus 56-0 Placebo and [(56+28)/2-0] Ginseng versus [(56+28)/2-0] Placebo.

Variable	56-0 Ginseng	56-0 Placebo	[(56+28)/2-0]Ginseng	[(56+28)/2-0]Placebo
Mean arterial blood pressure mmHg	7.9 ± 29.55	-3.83 ± 16.12	5.14 ± 7.08	-1.68 ± 5.27
Diastolic blood pressure mmHg	9.55 ± 20.96	5.41 ± 15.72	5.9 ± 4.21	7.07 ± 4.88
Systolic blood pressure mmHg	13.13 ± 28.45	2.89 ± 19.53	7.45 ± 7.12	0.93 ± 7.64

Table 21. P values for the systemic arterial blood pressure parameters for each of the 2 ANOVA analyses.

Variable	P Value 56m0 Ginseng versus 56m0 Placebo	P Value [(56+28)/2-0]Ginseng versus [56+28)/2-0]Placebo
Mean arterial pressure	0.43	0.19
Diastolic blood pressure	0.53	0.91
Systolic blood pressure	0.09	0.43

Table 22. P values for all systemic blood pressure parameters for the two ANOVA analyses where the effect of drug order and insulin type were investigated.

Variable	P Value 8m1 Ginseng versus 8m1 Placebo	P Value [(8+4)/2-1] Ginseng versus [(8+4)/2-1]Placebo
Mean arterial pressure	0.43	0.36
Diastolic blood pressure	0.52	0.12
Systolic blood pressure	0.09	0.57

Table 23. Results for the systemic blood pressure parameters in 8 dogs with spontaneous diabetes mellitus receiving exogenous insulin and ginseng versus placebo treatments. Data represents the mean ± SD for the average of days 28 and 56 for all arterial blood pressure parameters for ginseng versus placebo treatments.

Variable	Ginseng	Placebo
Mean arterial blood pressure mmHg	108.79 ± 5.68	105.58 ± 5.08
Diastolic blood pressure mmHg	91.97 ± 5.69	85.09 ± 4.34
Systolic blood pressure mmHg	134.22 ± 5.57	138.96 ± 6.72

Comparison of the Mean Values for the Mean, Systolic and Diastolic Arterial Blood Pressures for Dogs on Ginseng versus Placebo. Data represent mean ± SD of results for days 0, 28 and 56 and the average of days 28 and 56.

Fig. 64 Comparison of the means for the mean arterial blood pressure for all dogs on days 0, 28, and 56 for Ginseng versus Placebo

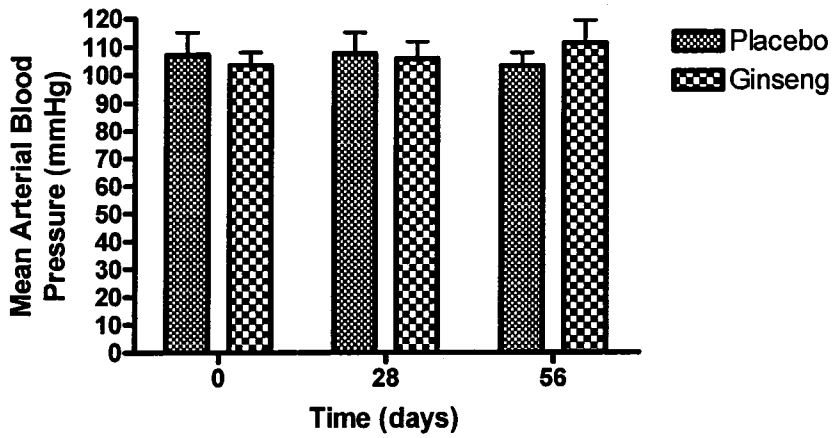
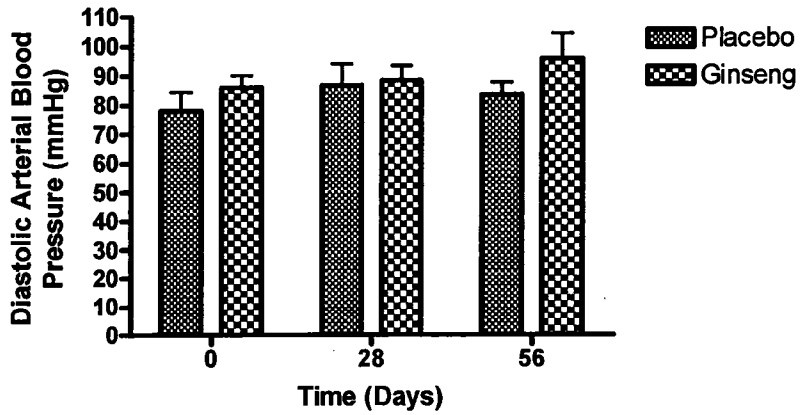


Fig. 65 Comparison of the means for the diastolic arterial blood pressure for all dogs on days 0, 28, and 56 for Ginseng versus Placebo



Comparison of the Mean Values for the Mean, Systolic and Diastolic Arterial Blood Pressures for Dogs on Ginseng versus Placebo. Data represent mean ± SD of results for days 0, 28 and 56 and the average of days 28 and 56.

Fig. 66 Comparison of the means for the systolic arterial blood pressure for all dogs on days 0, 28, and 56 for Ginseng versus Placebo

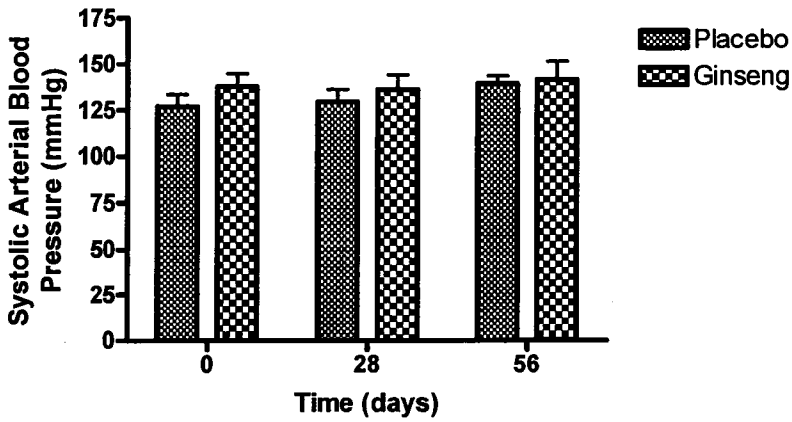
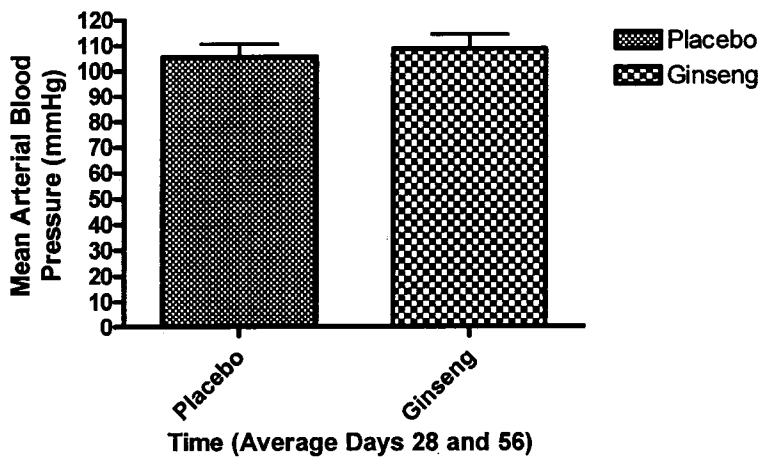


Fig. 67 Comparison of the means for the mean arterial blood pressure for all dogs for the average of days 28, and 56 for Ginseng versus Placebo



Comparison of the Mean Values for the Mean, Systolic and Diastolic Arterial Blood Pressures for Dogs on Ginseng versus Placebo. Data represent mean ± SD of results for days 0, 28 and 56 and the average of days 28 and 56.

Fig. 68 Comparison of the means for the diastolic arterial blood pressure for all dogs for the average of days 28 and 56 for Ginseng versus Placebo

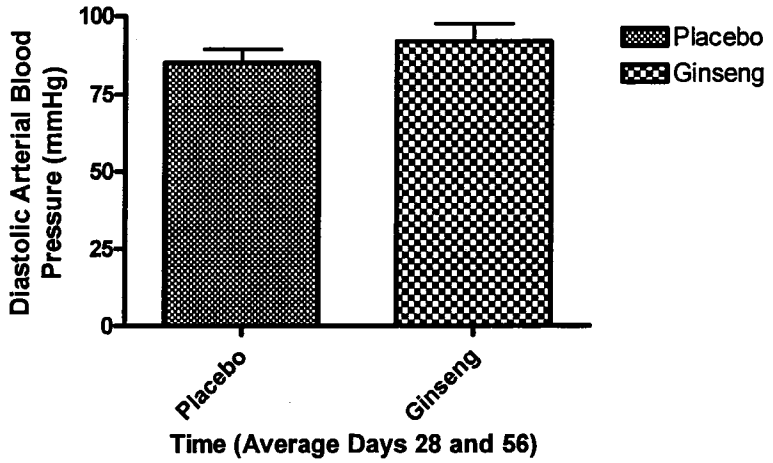
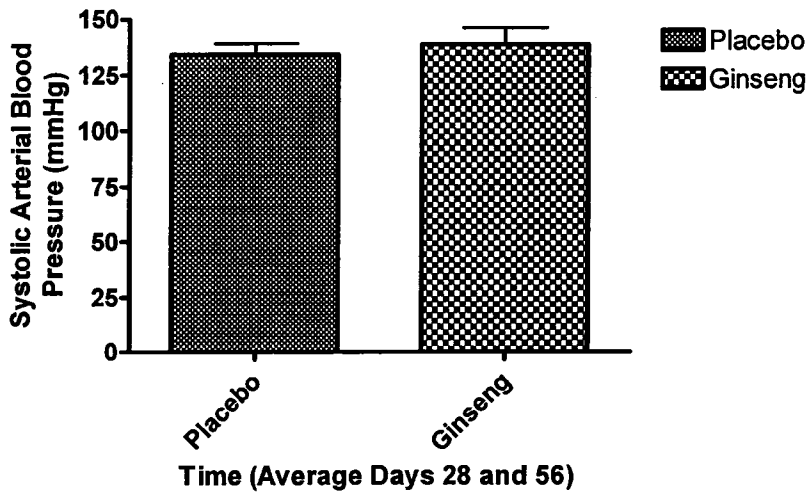


Fig. 69 Comparison of the means for the systolic arterial blood pressure for all dogs for the average of days 28, and 56 for Ginseng versus Placebo



Discussion

The findings from this pilot study failed to show that American ginseng (*Panex quinquefolius*) given at a dose of 500 to 1000 mg orally twice daily had any significant antihyperglycemic or antihypertensive effects in dogs with spontaneous type I diabetes mellitus. However, with only 8 dogs, the power of this study was very low and this may have increased the probability of a type II error occurring. Specifically, this may have affected the ability of this study to detect any statistically significant effect of American ginseng on the parameters evaluated.

Other than insufficient power, other factors that could have influenced the lack of statistically significant findings in this study include the dose of American ginseng used, the timing of administration of the American ginseng relative to feeding, the type of diabetes mellitus in dogs, the source of American ginseng used in this study, and the significant random intra- and inter-dog variability with respect to diabetic control.

First, the dose of American ginseng may have been too low to have any significant effect on glycemic and systemic blood pressure parameters. In most human studies where administration of American ginseng was shown to significantly improve glycemic parameters, the dose of American ginseng varied from 1 to 9 g per person per day (6, 9, 10-14, 203, 222-224, 276). The average body mass index for the patients involved in these studies was 26.24 kg/m^2, so the ginseng doses used were equivalent to an average oral dose of 12 to 110mg/kg BW American ginseng daily (6, 9, 10-14, 203, 222-224, 276) . Jenkins et al (2000), who investigated the effect of escalation of the dose of American ginseng on postprandial glycemia in healthy normal human subjects, showed there was no additional influence on postprandial glycemia detected when the

dose of American ginseng was increased from 3 to 6 and then to 9 g (221). In experiments involving mice and rats models, where administration of American ginseng resulted in significant improvement in glycemic parameters, doses varied from 10 mg/kg up to 300-400 mg/kg (8, 186-186, 205, 209-212). The dose of American ginseng received by dogs in this study varied from 24 mg/kg up to 64 mg/kg. See Table 5 for a summary of the mg/kg dose received by each dog. It is possible that a higher dose of American ginseng (either 3 to 6 g or 300-400 mg/kg) may have resulted in a significant effect on glycemic and systemic blood pressure parameters in dogs with spontaneous diabetes mellitus. The dose used in this study (500 to 1000 mg depending on the body weight of the dog) was extrapolated from human studies and seemed reasonable. However, oriental medical practice typically recommends that herbal remedies be taken at a daily dose of approximately 10 g with 3 g as the minimum dose per person (249).

The timing of administration of the American ginseng relative to feeding may also have affected the results in this study. Oriental medicine also stipulates that herbal remedies should be taken between meals, not in combination with them. In our study, the medications were given with meals and at the same time as the dog received their insulin injection. If the dogs had received the American ginseng 1-2 hours prior to being fed and receiving their insulin, then perhaps the American ginseng might have had more effect. Vuksan et al showed that the postprandial anti-hyperglycemic effect of ginseng in healthy individuals appears to occur in a manner dependant on the time of administration (13). Only when ginseng was administered 40 minutes before an oral glucose challenge were significant differences in the postprandial glycemia seen between American ginseng compared to a placebo. When American ginseng was administered 20, 10, and 0 minutes before challenge, no anti-hyperglycemic effect was seen

compared to placebo (13). Jenkins et al showed that there was no additional effect on postprandial glycemia with escalation of time of administration from 40 to 80 to 120 minutes prior to an oral glucose tolerance challenge (221). From this data, it appears as if the best time to administer American ginseng is 40 minutes prior to eating in humans. For dogs it may be that administering American ginseng prior to feeding would result in anti-hyperglycemic effects. We chose to have the owners administer the American ginseng and placebo at the same time the dogs were fed and received their insulin in order to maximize compliance for administration of the study drug. Cats and dogs usually receive their insulin at the same time they are fed for practical reasons and to help prevent iatrogenic hypoglycemia from occurring. Ideally, diabetic dogs should eat just before the anticipated time of peak insulin activity; however, this is impractical for owners of diabetic pets. The extreme intra- and inter-dog variability in the metabolic effects caused by the same type of insulin from day to day, as well as the marked differences in how the effects of different insulin types in different dogs, makes judging when to feed highly impractical (19, 24, 98). The other primary reason why insulin therapy is timed to coincide with feeding is to decrease the risk of iatrogenic hypoglycemia if the pet does not eat. To avoid such a life-threatening consequence of insulin therapy, a dog or cat's full dose of insulin is only given after they eat. It is possible that if American ginseng was administered 40 minutes prior to feeding and the pet did not eat, a hypoglycemic effect might have been seen.

Although most studies looking at the antihyperglycemic effects of American ginseng in people and experimental animal models have focused on its ability to attenuate postprandial glycemia, this does not appear to be the only anti-hyperglycemic benefit of American ginseng. Several studies have observed long term benefits in glycemic control as assessed by decreased

glycosylated hemoglobin (HbA1c) concentrations seen with only once-daily administration of ginseng compared to a placebo. The decrease in glycosylated hemoglobin concentration occurred without regard to the timing of administration of American ginseng relative to mealtimes (6, 12). Sontanemi et al. also did not observe differences in the oral glucose tolerance test at the beginning and the end of ginseng treatments, and no significant effects were seen for any of the other glycemic parameters, including the postprandial glucose for ginseng compared to placebo treatments, despite the improvement in glycosylated hemoglobin (6). In another study where American ginseng was administered to 24 patients with type II diabetes mellitus 40 minutes prior to each meal, there was also a decrease in HbA1c as well as a reduction in fasting blood glucose concentrations compared to placebo (12). In a long term study where 3-4.5 g/day of Korean red ginseng was administered to 24 people with type II diabetes mellitus for 24 months, a reduction in HbA1c compared to a placebo was seen (250). No significant effect on glycosylated hemoglobin concentration was seen in the diabetic dogs in our study. However, perhaps administration for a longer period of time than 8 weeks, such as 6-24 months, may be required to see such an effect.

Another reason why this study may not have shown a significant antihyperglycemic effect of administration of American ginseng may be the type of diabetes mellitus present in dogs. All diabetic dogs, with rare exceptions, have type I diabetes mellitus. All of the research done in diabetic people with administration of American ginseng has been done with subjects that had type II diabetes mellitus. If the major mechanism responsible for American ginseng's antihyperglycemic effect turns out to be promotion of insulin secretion from pancreatic beta cells, then one might expect very limited, if any, improvement in glycemic parameters in patients with

type I diabetes mellitus. This is because they lack any residual beta cell insulin secreting ability. From this standpoint, cats may be a better companion animal model for studying the antihyperglycemic effects of American ginseng because 30-70% of cats are believed to suffer from type II diabetes mellitus and should have some residual beta cell insulin secreting ability. Cats with transient diabetes mellitus might also be excellent candidates for investigating the antihyperglycemic properties of American ginseng versus placebo. Research to investigate the anti-hyperglycemic effects of American ginseng in feline diabetic patients is therefore warranted to see if any significant benefit in glycemic control can be detected.

If the antihyperglycemic mechanism of American ginseng involves its ability to modulate glucose disposal by affecting insulin sensitivity, then administration of American ginseng to dogs, cats, and people with type I diabetes may still prove to have positive antihyperglycemic benefits. A future pilot study using healthy dogs could be done to determine if oral administration of escalating doses of American ginseng (1g, 3 g and 6 g) given at different times (0 and 40 minutes) prior to an oral glucose tolerance challenge test has an effect on insulin secretion, plasma nitric oxide concentrations, and amelioration or attenuation of postprandial hyperglycemia compared to a placebo. If a significant increase in insulin secretion was seen compared to the placebo, this would support increased insulin secretion versus improved insulin sensitivity in dogs as being important in the mechanism of action of American ginseng in this species.

The significant intra- and inter-dog variability seen in this study may also have affected the ability of this pilot study to detect any significant antihyperglycemic or antihypertensive effects of American ginseng. It was clear that the glycemic control was not equal in all the dogs in this

study. For instance, dog 1 had fairly tight glycemic control with an average glucose nadir of 5.85 mmol/L during all six of his 12-hour glucose curves, and for most of his glucose curves his serum blood glucose stayed below 12 mmol/L. Dog 6, on the other hand, had an average glucose nadir of 10.7 mmol/L, and her serum blood glucose did not stay below 12 for the majority of time during her 12 hour glucose curves. However, since all dogs did qualify for entry into the study based on their glycemic regulation being assessed as good, and because each dog acted as their own control, the effect of intradog variability should have been minimized. Based on the initial fructosamine concentrations for each dog on day 0 of the study the glycemic regulation for each dog would be classified (see Table 3) as excellent in 3 dogs (Dogs 3, 5 and 8), fair in one dog (Dog 2), and poor in 4 dogs (Dogs 1, 4, 6 and 7). Based on the initial glycosylated hemoglobin values for each dog on day 0 of the study the glycemic regulation for all the dogs would be classified as excellent in 3 dogs (Dogs 5, 7 and 8), fair in 3 dogs (Dogs 1, 2 and 3) and poor in 2 dogs (Dogs 4 and 6). However, based on owner assessment of glycemic regulation, all the dogs had good to excellent control and based on their initial glucose curves all the dogs had good to excellent control (see Table 6, Appendix B and figures 1-48). These findings further substantiate the significant degree of intra- and inter-dog variability seen in this study. However, as a previous study (122) has shown, and as can be seen from even a cursory glance of the glucose curves for individual dogs (figures 1-48), there can be tremendous day to day variation in the profile of a 12-hour glucose curve for diabetic dogs. An increased number of study dogs would undoubtedly have helped to minimize the effects of such intra-and inter-dog variability, but this was not feasible or practical given the financial constraints and the difficulty enrolling suitable patients into the study. The relative geographic isolation of Prince Edward Island and the limited

population of diabetic dogs there contributed significantly to our difficulty recruiting suitable dogs for the study.

A continuous glucose monitoring device which is an instrument capable of measuring interstitial glucose concentrations every 5 minutes for up to 72 hours, may prove useful for future studies investigating the effects of herbal remedies for the treatment of diabetes mellitus in dogs and cats (251). These devices use an electrode implanted into the subcutaneous tissues to measure interstitial glucose concentrations, which have been shown to be positively correlated to whole blood glucose concentrations in clinically normal and diabetic dogs and cats (251-252). Such a device was not available at the time of this study, but would have been ideal because it allows glucose curves to be conducted over longer periods of time and potentially even in a dog's home environment. Therefore, more data could have been collected from the individual dogs and the results of 24-hour curves over 3 successive days could have been averaged for analysis. This may have helped minimize the influence of intra-dog variability. These devices also eliminate the need for multiple blood sampling and the stress associated with obtaining these samples, which may interfere with the results of a blood glucose curve. In addition, such devices can be worn by dogs in their home environment. Glucose curves performed in the dog's familiar environment should provide a more accurate assessment of the pet's glycemic control because they help to limit the influence of stress-induced hyperglycemia commonly seen with curves done in the hospital.

Although compliance appeared to be good in this study, this may not have been true and if so could also have influenced the results.

For budgetary reasons, the ginsenoside profile of the commercial ginseng preparation used in

this study was not evaluated. It is possible that the batch or the brand of American ginseng used was of poor quality. If this was the case and either the quantity of the ginsenosides contained in the preparation used were too low, or the profile of the ginsenosides was inappropriate, then this could have resulted in a failure to detect an antihyperglycemic effect compared to the placebo. The lack of standardization within and between commercial ginseng products is a major problem with many unregulated herbal remedies, and several studies that have evaluated different commercial ginseng products confirm this is a problem with this herb (353-257). Because of the poor standardization of ginseng, it is not known whether the observed glucose lowering effects seen in the studies reported would apply to all species of ginseng or even to all American ginseng products, or to different batches of the same American ginseng product (258). Ginsenoside concentrations in commercial ginseng products have been shown to vary as much as 15 fold in capsules and 36 fold in liquid preparations (243). This could be an uncontrolled source of experimental error in this study. Analyses of the ginsenoside profile of the American ginseng product used would have permitted confirmation of the genus and species of ginseng used, and allowed assessment of the quality of the product used.

Phenotypic differences in the response to ginseng administration in people have also been implicated in the variable response seen with this herb (258). In one study, the effect of ginseng type on peak plasma insulin was dependent upon the weight status of the participants. Vietnamese ginseng significantly lowered plasma insulin compared to placebo in overweight participants only (258). Obesity or other causes of insulin resistance, such as hypertriglyceridemia, are sources of biological variability that may affect an individual's response to ginseng. It is possible that an unappreciated phenotypic factor affected the response

to ginseng by the dogs in this study. The limited power of this study would make it difficult to detect significant differences.

Other sources of variability that may have influenced the results of this study include the necessity to change the insulin dose in two of the dogs (Dog 3 and 6) during the course of the study. Dog 3, who received American ginseng first followed by placebo, developed a head tilt and bilateral tarsal joint effusion during the washout phase of the study. Further diagnostic tests and the clinical presentation were consistent with a diagnosis of chronic degenerative joint disease and idiopathic vestibular disease. The dog was not withdrawn from the study, her diabetic control continued to be good and her head tilt gradually resolved over a 3-4 week period. Because of her reduced activity level during this period, her insulin dose and her daily intake of food were both proportionately decreased. Her insulin dose therefore ended up being decreased during the placebo phase of the experiment compared to when she was receiving American ginseng. Evaluation of the serial blood glucose curves from this dog showed that her glycemic control was worse on days 28 and 56 while she was receiving American ginseng compared to days 28 and 56 while she was receiving the placebo. This certainly could have influenced our results, however, because the dog's glycemic control was worse despite the increased insulin dose while on ginseng the change in insulin dose likely would not have masked a beneficial ginseng effect. This dog was still alive 2 years after the end of the study, with no signs of progressive neurologic disease, so there is little doubt that the presumptive diagnosis of idiopathic vestibular disease made during the study was correct. The insulin dose for dog 6 needed to be increased during the placebo phase of the study on day 28. This was necessary because she had a return of clinical signs associated with unregulated diabetes mellitus. The

worsening of this dog's glycemic regulation based on clinical signs coincided with development of a concurrent urinary tract infection and pyoderma. Comparing this dog's overall glycemic regulation throughout this study (see glycemic parameters in Appendixes B and C), it is also clear that this dog's glycemic regulation was never as good as some of the other dogs in this study. Treatment of the dog's urinary tract infection and superficial pyoderma with antibiotics quickly resolved these secondary infections. Despite this, the dog's insulin dose could not be reduced following resolution of these secondary infections based on the results of a subsequent blood glucose curve and serum fructosamine concentration on day 28 of the placebo phase. By day 56 of the placebo phase her control had improved, but her insulin dose was not decreased based on the results of her glucose curve.

At the doses used in this study, American ginseng appears to be safe in dogs. No adverse reactions were reported during the study. Hypoglycemia related to an interaction with the insulin therapy the dogs were receiving was also not reported. One dog (dog 1) did experience a documented episode of hypoglycemia on day 56 of the placebo phase of the trial (see Appendix C), but this was attributed to an accidental insulin overdose by the owner. However, given the small number of dogs in this study, interactions of ginseng with insulin or other oral hypoglycemic supplements or drugs, still remains a possibility.

Contamination of commercial herbal remedies by undeclared pharmaceuticals and potentially toxic levels of heavy metals has been reported (247). Without chemical analysis of the American ginseng product used, it is impossible to completely rule out contamination of the product as a possible reason for the lack of anti-hyperglycemic effect seen in this study. A recent advisory by the American Federal Drug Administration reported that a ginseng preparation

marketed specifically as a diabetes remedy actually contained a sulfonlyurea drug (248). If this was true for the American ginseng product we used in this study it likely would not have impacted glycemic control given that all the dogs had IDDM. However, this could be an issue if American ginseng was administered to cats with type II diabetes that were being treated with other conventional medications (e.g., insulin or other oral hypoglycemic medications). For these reasons, if practitioners know owners of diabetic cats and dogs are administering American ginseng or other herbal remedies to their pets for diabetes mellitus or other chronic conditions, they should warn owners about the potential for interactions with other diabetic medications and the potential for adverse reactions related to contaminants. Certainly owners of diabetic pets who are also receiving anticoagulants or some behavioral drugs such as monoamine oxidase inhibitors need to be warned against giving their pet's ginseng concurrently.

Finally another factor that may have affected the results in this study could be the impact of NSAIDs and acupuncture on glycemic control. Three of the dogs in this study were on NSAIDs (Dog 3, 4, and 6) and one dog (Dog 8) was having acupuncture performed intermittently throughout the study for concurrent osteoarthritis. Dog 8 was also started on a topical NSAID on day 56 of the experimental arm while receiving American ginseng. Insulin resistance is increasingly recognized as a chronic, low-level, inflammatory state characterized by a dynamic proinflammatory milieu of cytokines (259). By suppressing production of these proinflammatory cytokines NSAIDs have been shown to have anti-diabetic effects by decreasing insulin resistance (259). Although the mechanisms by which NSAIDS affect glucose metabolism are not completely known, studies have described both inhibitory effects on hepatic glucose production, and improved insulin action from inhibition of intracellular kinases (Kinase kB and kA) that are

involved in tissue inflammation (260). Similarly acupuncture has been used for the treatment of diabetes and for the treatment and prevention of diabetic complications for several decades. The effects of acupuncture on diabetes have been observed experimentally and clinically (261). Animal experiments have shown that acupuncture can activate glucose-6-phosphatase (an important enzyme in carbohydrate metabolism), enhance insulin synthesis by beta cells, increase the number of insulin receptors on target cells, and can accelerate the utilization of glucose. Data from other studies have shown a beneficial anti-obesity effect of acupuncture, which is one of the most modifiable risk factors for type II diabetes and can impact insulin sensitivity (261-263). However, if these treatments had impacted glycemic control they should have improved the glycemic control in the dogs receiving these medications during the study. This could potentially increase the likelihood of a type I statistical error occurring. If this was the case, an anti-hyperglycemic effect of American ginseng would have being shown when in fact the American ginseng really had no anti-hyperglycemic effect. However, in all cases the dogs were receiving the NSAIDs or acupuncture while on both the placebo and ginseng treatments so the effect of these treatments on the glycemic and systemic blood pressure parameters should have been minimal.

Based on the initial systemic blood pressure measurements for all 8 dogs, four dogs were classified as having normal blood pressure and the remaining four dogs had mild systemic hypertension which did not warrant specific therapy. At the dose administered in this study no significant anti-hypertensive effect of American ginseng treatment was detected; however, the limited power of the study and the fact that none of the dogs had moderate to severe hypertension to begin with, may have impacted the ability of this study to show any beneficial anti-

hypertensive effect of American ginseng therapy in dogs with type I diabetes mellitus.

In conclusion, the results of the present study failed to demonstrate any anti-hyperglycemic or anti-hypertensive effects of American ginseng administration over placebo in dogs with type I diabetes mellitus. However, despite the lack of anti-hyperglycemic or anti-hypertensive effects, administration of this brand of American ginseng at the doses used in this study does appear to be safe in dogs with type I diabetes mellitus. Future research should evaluate the long-term efficacy and safety of American ginseng in cats with type II diabetes mellitus being treated with either insulin or other oral hypoglycemic agents. More work also needs to be done to verify the compositional markers responsible for the antihyperglycemic effects of ginseng seen. This may allow production of purified forms of these compounds for administration. If this were possible, the antihyperglycemic benefits could be taken advantage of and problems associated with the poor standardization and contamination of existing products would be avoided.

References

1. Leiter LA. Alternative and "alternative" diabetes therapies. Can J Diabetes Care 2000;24:21-22.

2. Ryan EA, Pick ME, Marceau C. Use of alternative medicines in diabetes mellitus. Diab Med 2001;18:242-245.

3. Winslow LC, Shapiro H. Physicians want education about complementary and alternative medicine to enhance communication with their patients. Arch Intern Med 2002, 162, 1176-1181.

4. McSherry J, Dunbar CB, Dunbar M. Alternative medicine and diabetes. Can Diab 2000;13:1-2.

5. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States 1990-1997, results of a follow-up national survey. J Am Med Assoc 1998;280:1569-1575.

6. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependant diabetic patients: effects on psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminal propeptide concentration, and body weight. Diabetes Care 1995;18:1373-1375.

7. Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. Anti-hyperglycemic effects of ginseng: comparison between root and berry. Phytomedicine 2003;10:600-605.

8. Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS. Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. Diabetes 2002;51:1851-1858.

9. Vuksan V, Sievenpiper JL, Xu Z, Beljan-Zdravkovic U, Jenkins AL, Arnason JT, Bateman R, Leiter LA, Josse RG, Francis T, Stavro MP. Ginseng and diabetes: A new way to use an old medicine. Can J Diabetes Care 2001;25:111-120.

10. Vuksan V, Sievenpiper JL, Koo VY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E. American ginseng (Panax quinquefolius) reduces postprandial glycemia in nondiabetic subjects with type 2 diabetes mellitus. Arch Intern Med 2000; 160; 1009-1013.

11. Vuksan V, Sievenpiper JL. Herbal remedies in the management of diabetes mellitus: Lessons learned from the study of ginseng. Nutrition, Metabolism and Cardiovascular Diseases 2005; 15: 149-160.

12. Vuksan, Xu Z, Jenkins AL, et al. American ginseng (Panax quinquefolius) improves long-term glycemic control in type 2 diabetes mellitus [abstract]. Diab 49 (suppl 1) 2000;A95.

13. Vuksan V, Sievenpiper JL, Xu Z, Wong EY, Jenkins AL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Stavro MP. Konjac-mannan and American ginseng: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr 2001;20:370S-380S; discussion 381S-383S.

14. Vuksan V, Sievenpiper JL, Wong J, Xu Z, Beljan-Zdravkovic U, Arnason JT, Assinewe V, Stavro MP, Jenkins AL, Leiter LA, Francis T. American Ginseng (Panax quinquefolius L) attenuates postprandial glycemia in a time dependant but not dose dependent manner in healthy individuals. Am J Clin Nutr 2001;73:753-758.

15. Skylar JS. Diabetes Mellitus: Types I and II. *In* Humes HD (eds). Kelley's Textbook of Internal Medicine 4th ed. Philadelphia: Lippincot Williams and Wilkens Co., 2000. pp 2757-2769.

16. Engelking LR. Physiology of the endocrine pancreas. Sem Vet Med Surg (Small Animal) 1997; 12:224-229.

17. Engelking LR. Diabetes Mellitus. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp 112-113.

18. Nelson RW. Diabetes Mellitus. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine Sixth Edition. St. Louis, Elsevier Saunders, 2005, pp 1563-1591.

19. Feldman EC, Nelson RW. Canine diabetes mellitus. *In* Canine and Feline Endocrinology and Reproduction. St. Louis, Saunders, 2004, pp 486-538.

20. Feldman EC, Nelson RW. Feline diabetes mellitus. *In* Canine and Feline Endocrinology and Reproduction. St. Louis, Saunders, 2004, pp 539-579.

21. Hoenig M. Pathophysiology of canine diabetes. Vet Clin North Am Sm Anim Pract 1995;25:553-561.

22. Sai P, Gouin E. Spontaneous animal models for insulin-dependent diabetes (type 1 diabetes). Vet Res 1997;28:223-229.

23. Anderson NR. Deaths: leading causes for 1999. National vital statistics reports, vol. 49. National Center for Health Statistics, MD, Hyattsville. 2001.

24. Fleeman LM, Rand JS. Management of canine diabetes. Vet Clin North Am Small Anim Pract 2001;31:855-879.

25. Plotnick AN, Greco DS. Diagnosis of diabetes mellitus in dogs and cats: contrasts and comparisons. Vet Clin North Am Small Anim Pract 1995;25:563-570.

26. Ling GV, Lowenstine LJ, Pulley LT, Kaneko JJ. Diabetes mellitus in dogs: A review of initial evaluation, immediate and long term management and outcome. J Am Vet Med Assoc 1977;170:521-530.

27. Marmor M, Willeberg P, Glickman LT, Priester WA, Cypess RH, Hurvitz AI.. Epizootiologic patterns of diabetes mellitus in dogs. Am J Vet Res 1982; 43: 465-470.

28. Kramer JW, Nottingham S, Robinette J, Lenz G, Sylvester S, Dessouky MI. Inherited, early onset, insulin-requiring diabetes mellitus in keeshond dogs. Diabetes 1980;29:558-65.

29. Kramer JW. The dm Keeshond dog with inherited, insulin-dependant diabetes. Lessons from animal diabetes 1995;217-223.

30. Kramer JW, Klaassen JK, Baskin DG, Prieur DJ, Rantanen NW, Robinette JD, Graber WR, Rashti L. Inheritance of diabetes mellitus in keeshond dogs. Am J Vet Res 1988;49:428-431.

31. Willams M, Gregory R, Schall W. Diabetes mellitus in a colony of golden retrievers. Proc Fed Am Soc Exp Biol 1980;39:637.

32. Kimmel SE, Ward CR, Henthorn PS, Hess RS. Familial insulin-dependent diabetes mellitus in Samoyed dogs. J Am Anim Hosp Assoc. 2002;38:235-238.

33. Gershwin LJ. Familial canine diabetes mellitus. J Am Vet Med Assoc 1975;167:479-480.

34. Hess RS, Kass PH, Ward CR. Breed distribution of dogs with diabetes mellitus admitted to a tertiary care facility. J Am Vet Med Assoc 2000;216:1414-1417.

35. Panciera DL, Thomas CB, Eicker SW, Atkins CE. Epizootiologic patterns of diabetes mellitus in cats: 333 cases (1980-1986). J Am Vet Med Assoc 1990; 197: 1504-1508.

36. Rand JS, Bobbermien LM, Hendrikz JK, Copland M. Over representation of Burmese cats with diabetes mellitus. Aust Vet J 1997; 75:402-405.

37. Greco DS. Diagnosis of Diabetes Mellitus in cats and dogs. Vet Clin North Am Small Anim Pract. 2001;31:845-853.

38. Harris MI. Definition and Classification of Diabetes Mellitus and the Criteria for Diagnosis. *In* Diabetes mellitus: a fundamental and clinical text. Derek LeRoith, Simeon I. Taylor, Jerrold M. Olefsky (eds). 3rd ed Philadelphia : Lippincott Williams & Wilkins, 2004 pp 457-470.

39. Unger RH, Foster DW. Diabetes Mellitus. *In* Wilson JD, et al (eds): Williams Textbook of Endocrinology, 9th ed. Philadelphia, WB Saunders 1998, pp 973-1059.

40. Nelson RW, Feldman EC. Diabetes mellitus in dogs and cats. Diabetes Spectrum 1992; 5: 324-371.

41. Leahy JL. Natural history of B-cell dysfunction in NIDDM. Diabetes Care 1990;13:992–1010.

42. Scarlett JM, Donoghue S. Associations between body condition and disease in cats. J Am Vet Med Assoc 1998; 212:1725-1731.

43. Baunstein SN, White JR. Trends in the management of type 2 diabetes: an emerging role for insulin. J Manag Care Pharm 2005;11:S2-11.

44. Rand JS, Martin GJ. Management of feline diabetes mellitus. Vet Clin North Am Small Anim Pract 2001;31:881-913.

45. Kirk CA, Feldman EC, Nelson RW. Diagnosis of naturally acquired type-I and type-II diabetes mellitus in cats. Am J Vet Res 1993;54:463-467.

46. Sparkes AH, Adams DT, Cripps PJ, Gruffydd-Jones TJ, Burnett M. Inter- and intra-individual variability of the response to intravenous glucose tolerance testing in cats. Am J Vet Res 1996;57:1294-1298.

47. Hoenig M. Comparative aspects of diabetes mellitus in dogs and cats. Mol Cell Endocrinol 2002;197:221-229.

48. Goossens MM, Nelson RW, Feldman EC, Griffey SM. Response to insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995). J Vet Intern Med 1998;12:1-6.

49. Hall DG, Kelley LC, Gray ML, Glaus TM. et al. Lymphocytic inflammation of pancreatic islets in a diabetic cat. J Vet Diagn Invest 1997;9:98-100.

50. Behrend EN, Greco DS. Treatment of Feline Diabetes mellitus: overview and therapy. Compend Contin Educ Pract Vet 2000;22:423-438.

51. Lutz TA, Rand JS. A review of new developments in type 2 diabetes mellitus in human beings and cats. Br Vet J 1993;149:527-536.

52. Engelking LR. Diabetes mellitus. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp112-113.

53. Alejandro R, Feldman EC, Shienvold FL, Mintz DH. Advances in canine diabetes mellitus research: etiopathology and results of islet transplantation. J Am Vet Med Assoc. 1988;193:1050-1055.

54. Atkins CE, LeCompte PM, Chin HP, Hill JR, Ownby CL, Brownfield MS. Morphologic and immunocytochemical study of young dogs with diabetes mellitus associated with pancreatic islet hypoplasia. Am J Vet Res 1988:49;1577-1581.

55. Gepts W, Toussaint D. Spontaneous diabetes in dogs and cats. A pathological study. Diabetolgia 1967;3:249-265.

56. Sai P, Debray-Sachs M, Jondet A, Gepts W, Assan R. Anti-beta-cell immunity in insulinopenic diabetic dogs. Diabetes 1984;33:135-140.

57. Elie M, Hoenig M. Canine immune mediated diabetes mellitus. A case report. J Am Anim Hosp Assoc 1995;31:295-299.

58. Hoenig M, Dawe DL: A qualitative assay for beta cell antibodies: preliminary results in dogs with diabetes mellitus. Vet Immunol Immunopathol 1992;32:195-203.

59. Haines DM. A re-examination of islet cell cytoplasmic antibodies in diabetic dogs. Vet Immunol Immunopathol 1986;11:225-233.

60. Anderson NV, Strafuss AC. Pancreatic disease in dogs and cats. J Am Vet Med Assoc 1971;159:885-891.

61. Cotton RB, Cornelius LM, Theran P. Diabetes mellitus in the dog: A clinicopathologic study. J Am Vet Med Assoc 1971;159:863-870.

62. Dixon JB, Sanford J. Pathological features of spontaneous canine diabetes mellitus. J Comp Pathol 1962;72:153-167.

63. McCann JP, Concannon PW. Effects of sex, ovarian cycles, pregnancy and lactation on insulin and glucose response to exogenous glucose and glucagons in dogs [abstract] Biol Reprod. 1983;28: 41.

64. Eigenmann JE, Eigenmann RY, Rijnberk A, van der Gaag I, Zapf J, Froesch ER. Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly. Acta Endorcinol 1983;104:167-176.

65. Selman PJ, Mol JA, Rutteman GR, Rijnberk A. Progestin treatment in the dog: Effects on growth hormone, insulin-like growth factor I and glucose homeostasis. Eur J Endocrinol 1994;131:413- 421.

66. Peterson ME, Altszuler N, Nichols CE. Decreased insulin sensitivity and glucose tolerance in spontaneous canine hyperadrenocorticism. Res Vet Sci 1984;36:177-182.

67. van Keulen LJ, Wesdorp JL, Kooistra HS. Diabetes mellitus in a dog with a growth-hormone-producing acidophilic adenoma of the adenohypophysis. Vet Pathol 1996;33:451-453.

68. Ford SL, Nelson RW, Feldman EC, Niwa D. Insulin resistance in three dogs with hypothyroidism and diabetes mellitus. J Am Vet Med Assoc 1993;202:1478-1480.

69. Hoenig M, Ferguson DC. Impairment of glucose tolerance in hyperthyroid cats. J Endocrinol 1989;121:249-251.

70. Behrend EN, Greco DS. Feline diabetes mellitus: evaluation of treatment. Compend Contin Educ Pract Vet 2000; 22: 440-452.

71. Peterson ME. Diagnosis and management of insulin resistance in dogs and cats with diabetes mellitus. Vet Clin North Am Small Anim Pract 1995;25:691-713.

72. Truett AA, Borne AT, Monteiro MP, West DB. Composition of dietary fat affects blood pressure and insulin responses to dietary obesity in dogs. Obes Res 1998;6:137-146.

73. Olefsky J Kolterman O. Mechanisms of insulin resistance in obesity and noninsulin-dependent (type II) diabetes. Am J Med 1981;70:151-168.

74. Truglia JA, Livingston JN, Lockwood DH. Insulin resistance: receptor and post-binding defects in human obesity and non-insulin-dependent diabetes mellitus. Am J Med 1985;79:13-22.

75. Biourge V, Nelson RW, Feldman EC, Willits NH, Morris JG, Rogers QR. Effect of weight gain and subsequent weight loss on glucose tolerance and insulin response in healthy cats. J Vet Intern Med 1997;11:86-91.

76. Fettman MJ, Stanton CA, Banks LL, Johnson DE, Hamar DW, Hegstad RL, Johnston S. Effects of weight gain and loss on metabolic rate, glucose tolerance, and serum lipids in domestic cats. Res Vet Sci 1998;64:11-16.

77. Nelson RW, Griffey SM, Feldman EC, Ford SL. Transient clinical diabetes mellitus in cats: 10 cases (1989-1991). J Vet Intern Med 1999;13:28-35.

78. Unger RH, Grundy S. Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: Implications for the management of diabetes. Diabetologia 1985;28:119- 121.

79. Link KR, Rand JS. Glucose toxicity in cats (Abstr). J Vet Intern Med 1996;10:185.

80. Rand JS, Link KR. Glucose toxicity: its pathogenesis and clinical significance. In Proceedings of the 13th American College of Veterinary Internal Medicine Forum. 1995; p 144.

81. Service FJ. Hypoglycemic disorders. N Engl J Med 1995;332:1144-1152.

82. Cryer PE, Polonsky KS. Glucose homeostasis and hypoglycemia. *In* Diabetes Mellitus. Wilson JD, et al (eds): Williams Textbook of Endocrinology, 9th ed. Philadelphia, WB Saunders 1998, pp 939- 971.

83. Engelking LR. Endocrine pancrease I. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp104-105.

84. Engelking LR. Endocrine pancrease II. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp105-106.

85. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev 2005;26;19-39.

86. Henquin JC. Cell Biology of Insulin Secretion. *In* Joslin's Diabetes Mellitus. Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ (eds),14th ed 2005 Lippincott Williams & Wilkins, Philadelphia, pp 83-107.

87. Engelking LR. Insulin. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp106-107.

88. Engelking LR. Biochemical and physiological manifestations of acute insulin withdrawl. Sem Vet Med Surg (Sm Anim) 1997;12:230-235.

89. Engelking LR. Glucagon. *In* Quick look: Metabolic and endocrine physiology. Enkelking LR ed, 2000 Teton NewMedia, Jackson Hole Wyoming, pp108-109.

90. Collyer JH, Gripper PL. Peripheral neuropathy in a diabetic bitch. Vet Rec 1987;121:207.

91. Katherman AE, Braund KG. Polyneuropathy associated with diabetes mellitus in a dog. Am J Vet Med Assoc 1983;182;522-524.

92. Johnson CA, Kittleson MD, Indrieri RJ. Peripheral neuropathy and hypotension in a diabetic dog. J Am Vet Med Assoc 1983;183:1007-1009.

93. Salgado D, Reusch C, Spiess B. Diabetic cataracts: different incidence between dogs and cats. Schweiz Arch Tierheilkd. 2000;142:349-353.

94. Fleeman LM, Rand JS. Long-term management of the diabetic dog. Waltham Focus 2000; 10: 16-23.

95. Foster SJ. Diabetes mellitus: a study of the disease in the dog and cat in Kent. J Small Anim Pract 1975; 16: 295-315.

96. Struble AL, Feldman EC, Nelson RW, Kass PH. Systemic hypertension and proteinuria in dogs with diabetes mellitus. J Am Vet Med Assoc. 1998;213:822-825.

97. McGuire NC, Schulman R, Ridgway MD, Bollero G. Detection of occult urinary tract infections in dogs with diabetes mellitus. J Am Anim Hosp Assoc. 2002;38:541-544.

98. Greco DS, Broussard JD, Peterson ME. Insulin Therapy. Vet Clin North Amer Small Anim Pract 1995;25:677-689.

99. Freiherr von Bolcshazy G. Examination of immune reaction due to use of swine insulin in diabetic dogs [abstract]. In Proceedings of the World Small Animal Veterinary Association Conference, 1999.

100. Neubauer HP, Schone HH. The immunogenicity of different insulins in several animal species. Diabetes 1978;27:8-15.

101. Feldman EC, Nelson RW, Karam JH. Reduced immunogenicity of pork insulin in dogs with spontaneous insulin-dependant diabetes mellitus (IDDM). Diabetes 1983;32:153A.

102. Harb-Hauser M, Nelson R, Gershwin L. Prevalence of insulin antibodies in diabetic dogs [abstract]. In Proceedings of the 16th American College of Veterinary Internal Medicine Forum. 1997; p 703.

103. Behrend EN. Diabetes mellitus: An update on oral hypoglycemic agents and monitoring options. Vet Med 2003; 97: 743-751.

104. Garcia JL, Bruyette DS. Using oral hypoglycemic agents to treat diabetes mellitus in cats. Vet Med 1998;93:736-742.

105. Porksen NK, Munn SR, Steers JL, Schmitz O, Veldhuis JD, Butler PC. Mechanisms of sulfonylurea's stimulation of insulin secretion in vivo: Selective amplification of insulin secretory burst mass. Diabetes 1996;45:1792-1797.

106. Lebovitz HE. Management of hyperglycemia with oral antihyperglycemic agents in type 2 diabetes. *In* Joslin's Diabetes Mellitus. Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ (eds),14th ed 2005 Lippincott Williams & Wilkins, Philadelphia, pp 687-710.

107. Robertson J, Nelson R, Kass P, Neal L. Effects of the α-glucosidase inhibitor acarbose on postprandial serum glucose and insulin concentrations in healthy dogs. Am J Vet Res 1999; 60: 541-545.

108. Nelson RW, Robertson J, Feldman EC, Briggs C. Effect of the alpha-glucosidase inhibitor on control of glycemia in dogs with naturally acquired diabetes mellitus. J Am Vet Med Assoc 2000;216:1265-1269.

109. Spears JW, Brown TT, Sunvold GD, et al. Influence of chromium on glucose metabolism and insulin sensitivity. In Reinhart GA, Carey DP (eds): Recent advances in canine and feline nutrition, vol II. 1998 IAMS Nutrition symposium Proceedings. 1998; p 103.

110. Schachter S, Nelson RW, Kirk C. Oral chromium picolinate and control of glycemia in insulin-treated diabetic dogs. J Vet Intern Med 2001;15:379-84.

111. Remillard RL. Nutritional management of diabetic dogs. Compend Contin Educ Pract Vet 1999;21:699-713.

112. Blaxter AC, Cripps PJ, Gruffydd-Jones TJ. Dietary fiber and postprandial hyperglycemia in normal and diabetic dogs. J Small Anim Pract 1990;31:229-233.

113. Nelson RW, Ihle SL, Lewis LD, Salisbury SK, Miller T, Bergdall V, Bottoms GD. Effects of dietary fiber supplementation on glycemic control in dogs with alloxan-induced diabetes mellitus. Am J Vet Res 1991;52:2060-2060.

114. Nelson RW, Briggs C, Scott-Moncrieff JC, et al. Effect of dietary fiber type and quantity on control of glycemia in diabetic dogs [abstract]. In Proceedings of the 18th American College of Veterinary Internal Medicine Forum, Seattle 2000, p 753.

115. Kimmel SE, Michel KE, Hess RS, Ward CR. Effects of insoluble and soluble dietary fiber on glycemic control in dogs with naturally occurring insulin-dependant diabetes mellitus. J Am Vet Med Assoc 2000;216:1076-1081.

116. Nelson RW, Duesberg CA, Ford SL, Feldman EC, Davenport DJ, Kiernan C, Neal L. Effect of dietary insoluble fiber on control of glycemia in dogs with naturally acquired diabetes mellitus. J Am Vet Med Assoc 1998;212:380-386.

117. Nuttall FQ. Dietary fiber in the management of diabetes. Diabetes 1993;42:503-508.

118. Miller E. Long-term monitoring of the diabetic dog and cat. Clinical signs, serial blood glucose determinations, urine glucose, and glycated blood proteins. Vet Clin North Am Small Anim Pract 1995;25:571-584.

119. Briggs C, Nelson RW, Feldman EC, Elliott DA, Neal LA. Reliability of history and physical examination findings for assessing control of glycemia in dogs with diabetes mellitus: 53 cases (1995-1998). J Am Vet Med Assoc 2000;217:48-53.

120. Stein JE, Greco DS. Portable blood glucose meters as a means of monitoring blood glucose concentrations in dogs and cats with diabetes mellitus. Clin Tech Small Anim Pract 2002;17:70-72.

121. Thompson B. Monitoring comes of age. The Editor's Desk. Compend Contin Educ Pract Vet 2006;28:252-254.

122. Fleeman LM, Rand JS. Evaluation of day-to-day variability of serial blood glucose concentration curves in diabetic dogs. J Am Vet Med Assoc 2003;222:317-21.

123. Crenshaw KL. CVT Update: monitoring treatment of diabetes mellitus in dogs and cats. In Kirk's Current Veterinary Therapy. Small Animal Practice. Bonagura JD (ed). Philadelphia : W.B. Saunders, 2000, pp 348-350.

124. Feldman RW, Nelson EC. Complications associated with insulin treatment of diabetes mellitus. In Kirk's Current Veterinary Therapy. Small Animal Practice. Bonagura JD (ed). Philadelphia : W.B. Saunders Co., 2000, pp 354-357.

125. Wess G, Reusch C. Capillary blood sampling from the ear of dogs and cats and use of portable meters to measure glucose concentration. J Small Anim Pract 2000; 41:60-66.

126. Mathes MA. Home monitoring of the diabetic pet. Clin Tech Small Anim Pract 2002:17:86-95.

127. Casella M, Wess G, Hassig M, Reusch CE. Home monitoring of blood glucose concentration by owners of diabetic dogs. J Small Anim Pract 2003;44:298-305.

128. Elliott DA, Nelson RW, Feldman EC, Neal LA. Glycosylated hemoglobin concentrations in the blood of healthy dogs and dogs with naturally developing diabetes mellitus, pancreatic beta-cell neoplasia, hyperadrenocorticism and anemia. J Am Vet Med Assoc 1997;211:723-727.

129. Jensen AL. Glycated blood proteins in canine diabetes mellitus. Vet Rec 1995;137:401-405.

130. Marca MC, Loste A. Glycosylated hemoglobin assay of canine blood samples. J Small Anim Pract 2000;41:189-192.

131. Jensen AL. Various protein and albumin corrections of the serum fructosamine concentration in the diagnosis of canine diabetes mellitus. Vet Res Commun 1993;17:13-23.

132. Graham PA, Nash AS. The critical evaluation of tests for monitoring glycemic control in canine diabetes mellitus [abstract]. J Vet Intern Med 1997;11:123.

133. Elliott DA, Nelson RW, Reusch CE, Feldman EC, Neal LA. Comparison of serum fructosamine and blood glycosylated hemoglobin concentrations for assessment of glycemic control in cats with diabetes mellitus. J Am Vet Med Assoc. 1999;214:1794-1798.

134. Loste A, Marca MC. Fructosamine and glycated hemoglobin in the assessment of glycaemic control in dogs. Vet Res 2001;32:55-62.

135. Loste A, Marca MC. Study of the effect of total serum protein and albumin concentrations on canine fructosamine concentration. Can J Vet Res 1999;63:138-141.

136. Crenshaw KL, Peterson ME, Heeb LA, Moroff SD, Nichols R. Serum fructosamine concentration as an index of glycemia in cats with diabetes mellitus and stress hyperglycemia. J Vet Intern Med 1996;10:360-364.

137. Jain NC. Erythrocyte physiology and changes in disease. In Essentials of Veterinary Hematology. Jain NC (eds); Philadelphia, WB Saunders Co., 1993 pp133.

138. Loste A, Marca MC. Diabetes mellitus in dogs: a study of the critical difference in canine serum fructosamine. Vet Rec. 1998;142:547-8.

139. Staudacher G. Fructosamine as a valuable criterion for the evaluation of diabetic animals and its photometric determination. Tierarztl Prax. 1990;18:441-446.

140. Kawamoto M, Kaneko JJ, Heusner AA, Feldman EC, Koizumi I. Relation of fructosamine to serum protein, albumin, and glucose concentration in healthy and diabetic dogs. Am J Vet Res 1992;53:851–855.

141. Reusch CE, Liehs MR, Hoyer M, Vochezer R. Fructosamine: A new parameter for diagnosis and metabolic control in diabetic dogs and cats. J Vet Intern Med 1993;7:177-182.

142. Coppo JA, Coppo NB. Serum fructosamine: a reference interval for a heterogenous canine population. Vet Res Commun 1997;21:471-476.

143. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med. 1998;128:517-23.

144. Rosenzweig JL. Diabetes and the healthcare system: economic and social costs. *In* Joslin's Diabetes Mellitus. Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ (eds),14th ed 2005 Lippincott Williams & Wilkins, Philadelphia, pp 777-792.

145. Davidson JA. Treatment of the patient with diabetes: importance of maintaining target HbA (1c) levels. Curr Med Res Opin 2004;20:1919-1927.

146. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. Arch Intern Med 1994;154:2169-2178.

147. Gaster B, Hirsch IB. The effects of improved glycemic control on complications in type 2 diabetes. Arch Intern Med 1998;158:134-140.

148. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med1993;328:1676-85.

149. King GL, Loeken MR. Hyperglycemia-induced oxidative stress in diabetic complications. Histochem Cell Biol 2004;122:333-338.

150. Basher AW, Roberts SM. Ocular manifestations of diabetes mellitus: diabetic cataracts in dogs. Vet Clin North Am Small Anim Pract 1995;25:661-676.

151. Beam S, Correa MT, Davidson MG. A retrospective-cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases. Vet Ophthalmol 1999;2:169-172.

152. Barnett KC. Diabetic retinopathy in the dog. Br J Ophthalmol 1981;65:312-314.

153. Toole DO, Miller GK, Hazel S. Bilateral retinal microangiopathy in a dog with diabetes mellitus and hypoadrenocorticism. Vet Pathol 1984;21:120-121.

154. Patz A, Berkow JW, Maumenee AE, Cox J. Studies on diabetic retinopathy. II. Retinopathy and nephropathy in spontaneous canine diabetes. Diabetes 1965;14:700-708.

155. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes 1987;36:808-12.

156. Munana KR. Long-term complications of diabetes mellitus, part I: retinopathy, nephropathy, neuropathy. Vet Clin North Am Small Anim Pract 1995;25:715-730.

157. Mizisin AP, Shelton GD, Burgers ML, Powell HC, Cuddon PA. Neurological complications associated with spontaneously occurring feline diabetes mellitus. J Neuropathol Exp Neurol 2002;61:872-84.

158. Kramek BA, Moise NS, Cooper B, Raffe MR. Neuropathy associated with diabetes mellitus in the cat. J Am Vet Med Assoc 1984;184:42-45.

159. Braund KG, Steiss JE. Distal neuropathy in spontaneous diabetes mellitus in the dog. Acta Neuropathol 1982;57:263-269.

160. Steiss JE, Orsher AN, Bowen JM. Electrodiagnostic analysis of peripheral neuropathy in dogs with diabetes mellitus. Am J Vet Res 1981;42:2061-2064.

161. Mizisin AP, Shelton GD, Wagner S, Rusbridge C, Powell HC. Myelin splitting, Schwann cell injury, and demyelination in feline diabetic neuropathy. Acta Neuropathol 1998;95:171-174.

162. Janle-Swain E, Thornhill JA, Carter JM, Hinsman E, Jackson HD, Ash SR. Case study of a diabetic dog with chronic membranous glomerulopathy treated with continuous intraperitoneal insulin infusion. Am J Vet Res 1982;43:2044-2049.

163. Steffes MW , Buchwald H, Wigness BD, Groppoli TJ, Rupp WM, Rohde TD, Blackshear PJ, Mauer SM. Diabetic nephropathy in the uninephrectomized dog. Microscopic lesions after one year. Kidney Int 1982;21:721 -724.

164. Kirsch M, Reusch C. [Urine characteristics in dogs with diabetes mellitus. Is there a diabetic nephropathy in the dog?] Tierarztl Prax. 1993;21:345-348.

165. Jeraj K, Basgen J, Hardy RM, Osborne CA, Michael AF. Immunofluorescence studies of renal basement membranes in dogs with spontaneous diabetes. Am J Vet Res 1984;45:1162-1165.

166. Sowers JR, Zemel MB. Clinical implications of hypertension in the diabetic patient. Am J Hyperten 1990;3:415-424.

167. Christopher MM. Hematologic complications of diabetes mellitus. Vet Clin North Am Small Anim Pract 1995;25:625-637.

168. Sottiaux J. Atherosclerosis in a dog with diabetes mellitus. J Small Anim Pract 1999;40:581-584.

169. Webb CB. Troubleshooting the diabetic small animal patient. Clin Tech Small Anim Pract 2002;17:79-85.

170. Duesberg C, Havel P, Elliot E, et al. Impaired counterregulatory response to insulin-induced hypoglycemia in diabetic dogs [abstract]. J Vet Intern Med 1995;9:181.

171. Hackendahl N, Schaer M. Insulin resistance in diabetic patients: mechanisms and classifications. Compend Contin Educ Pract Vet 2006:28:262-270.

172. Hackendahl N, Schaer M. Insulin resistance in diabetic patients: causes and management. Compend Contin Educ Pract Vet 2006:28:271-283.

173. Wolfsheimer KJ. Problems in diabetes mellitus management. Insulin resistance. Probl Vet Med 1990;2:591-601.

174. Vail DM, Ogilvie GK, Wheeler SL, Fettman MJ, Johnston SD, Hegstad RL. Alterations in carbohydrate metabolism in canine lymphoma. J Vet Intern Med 1990;4:8-11.

175. Astin JA. Why patients use alternative medicine: results of a national study. J Am Med Assoc 1998;279:1548-1553.

176. Shapiro K, Gong WC. Natural products used for diabetes. J Am Pharm Assoc 2002;42:217-226.

177. Savickiene N, Dagilyte A, Lukosius A, Aitkevicius V. [Importance of biologically active components and plants in the prevention and complication of diabetes mellitus.] Medicina 2002; 38: 970-975.

178. Borins M. The dangers of using herbs. What your patients need to know. Postgrad Med 1998;104:91-5, 99-100.

179. Cheng TO. Panax (Ginseng) is not a panacea. Arch Intern Med 2000;160:3329.

180. Novelli S. Agriculture and Agri Food Canada. Bi-weekly Bulletin 2003 Volume 16 Number 5. http://www.agr.gc.ca/mad-dam/e/bulletine/v16e/v16n05_e.htm

181. O'Brian J. A new way to use and old medicine: American ginseng and diabetes. Diab Dialogue 2001;18-21.

182. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomized clinical trials. Eur J Clin Pharmacol 1999;55:567-575.

183. Sticher O. Biochemical, pharmaceutical and medical perspectives of ginseng. Amer Chem Soc 1998;221-240.

184. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 2003;26:1277-1294.

185. Li W, Gu C, Zhang H, Awang DV, Fitzloff JF, Fong HH, van Breemen RB. Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish Panax ginseng C. A. Meyer (Asian ginseng) and Panax quinquefolius L. (North American ginseng). Anal Chem. 2000;72:5417-22.

186. Xie JT, Aung HH, Wu JA, Attel AS, Yuan CS. Effects of American ginseng berry extract on blood glucose levels in ob/ob mice. Am J Chin Med 2002;30:187-194.

187. Xie JT, Wu JA, Mehendale S, Aung HH, Yuan CS. Anti-hyperglycemic effect of the polysaccharides fraction from American ginseng berry extract in *ob/ob* mice. Phytomedicine 2004;11:182-187.

188. Kiefer D, Pantuso T. Panax ginseng. Am Fam Physician 2003;68:1539-1542.

189. Coleman CI, Hebert JH, Reddy P. The effects of Panax ginseng on quality of life. J Clin Pharm Ther 2003;28:5-15.

190. Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer. Drugs Exp Clin Res 1990;16:537-542.

191. Gillis CN. Panax ginseng pharmacology: a nitric oxide link? Biochem Pharmacol 1997;54:1-8.

192. Xu Z, Beljan-Zdravkovic U, Bateman RM, Jenkins AL, Sievenpiper JL, Stavro MP, Vuksan V. American ginseng increases plasma nitric oxide concentration in type 2 diabetes. Can J Diabetes Care 2000;24:100.

193. Chang HK, Jang MH, Lim BV, Lee TH, Shin MC, Shin MS, Kim H, Kim YP, Kim EH, Kim CJ. Administration of ginseng radix decreases nitric oxide synthase expression in the hippocampus of streptozotocin-induced diabetic rats. Am J Chin Med 2004;32:497-507.

194. Vasavada N, Agarwal R. Role of oxidative stress in diabetic nephropathy. Adv Chronic Kidney Dis 2005;12:146-154.

195. Neri S, Signorelli SS, Torrisi B, Pulvirenti D, Mauceri B, Abate G, Ignaccolo L, Bordonaro F, Cilio D, Calvagno S, Leotta C. Effects of antioxidant supplementation

on postprandial oxidative stress and endothelial dysfunction: a single-blind, 15-day clinical trial in patients with untreated type 2 diabetes, subjects with impaired glucose tolerance, and healthy controls. Clin Ther 2005;27:1764-73.

196. Wardle EN. Vascular permeability in diabetics and implications for therapy. Diabetes Res Clin Pract 1994;23:135-139.

197. Green K, Brand MD, Murphy MP. Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes. Diabetes 2004;53:S110-118.

198. Jung CH, Seog HM, Choi IW, Choi HD, Cho HY. Effects of wild ginseng (Panax ginseng C.A. Meyer) leaves on lipid peroxidation levels and antioxidant enzyme activities in streptozotocin diabetic rats. J Ethnopharmacol 2005;98:245-50.

199. Ryu JK, Lee T, Kim DJ, Park IS, Yoon SM, Lee HS, Song SU, Suh JK. Free radical-scavenging activity of Korean red ginseng for erectile dysfunction in non-insulin-dependent diabetes mellitus rats. Urology 2005;65:611-615.

200. Bae JW, Lee MH. Effect and putative mechanism of action of ginseng on the formation of glycated hemoglobin in vitro. J Ethnopharmacol 2004;91:137-140.

201. Teng CM, Kuo SC, Ko FN, Lee JC, Lee LG, Chen SC, Huang TF. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. Biochim Biophys Acta 1989;990:315-320.

202. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. J Am Med Assoc 1979;241:1614-1615.

203. Vuksan V, Stavro MP, Sievenpiper JL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Xu Z. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care 2000;23:1221-1226.

204. Rotshteyn Y, Zito SW. Application of modified in vitro screening procedure for identifying herbals possessing sulfonylurea-like activity. J Enthnopharm 2004;93:337-344.

205. Kimura M, Waki I, Chujo T, Kikuchi T, Hiyama C, Yamazaki K, Tanaka O. Effects of hypoglycemic components in ginseng radix on blood insulin level in alloxan diabetic mice and one insulin release from perfused rat pancreas. J Pharmacobiodyn1981;4:410-417.

206. Kimura M, Suzuki J. The pattern of action of blended Chinese traditional medicines to glucose tolerance curves in genetically diabetic KK-CAy mice. J Pharmacobiodyn 1981;4:907-15.

207. Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E, Yano H, Tanigawa K, Seino Y. Effect of ginseng radix on GLUT 2 protein content in mouse liver in normal and epinephrine-induced hyperglycemic mice. Biol Pharm Bull 1996;19:1238-1240.

208. Martinez B, Staba EJ. The physiological effects of Aralia, Panax, and Eleutherocooccus on exercised rats. Jpn J Pharmacol 1984;35:79-85.

209. Yokozawa T, Kobayashi T, Oura H, Kawashima Y. Studies on the mechanism of the hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats. Chem Pharm Bull 1985;33:869-872.

210. Kimura M, Waki I, Tanaka O, Nagai Y, Shibata S. Pharmacological sequential trials for the fractionation of components with hypoglycemic activity in alloxan diabetic mice from ginseng radix. J Pharmacobiodyn1981;4:402-409.

211. Chung SH, Choi CG, Park SH. Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanisms in KKAy mice. Arch Pharm Res 2001;24:214-218.

212. Yun SN, Moon SJ, Ko SK, Im BO, Chung SH. Wild ginseng prevents the onset of high-fat diet induced hyperglycemia and obesity in ICR mice. Arch Pharm Res 2004;27:790-796.

213. Ng TB, Yeung HW. Hypoglycemic constituents of Panax ginseng. Gen Pharmacol 1985;16:549-552.

214. Konno C, Sugiyama K, Kano M, Takahashi M, Hikino H Isolation and hypoglycaemic activity of panaxans A, B, C, D and E, glycans of Panax ginseng roots. Planta Med 1984; 50: 434-436.

215. Konno C, Murakami M, Oshima Y, Hikino H. Isolation and hypoglycemic activity of panaxans Q, R, S, T and U, glycans of Panax ginseng roots. J Ethnopharmacol 1985;14:69-74.

216. Oshima Y, Konno C, Hikino H. Isolation and hypoglycemic activity of panaxans I, J, K, and L, glycans of Panax ginseng roots. J Ethnopharmacol 1985;14:255-259.

217. Hikino H, Takahashi M, Otake K, Konno C. Isolation and hypoglycemic activity of eleutherans A, B, C, D, E, F and G: glycans of Eleutherococcus senticosus roots. J Nat Prod 1986;49:293-297.

218. Oshima Y, Sato K, Hikino H. Isolation and hypoglycemic activity of quiquefolans A, B, and C glycans of Panax quinquefolium roots. J Nat Prod. 1987;50:188-190.

219. Vuksan V, Sievenpiper JL, Wong J, Xu Z, Beljan-Zdravkovic U, Arnason JT, Assinewe V, Stavro MP, Jenkins AL, Leiter LA, Francis T. American Ginseng (Panax quinquefolius L) attenuates postprandial glycemia in a time dependant but not dose dependent manner in healthy individuals. J Am Clin Nutr 2001;73:753-758.

220. Vuksan V, Stavro MP, Sievenpiper JL, Koo VY, Wong E, Beljan-Zdravkovic U, Francis T, Jenkins AL, Leiter LA, Josse RG, Xu Z. American ginseng improves glycemic control in individuals with normal glucose tolerance: effect of dose and time escalation. J Am Coll Nutr 2000;19:738-744.

221. Jenkins L, Starvo MP, Sievenpiper JL, et al. Effect of dose and time escalation of American ginseng on postprandial glycemia in individuals with normal glucose tolerance. Can J Diab Care 2000;24; 87.

222. Starvo PM, Woo M, Heim TF, Leiter LA, Vuksan V. North American ginseng extract exerts a neutral effect on blood pressure in individuals with hypertension. Hypertension 2005;46,406-411.

223. Stavro PM, Woo M, Leiter LA, Heim TF, Sievenpiper JL, Vuksan V. Long-term intake of North American ginseng has no effect on 24-hour blood pressure and renal function. Hypertension 2006;47:791-796.

224. Starvo MP, Xu Z, Jenkins A, et al. American Ginseng improves blood pressure in type 2 diabetes [Abstract]. Can J Diab Care 2000; 24: 68.

225. Waki I, Kyo H, Yasuda M, Kimura M. Effects of hypoglycemic component of ginseng radix on insulin biosynthesis in normal and diabetic animals. J Pharm Dyn 1982; 5: 547-554.

226. Onomura M, Tsukada H, Fukuda K, Hosokawa M, Nakamura H, Kodama M, Ohya M, Seino Y. Effects of ginseng radix on sugar absorption in the small intestine. Am J Chin Med 1999;27:347-354.

227. Jenkins DJ, Wolever TM, Leeds AR, Gassull MA, Haisman P, Dilawari J, Goff DV, Metz GL, Alberti KG. Dietary fibers, fiber analogues, and glucose tolerance: importance of viscosity. Br Med J 1978;1:1392-1394.

228. Jenkins DJ, Taylor RH, Nineham R, Goff DV, Bloom SR, Sarson D, Alberti KG. Combined use of guar and acarbose in reduction of postprandial glycemia. Lancet 1979;2:924-927.

229. Roy D, Perrault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscle and adipose tissue in vivo is NO dependant. Am J Physiol 1998;274:E692-699.

230. Spinas GA, Laffranchi R, Francoys I, David I, Richter C, Reinecke M. The early phase of glucose-stimulated insulin secretion requires nitric oxide. Diabetologia 1998;41:292-299.

231. Vuksan V, Sievenpiper JL, Koo VYY, Beljan U, Xu Z: American ginseng (Panax quinquefolius L.) reduces postprandial glycemia when taken prior to the test meal. Proceedings of the 17th International symposium of Diabetes and Nutrition, p. 12, A17, Versailles, France, July 1999.

232. Salim KN, McEwen BS, Chao HM. Ginsenoside Rb1 regulates ChAT, NFG and trkmRNA expression in the rat brain. Brain Res Mol Brain Res 1997;47:177-182.

233. Yamaguchi Y, Higashi M, Kobayashi H. Effects of ginsenosides on maze performance and brain choline acetyltransferase activity in scopolamine-treated young rats and aged rats. Eur J Pharmacol 1997;329:37-41.

234. Kim HS, Lee JH, Goo YS, Nah SY. Effects of ginsenosides on Ca2+ channels and membrane capacitance in rat adrenal chromaffin cells. Brain Res Bull 1998;46:245-251.

235. Tachikawa E, Kudo K, Harada K, Kashimoto T, Miyate Y, Kakizaki A, Takahashi E. Effects of ginseng saponins on responses induced by various receptor stimuli. Eur J Pharmacol 1999;369:23-32.

236. Kudo K, Tachikawa E, Kashimoto T, Takahashi E. Properties of ginseng saponin inhibition of catecholamines secretion in bovine adrenal chromaffin cells. Eur J Pharmcol 1998;341:139-144.

237. Lekas MC, Fisher SJ, El-Bahrani B, van Delangeryt M, Vranic M, Shi ZQ. Glucose uptake during centrally induced stress is insulin dependent and enhanced by adrenergic blockade. J Appl Physiol 1999;87:722-731.

238. Xie H, Lautt WW. Insulin resistance caused by hepatic cholinergic interruption and reversed by acetylcholine administration. A J Physiol 1996;271:E587-592.

239. Chen NG, Romsos DR. Enhanced sensitivity of pancreatic islets from preobese 2-week-old ob/ob mice to neurohormonal stimulation of insulin secretion. Endocrinology 1995;136:505-511.

240. Tassava TM, Okuda T, Romsos DR. Insulin secretion from ob/ob mouse pancreatic islets: effects of neurotransmitters. Am J Physiol 1992;262:E338-343.

241. Lee WK, Kao ST, Liu IM, Cheng JT. Increase of insulin secretion by ginsenoside Rh2 to lower plasma glucose in Wistar rats. Clin Exp Pharmacol Physiol 2006;33:27-32.

242. Wang BX, Zhou QL, Yang M, Wang Y, Cui ZY, Liu YQ, Ikejima T. Hypoglycemic mechanism of ginseng glycopeptide. Acta Pharmacol Sin 2003; 24:61-6.

243. Harley MR, Henderson GL, Gershwin ME, Stern JS, Hickman RM. Variability in commercial ginseng products: an analysis of 25 preparations. Am J Chin Nutr 2001;73:1101-1106.

244. Sievenpiper JL, Arnason JT, Vidgen E, Leiter LA, Vuksan V. A systematic quantitative analysis of the literature of the high variability in ginseng (Panax spp.): should ginseng be trusted in diabetes? Diabetes Care 2004;27:839-40.

245. Sticher O. Getting to the root of ginseng. Chemtech 1998;26-31.

246. http://www.consumerlab.com/results/ginseng.asp Product review Ginseng.

247. Ko RJ. Adulternats in Asian patent medicine. N Engl J Med 1998;339;847.

248. Leiter LA. Alternative and "alternative" diabetes therapies. Can J Diabetes Care 2000;24:21-22.

249. Bone K. Dosage concentrations in herbal medicine. Br J Phytotherapy 1993/1994; 3:128-137.

250. Tetsutani T, Yamamura M, Yamaguchi T, Onoyama O, Kono M. Can red ginseng control blood glucose in diabetic patients? The Ginseng Review 2000:28;44-47.

251. Wiedmeyer CE, Johnson PJ, Cohn LA, Meadows RL. Evaluation of a continuous glucose monitoring system for use in dogs, cats, and horses. J Am Vet Med Assoc 2003;223:987-92.

252. DeClue AE, Cohn LA, Kerl ME, Wiedmeyer CE. Use of continuous blood glucose monitoring for animals with diabetes mellitus. J Am Anim Hosp Assoc 2004;40:171-3.

253. Wang W, Sakuma T, Asafu-Adjaye E, Shiu GK. Determination of ginsenosides in plant extracts from Panex ginseng and Panex quinquefolius L. by LC/MS/MS. Anal Chem 1999;71:1579-1584.

254. Chan TW, But PP, Cheng SW, Kwok IM, Lau FW, Xu HX. Differentiation and authentication of Panax ginseng, Panax quinquefolius, and ginseng products by using HPLC/MS. Anal Chem 2000;72:1281-1287.

255. Vanhaelen-Fastre RJ, Faes ML, Vanhaelen MH. High-performance thin-layer chromatographic determination of six major ginsenosides in Panax ginseng. J Chromatogr A 2000; 868:269-276.

256. Ligor T, Ludwiczuk A, Wolski T, Buszewski B. Isolation and determination of ginsenosides in American ginseng leaves and root extracts by LC-MS. Anal Bioanal Chem 2005;383:1098-105.

257. Cui J. Identification and quantification of ginsenosides in various commercial ginseng preparation. Eur J Pharm Sci 1995;3:77-385.

258. Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V. Decreasing, Null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: the role of ginseonsides. J Am Coll Nutr 2004; 23: 248-258.

259. Nobles-James C, James EA, Sowers JR. Prevention of cardiovascular complications of diabetes mellitus by aspirin. Cardiovasc Drug Rev 2004; 22: 215-226. Review.

260. Haas RM, Li P, Chu JW. Glucose-lowering effects of sulfasalazine in type 2 diabetes. Diabetes Care 2005;28:2238-2239.

261. Dey L, Attele AS, Yuan CS. Alternative therapies for type 2 diabetes. Altern Med Rev 2002; 7: 45-58.

262. Chen JF, Wei J.Changes of plasma insulin level in diabetics treated with acupuncture. J Tradit Chin Med 1985; 5: 79-84.

263. Hu H. A review of treatment of diabetes by acupuncture during the past forty years. J Tradit Chin Med 1995;15:145-54.

Appendix A

Health Questionnaire for Normal Dogs enrolled in the Ginseng Study

Please fill out this questionnaire. All questions require an answer. If the answer is unknown please state this.

General Health Information

Owners Name: _____ Date: _____

Dogs name: _____ Age of dog: _____

Sex of dog: M F Spayed/Neutered: Y N

Length of time you have owned your dog _____

When was your dog's last health exam? _____

When was your dog last vaccinated? _____

Diet

What diet do you feed your dog? _____

How much do you feed your dog daily (please supply a standard cup measurement?

_____

Rate your dog's appetite (circle one): 1 2 3 4 5

1 – POOR: very selective, only eats human food
2 – FAIR: eats most of his/her dog food but never eats all food offered
3 – GOOD: eats all food provided and is content.
4 – EXCELLENT: Eats all food offered and begs for treats and will eat anything eatable

How much water does your dog consume on a daily basis (estimate in cups)? Please measure the amount of water provided on a minimum of three days prior to starting medications.

_____

Has there been any change in your dog's appetite in the last 2 months? _____

General Health

Do you have any other pets in your household? If so how many and what species? _____

_____

Does your dog spend the majority of his/her time (circle one):
Indoors Outdoors Other (specify) _____

Describe your dog's energy level on a scale of 1 to 4: _____
1 - lethargic – sleep or rests most of the day > 16 hrs a day
2 - fair – exercises minimally but enjoys slow walks; sleeps between 14 and 16 hrs /day
3 - moderate – runs and plays when interacted with, but sleeps between 12 and 14 hrs/ day
4 - excellent – very energetic, active for much of the day; sleeps less than 10 hrs / day

Rate your dog's mental agility (circle one): Poor Good Excellent
Poor – slow to learn
Good – shows ability to learn but is not focused
Excellent – readily learns new commands

Please check below if your dog (elaborate if possible):
1. has ever had a major operation (other than a spay or neuter procedure) _____
2. has ever had a major medical problem requiring hospitalization or extended outpatient care _____
3. suffers from chronic (recurring) eye, ear or skin infections _____
4. has been on antibiotics for any reason in the last 3 months _____
   - If so, for what reason? _____
5. has ever had a drug reaction _____
6. has vomited more than once in the last month _____
7. has had an episode of diarrhea lasting more than 24 hours in the last month _____
8. regularly coughs or sneezes _____
9. has a history of seizures _____
10. has experienced any weight gain or weight loss (more than 2-3 lbs) in the last 4 months _____
11. has any unusual behavioral habits _____

Is there anything else regarding your pet's health or activity level you think it is important for us to know? _____

Diabetes Information

When was your dog first diagnosed with diabetes mellitus? _____

What type of insulin does your dog receive? _____

What dose of insulin does your dog receive? _____

How long has your dog been on this dose of insulin? _____

When was the last glucose curve done on your dog? _____

Has your dog ever been hospitalized overnight due to diabetes? _____

Has your dog been diagnosed with any of the following diseases that interfere with diabetic regulation (circle if appropriate)?

Cushings (hyperadrenocorticism)	Kidney disease
Liver disease	Cancer
Infection	Heart disease
Pancreatitis (or chronic inflammation elsewhere)	
Other (specify) _____	

Rate the level of control of your dog's diabetes mellitus? (circle one): Poor Good Excellent

- Poor – my dog continues to have the clinical signs typical of diabetes despite appropriate daily insulin injections (frequent urination, increased thirst, increased appetite, weight loss)

- Good – the clinical signs my dog showed prior to treatment (frequent urination, increased thirst, increased appetite, weight loss) have improved with daily insulin therapy but are still present to some extent

- Excellent – my dog's response to insulin therapy has been remarkable and all the clinical signs he showed before starting insulin therapy (frequent urination, increased thirst, increased appetite, weight loss) are dramatically improved or resolved

American Ginseng in the Treatment of Insulin-dependent Diabetes Mellitus in Dogs

It has been shown that humans with diabetes mellitus who are treated with American ginseng in addition to their usual treatments have improved sugar control. To determine if the same results occur in dogs, a study is underway to evaluate the efficacy of American Ginseng as an adjunct therapy in dogs with insulin-dependent diabetes mellitus. If ginseng consumption can lower the blood sugar response to food in dogs as it does in people, then the overall blood sugar levels may be improved, thus decreasing the risk of diabetic complications.

I, _____ consent to enrollment of my dog _____ in the study conducted by the Atlantic Veterinary College to evaluate the use of American ginseng as an additional treatment for diabetes mellitus. I understood that my dog will have a complete physical examination, blood and urine tests, blood pressure measurement, and a blood glucose curve evaluated initially and at monthly intervals while enrolled in the study. During two months of this time, my dog will receive oral American ginseng in addition to his/her usual insulin treatment, and during another two months he/she will receive a placebo in addition to the usual insulin treatment. I will be required to complete a short daily diary card concerning my dog and to bring him/her to the clinic for scheduled evaluations. I give my permission for the results of these tests to be included in the full study to help all dogs. I understand that neither I nor my dog will be identified in any of the study results.

If my dog is good overall health, is receiving insulin therapy for management of his/her diabetes and has moderate to good blood sugar control, has no major concurrent illness, and is receiving no other medications with the exception of antibiotics or l-thyroxine, he or she will be enrolled in the study. I understand there will be no charge for any of the tests performed while my pet is enrolled in the study. In addition, if I and my dog comply with the study I will receive a sum of $200 at the end of the study.

I understand the purpose of the study. All risks and possible benefits of this research study have been fully explained by the study veterinarian. I understand that I am free to withdraw my dog from this study at any time or that the veterinarian may remove my dog from the study if she believes it is in the best interest of my dog to do so.

I will allow my dog to enter this investigational ginseng study. I have read the above and have discussed any questions I may have with the veterinarian.

Client's Signature:_____ Date: _____

Investigator's Signature: _____ Date:_____

Appendix B Normal Reference Ranges for All Hematological, Serum Biochemical, Urinalysis, Glycemic Parameters and Systemic Blood Pressure Measurements

Table 1. Normal Canine Reference Ranges For Serum Biochemical Parameters

Parameter	Normal Canine Reference Value	Units
Na	144 - 162	mmol/L
K	3.6 – 6.0	mmol/L
Cl	106 - 126	mmol/L
Ca	2.24 - 3.04	mmol/L
Phos	0.82 - 1.87	mmol/L
Urea	3.0 – 10.5	mmol/L
Creatinine	33 - 113	umol/L
Glucose	3.3 – 5.6	mmol/L
Cholesterol	2.5 – 7.0	mmol/L
T bilirubin	0 - 17	umol/L
Amylase	300 - 1400	U/L
Alk Phos	23 - 87	U/L
CK	0 - 300	U/L
AST	20 – 50	U/L
ALT	5 - 69	U/L
GGT	0 - 8	U/L
T Prot	51-72	U/L
ALB	22 – 38	g/L
Globulin		g/L
A:G ratio	0.6 – 1.5	
Lipase	30 - 560	U/L
SDH	2 - 20	U/L

Table 2. Normal Reference Ranges for Canine Hematological Parameters

Parameter	Normal Reference Range	Unitis
Hemoglobin HgB	120-180	g/L
Hematocrit HCT	0.37-0.55	L/L
Red blood cell count RBC	5.5-8.5	X 10^{12}/L
Mean corpuscular volume MCV	60-70	Fl
Mean corpuscular hemoglobin MCH	19.5 – 24.5	pg
Mean corpuscular hemoglobin concentration MCHC	320 – 360	g/L
Reticulocytes	0 – 1.5 %	%
White blood cell count WBC	6.0 – 17.1	X 10^{9}/L
Segmented neutrophiles Segs	3.6 – 11.5	X 10^{9}/L
Band neutrophiles Bands	0.0 – 0.3	X 10^{9}/L
Eosinophiles Eos	0.01 – 1.25	X 10^{9}/L
Basophiles Bas	Rare	X 10^{9}/L
Lymphocytes Lymph	1.0 -4.8	X 10^{9}/L
Monocytes Monos	0.15 – 1.35	X 10^{9}/L
Platelets Plat	200 - 900	X 10^{9}/L

Table 3. Normal Reference Values for Canine Urinalysis

	Reference range
Color	Yellow/Clear
pH	5 – 7.5
Specific Gravity	1.001-1.060
Protein	Negative
Glucose	Negative
Ketones	Negative
Bilirubin	Trace – 2+
Blood	Negative
Casts	None
Hyaline	
Granular	
Other	
Leukocytes per LPF	0 – 5
Epithelial cells per LPF	0 – 5
Erythrocytes per HPF	0 – 5
Crystals	Variable
Bacteria	None

All urine samples were collected by Cystocentesis.

Normal Long-term Glycemic Parameters

A. Serum Fructosamine

Reference Range established by the Diagnostic Laboratory of the Atlantic Veterinary College.

Normal < 400 umol/L

Diabetic

- Excellent control < 400 umol/L
- Good control 400 – 500 umol/L
- Moderate control 500 – 600 umol/L
- Poor control > 600 umol/L

B. Glycosylated Hemoglobin

Normal reference cited is the range established by the Diagnostic Laboratory of the University of California Davis.

Normal 1.8 – 5.4 %

Normal Reference Ranges for Systemic Arterial Blood Pressure Measurements

Normal ranges for canine systolic, diastolic, and mean blood pressure are taken from:
Brown SA, Henik RA, Finco DR. CVT Update: Diagnosis of systemic hypertension in dogs and cats. In Kirk's Current Veterinary Therapy. Small Animal Practice. Bonagura JD (ed). Philadelphia : W.B. Saunders, 2000, pp 835-838.

Table 4. Normal Reference Ranges for Systemic Arterial Blood Pressure in Dogs

Parameter	Normal Values	Units
Mean	100	mmHg
Systolic	125	mmHg
Diastolic	80	mmHg

Hypertension Consensus Panel, American College of Veterinary Internal Medicine: Current recommendations for diagnosis and management of hypertension in cats and dogs. Report, Proceedings of the 20th Annual Veterinary Medical Forum, Dallas, 2002.

Current recommendations for both species suggest that systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg measured by any method are reasonable values at which concern is warranted. General guidelines for interpretation of systolic blood pressure (SBP, mmHg) are expressed in terms of risk of end-organ damage and are associated with recommendations for further action:

If SBP < 150/95: minimal risk-no further diagnostics indicated

If SBP 150/95 - 160/100: low risk

a) Confirm by repeated measurement if no clinical signs or compatible disease
b) Search for underlying disease
c) Monitor over time if no disease found

If SBP 160/100 - 180/120: moderate risk

a) Careful search for underlying disease
b) Therapy warranted if clinical signs are present
c) Consider therapy if no clinical signs but rapid resolution of underlying disease is not anticipated
d) Monitor over time if no disease found

If SBP > 180/120: high risk

a) If ocular or neurologic signs are present then treat first, then proceed with diagnostic work-up for underlying disease
b) If high risk associated disease is present then therapy is indicated
c) If no clinical signs and no associated disease then recheck frequently: if consistently abnormal, consider therapeutic trial of antihypertensive medication

Appendix B
Laboratory Values of for All Dogs At all Time Experimental Time Points
For Normal reference ranges and units please see earlier in Appendix A
Dog 1 Serum Biochemistry Results

	Placebo Treatment			Ginseng Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	148	141	145	150	153	159
K	4.5	4.4	4.6	4.8	4.9	4.2
Cl	115	104	107	114	118	120
Ca	2.8	2.81	2.72	2.8	3	2.87
Phos	1.19	1.08	1.42	1.46	1.59	1.47
Urea	5.4	4.3	4.1	4.2	3.8	4.3
Creatinine	66	61	72	68	61	63
Glucose	9.3	24.5	8	18.9	9.3	6.4
Cholesterol	7.21	7.5	6.97	7.75	7.83	8.1
T bilirubin	1	1	2	2	1	3
Amylase	264	236	246	239	269	329
Alk Phos	107	119	97	126	136	128
CK	88	116	328	289	126	283
AST	22	21	38	30	24	26
ALT	45	35	53	42	47	52
GGT	1	5	4	6	8	5
T Prot	66	64	63	67	71	71
ALB	34	33	34	35	36	37
Globulin	32	31	29	32	35	34
A:G ratio	1.06	1.06	1.17	1.09	1.03	1.09
Lipase	493	429	468	423	412	406
SDH	0	9	0	11	8	5

Dog 2 Serum Biochemistry Results

	Ginseng Treatment			Placebo Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	142	148	146	144	155	145
K	4.7	5.1	4.7	4.7	5.1	4.9
Cl	109	105	110	111	118	111
Ca	2.67	2.71	2.78	2.79	2.77	2.72
Phos	1.37	1.2	1.29	1.27	1.54	1.45
Urea	3.5	4.4	3.5	4.4	3.4	4.3
Creatinine	64	53	56	62	67	57
Glucose	12.6	23.2	16.9	6.4	10.4	6.1
Cholesterol	20.31	16.48	15	13.81	14.37	15.61
T bilirubin	2	2	1	2	0	1
Amylase	576	346	397	404	430	465
Alk Phos	230	203	215	259	279	256
CK	134	139	82	131	126	179
AST	24	33	22	32	25	28
ALT	39	37	43	40	43	25
GGT	6	4	5	5	5	2
T Prot	67	66	63	63	64	64
ALB	31	30	30	30	30	27
Globulin	36	36	33	33	34	37
A:G ratio	0.86	0.83	0.91	0.91	0.88	0.73
Lipase	567	392	458	387	451	366
SDH	6	12	8	7	6	7

Dog 3 Serum Biochemistry Results

	Placebo Treatment			Ginseng Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	148	147	146	148	144	147
K	4.7	4.6	4.7	4.7	5.3	4.8
Cl	111	111	106	110	106	110
Ca	2.65	2.68	2.72	2.62	2.78	2.81
Phos	1.54	1.74	1.54	1.39	1.42	1.67
Urea	4.8	4.5	5	3.5	4.2	4.2
Creatinine	50	43	43	45	52	48
Glucose	7.7	6	10.4	7.4	24.4	18.2
Cholesterol	12.34	11.22	12.93	11.53	14.94	12.09
T bilirubin	2	3	1	2	2	1
Amylase	537	528	484	486	489	452
Alk Phos	633	696	729	679	831	655
CK	86	149	412	128	401	1294
AST	30	43	44	34	44	66
ALT	127	154	197	130	148	108
GGT	9	11	9	5	7	10
T Prot	67	67	67	68	73	67
ALB	31	32	31	31	33	31
Globulin	36	35	36	37	40	36
A:G ratio	0.86	0.91	0.86	0.84	0.82	0.86
Lipase	241	186	197	195	211	201
SDH	13	16	13	9	14	16

Dog 4 Serum Biochemistry Results

	Placebo Treatment			Ginseng Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	141	136	153	144	145	148
K	4.4	5.5	4.6	4.9	4.6	4.3
Cl	103	103	113	106	109	110
Ca	2.74	2.62	2.83	2.76	2.72	2.75
Phos	1.56	1.38	1.43	1.25	1.36	1.4
Urea	3.3	4.6	3.8	3.4	3.5	3.8
Creatinine	28	20	5	42	10	51
Glucose	6.4	22.7	5	14.5	16.2	9.4
Cholesterol	11.68	16.85	11.97	13.99	15.93	3.26
T bilirubin	0	0	0	0	0	0
Amylase	475	375	437	420	372	405
Alk Phos	370	273	359	512	352	332
CK	127	136	101	212	133	162
AST	41	26	23	38	27	28
ALT	149	108	78	235	115	89
GGT	9	10	6	9	12	5
T Prot	64	68	69	65	66	65
ALB	31	31	31	32	30	31
Globulin	33	37	38	33	36	34
A:G ratio	0.94	0.84	0.82	0.97	0.83	0.91
Lipase	482	406	508	454	424	496
SDH	13	16	6	29	19	13

Dog 5 Serum Biochemistry Results

	Ginseng Treatment			Placebo Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	141	147	145	147	150	148
K	4.7	4.3	5	4.6	4.6	4.5
Cl	110	107	109	32	110	109
Ca	2.93	2.92	2.79	2.87	2.84	2.87
Phos	1	2.01	1.74	1.84	1.8	1.8
Urea	4.7	5.1	5.3	6.8	5.6	6.5
Creatinine	69	29	65	55	38	12
Glucose	14	19.3	18.7	17	13.3	20.9
Cholesterol	12.37	11.52	10.44	9.7	8.46	11.33
T bilirubin	0	0	0	0	0	0
Amylase	749	667	653	653	611	614
Alk Phos	280	319	234	237	201	233
CK	123	121	194	97	176	101
AST	38	24	29	23	31	31
ALT	30	45	51	34	41	58
GGT	4	8	6	7	5	6
T Prot	72	68	67	68	69	73
ALB	31	31	30	31	31	33
Globulin	41	37	37	37	38	40
A:G ratio	0.76	0.84	0.81	0.84	0.82	0.82
Lipase	675	577	665	589	680	647
SDH	4	12	19	11	13	21

Dog 6 Serum Biochemistry Results

	Ginseng Treatment			Placebo Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	144	144	148	149	139	145
K	4.7	5.5	5.7	4.9	6.2	5.4
Cl	102	104	106	109	98	103
Ca	3.02	2.88	2.79	2.93	2.86	2.97
Phos	1.69	1.55	1.38	1.5	1.66	1.74
Urea	3.6	3.6	4.7	4.1	5.6	5.8
Creatinine	23	30	33	39	23	27
Glucose	17.5	18.1	21.8	9.5	31.2	22.3
Cholesterol	17.62	14.75	12.64	12.21	14.3	13.12
T bilirubin	0	0	0	0	0	0
Amylase	793	662	646	738	712	776
Alk Phos	1706	1735	1065	1051	1131	1707
CK	41	91	90	69	114	142
AST	94	42	32	24	32	33
ALT	244	178	143	92	130	148
GGT	0	14	7	9	5	9
T Prot	69	68	69	72	73	72
ALB	29	31	30	32	30	32
Globulin	40	37	39	40	43	40
A:G ratio	0.73	0.84	0.77	0.8	0.7	0.8
Lipase	324	320	332	307	314	280
SDH	0	33	35	20	33	56

Dog 7 Serum Biochemistry Results

	Ginseng Treatment			Placebo Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	148	150	148	149	143	149
K	4.7	4.6	4.8	4.2	4.6	3.8
Cl	109	110	109	110	108	114
Ca	2.44	2.66	2.55	2.49	2.58	2.54
Phos	1.54	1.91	1.18	1.36	1.48	1.43
Urea	3.6	4.3	4	4.5	4.3	4.8
Creatinine	55	31	39	6	44	45
Glucose	18.6	8	17.9	15.3	19.1	4.4
Cholesterol	7.92	7.56	7.1	7.01	6.91	6.22
T bilirubin	1	2	3	1	1	1
Amylase	426	360	417	334	377	379
Alk Phos	1054	1470	1444	1732	1616	781
CK	374	271	295	265	141	114
AST	66	84	42	55	46	37
ALT	95	173	120	123	97	55
GGT	18	25	26	32	31	1
T Prot	69	63	64	64	61	58
ALB	29	29	29	28	27	28
Globulin	40	34	35	36	34	30
A:G ratio	0.73	0.85	0.83	0.78	0.79	0.93
Lipase	135	131	123	120	162	134
SDH	27	41	19	20	16	10

Dog 8 Serum Biochemistry Results

	Ginseng Treatment			Placebo Treatment		
Parameter	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
Na	152	149	154	151	151	148
K	5.3	4.8	4.8	4.6	4.6	4.4
Cl	115	113	115	115	111	114
Ca	2.76	2.62	2.69	2.77	2.79	2.92
Phos	1.27	1.83	1.76	1.16	1.28	1.05
Urea	7.5	9.2	5.9	8.5	8.5	7.9
Creatinine	54	50	67	65	68	58
Glucose	7.6	17.2	10.8	10.3	7.8	9.2
Cholesterol	4.97	5.31	5.8	6.44	6.04	6.28
T bilirubin	2	3	1	1	0	1
Amylase	699	521	462	543	577	516
Alk Phos	322	395	540	514	428	450
CK	160	180	219	244	277	350
AST	22	29	77	33	37	52
ALT	49	81	113	106	107	92
GGT	3	3	2	3	3	2
T Prot	65	64	64	60	59	63
ALB	33	33	33	31	30	32
Globulin	32	31	31	29	29	31
A:G ratio	1.03	1.06	1.06	1.07	1.03	1.03
Lipase	219	212	208	202	195	230
SDH	8	20	17	15	7	18

Hematological Parameters at all Time Points for Each Dog - See earlier for normal reference ranges and units.

Dog 1 Complete Blood Count Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	6.7	6.8	6.8	7.7	8.7	9.4
RBC	6.6	6.7	6.5	6.5	6.7	6.8
HGB	167	157	152	155	160	160
HCT	0.449	0.456	0.442	0.457	0.467	0.469
Platelets	380	368	382	400	398	341
Segs	4.76	4.42	3.94	6.24	6.61	7.24
Bands	0	0	0	0	0	0.18
Eos	0.46	0.54	0.2	0.07	0.17	0.28
Lymph	1.27	1.49	2.31	1.23	1.13	0.94
Mono	0.2	0.34	0.34	0.15	0.78	0.75

Dog 2 Complete Blood Count Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	7.4	9.4	7.6	9.4	8.2	8.5
RBC	7.6	7	7.2	7.3	7.1	7.2
HGB	171	161	167	166	161	160
HCT	0.507	0.464	0.48	0.49	0.473	0.475
Platelets	387	320	381	303	348	218
Segs	4.07	6.2	5.09	5.73	5.9	5.355
Bands	0	0	0	0	0	0
Eos	0.51	0.94	0.38	0.84	0.32	0.765
Lymph	2.44	1.88	1.9	2.25	1.64	1.7
Mono	0.37	0.37	0.22	0.56	0.32	0.68

Dog 3 Complete Blood Count Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	12	13.7	12.3	9.6	11.7	11.7
RBC	7.3	8.1	7.4	7.5	7.5	6.8
HGB	167	181	170	170	168	157
HCT	0.496	0.541	0.497	0.499	0.504	0.46
Platelets	463	549	463	471	403	302
Segs	9.96	11.83	9.92	6.84	9.83	9.24
Bands	0	0	0	0	0	0
Eos	0	0.4	0.24	0.57	0.46	0.46
Lymph	1.2	0.95	1.21	1.71	1.05	1.17
Mono	0.84	0.4	0.72	0.38	0.35	0.81

Dog 4 Complete Blood Count Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	5.8	5.3	5.8	6.6	4.8	6.1
RBC	6.4	6.1	5.8	5.7	5.7	5.9
HGB	145	145	138	135	138	141
HCT	0.428	0.409	0.395	0.387	0.392	0.411
Platelets	225	301	251	226	215	224
Segs	4	3.76	4	5.74	3.6	4.39
Bands	0	0	0	0	0	0
Eos	0.17	0.15	0.11	0	0.14	0.12
Lymph	1.21	1.11	1.21	0.66	0.76	1.34
Mono	0.4	0.26	0.46	0.19	0.28	0.24

Dog 5 Complete Blood Count Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	9.6	8.6	10.8	11.7	11.7	10.4
RBC	7.9	7.8	7.8	8	8	7.9
HGB	181	167	166	165	171	175
HCT	0.501	0.491	0.494	0.513	0.51	0.508
Platelets	361	291	318	296	314	346
Segs	7.39	7.31	9.07	9.95	10.41	8.94
Bands	0	0	0	0	0.11	0
Eos	0.09	0.25	0.32	0.11	0	0.2
Lymph	1.53	0.6	1.08	0.7	0.7	0.72
Mono	0.57	0.43	0.32	0.93	0.46	0.52

Dog 6 Complete Blood Count Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	6.8	8	7.6	7.8	11.1	8
RBC	5.6	5.6	5.7	6.9	5.88	5.9
HGB	145	128	130	149	134	136
HCT	0.377	0.376	0.376	0.453	0.38	0.4
Platelets	582	432	402	533	340	430
Segs	5.51	7.28	6.23	6.47	8.55	6.8
Bands	0.06	0	0	0	0.11	0
Eos	0.06	0.08	0.15	0.39	0	0.24
Lymph	0.81	0.56	0.6	0.54	2.1	0.7
Mono	0.34	0.08	0.6	0.39	0.33	0.24

Dog 7 Complete Blood Count Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	12.6	14.8	13.4	10.3	9.6	11
RBC	6.1	5.9	5.73	6.1	5.9	5.3
HGB	146	141	138	145	144	135
HCT	0.426	0.412	0.401	0.429	0.411	0.368
Platelets	559	342	471	502	523	476
Segs	8.57	9.18	8.58	6.28	6.24	6.93
Bands	0	0	0	0	0.09	0
Eos	0.12	0.14	0.53	0.61	0.09	0.33
Lymph	2.89	4.14	2.81	2.47	2.59	3.08
Mono	1	1.33	1.47	0.92	0.67	0.66

Dog 8 Complete Blood Count Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
WBC	13.1	14.1	12.8	11.5	12.9	13.8
RBC	7.4	7.2	7.6	7.1	7.3	7.3
HGB	166	166	177	168	173	175
HCT	0.479	0.484	0.514	0.484	0.501	0.506
Platelets	559	522	400	518	566	523
Segs	11.79	11.28	11.52	9.2	10.84	11.04
Bands	0	0.28	0	0	0	0
Eos	0	0	0	0.46	0.38	0.55
Lymph	0.39	1.26	0.38	1.15	0.77	0.69
Mono	0.91	1.26	0.89	0.69	0.9	1.51

Urinalysis Results for All Dogs at all Experimental Time Points

Dog 1 Urinalysis Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.052	1.046	1.05	1.046	1.042	1.046
Urine Protein	trace	trace	2+	1+	2+	4+
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	2+	3+	negative	1+	trace	2+

Dog 2 Urinalysis Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.03	1.031	1.023	1.026	1.027	1.02
Urine Protein	trace	negative	negative	2+	negative	negative
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	2+	2+	2+	trace	Trace	negative

Dog 3 Urinalysis Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.026	1.027	1.033	1.04	1.032	1.025
Urine Protein	trace	1+	trace	trace	1+	trace
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	negative	negative	negative	1+	2+	1+

Dog 4 Urinalysis Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.04	1.058	1.056	1.03	1.056	1.049
Urine Protein	negative	negative	trace	1+	trace	trace
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	trace	2+	negative	2+	trace	trace

Dog 5 Urinalysis Results

	Placebo Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.03	1.024	1.032	1.046	1.035	1.025
Urine Protein	2+	trace	negative	trace	negative	trace
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	2+	3+	negative	1+	1+	1+

Dog 6 Urinalysis Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.03	1.03	1.042	1.028	1.031	1.028
Urine Protein	3+	1+	2+	3+	2+	2+
Urine Culture	negative	negative	negative	negative	positive	negative
Urine Glucose	3+	1+	4+	2+	3+	3+

Dog 7 Urinalysis Results

	Ginseng Treatment			Placebo Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.043		1.032	1.033	1.033	1.032
Urine Protein	Trace	negative	negative	negative	negative	trace
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	1+	3+	3+	2+	2+	negative

Dog 8 Urinalysis Results

	Ginseng Treatment			Ginseng Treatment		
Variable	T = 0 days	T = 28 days	T= 56 days	T = 0 days	T = 28 days	T = 56 days
USG	1.052	1.05	1.052	1.05	1.03	1.062
Urine Protein	negative	negative	trace	negative	negative	negative
Urine Culture	negative	negative	negative	negative	negative	negative
Urine Glucose	2+	2+	1+	2+	negative	2+

Glycemic Parameters for Individual Dogs

Dog 1 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.56	0.54	0.55	0.54	0.53	0.57
Postprandial Blood Glucose mmol/L	19.3	19.7	14.6	21.3	21.2	17.7
Mean Blood Glucose mmol/L	12.2	9.49	8	12.08	13.3	7.8
Mid point Blood Glucose mmol/L	8.1	8.2	4	8	6.2	5.2
Fasting Blood Glucose mmol/L	18.9	12	4.5	18.6	14.9	17.7
Serum Fructosamine umol/L	547	542	484	265	485	581
Glycosylated haemoglobin %	6.9		6.5	7.9		7.9
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	148.9	117.3	87.45	151.4	153	105.2

Dog 2 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.62	0.62	0.61	0.59	0.56	0.62
Postprandial Blood Glucose mmol/L	14.6	17.6	16.7	18.8	18.9	15.4
Mean Blood Glucose mmol/L	9.6	8.6	9.8	15.8	17.5	13.88
Mid point Blood Glucose mmol/L	7.9	6.2	6.6	12.3	16.7	13.4
Fasting Blood Glucose mmol/L	12.2	18.1	16.6	8.2	18.8	16.6
Serum Fructosamine umol/L	489	447	502	604	692	607
Glycosylated haemoglobin %	6.9		5.8	6.3		6.5
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	114.7	110.5	119.5	191	210.5	167.8

Dog 3 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.63	0.63	0.66	0.62	0.65	0.63
Postprandial Blood Glucose mmol/L	13.5	12.7	10.1	18	20.3	13
Mean Blood Glucose mmol/L	7.4	5.5	7.1	13.8	17.15	11
Mid point Blood Glucose mmol/L	4.15	4.6	6.25	9.7	16.15	9.6
Fasting Blood Glucose mmol/L	9.1	5.8	8.3	15	21.5	13.3
Serum Fructosamine umol/L	381	427	551	482	464	471
Glycosylated haemoglobin %	6.3		6.8	7		6.7
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	75.8	64.2	81.8	136	205.5	130.9

Dog 4 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.8	0.83	0.83	0.8	0.787	0.88
Postprandial Blood Glucose mmol/L	10.2	8.6	17.7	13.9	23.7	14.6
Mean Blood Glucose mmol/L	10.08	9.06	8.55	7.55	17	7.2
Mid point Blood Glucose mmol/L	11.2	9.2	7.7	7.3	16	7.5
Fasting Blood Glucose mmol/L	9.4	6.4	3.1	6.3	17.6	5.4
Serum Fructosamine umol/L	505	601	471	513	615	438
Glycosylated haemoglobin %	9.2			7.7		5.3
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	114.7	110.5	119.5	191	210.5	167.8

Dog 5 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.77	0.76	0.76	0.76	0.77	0.76
Postprandial Blood Glucose mmol/L	11.2	16.4	19.3	12.5	17.2	13
Mean Blood Glucose mmol/L	9.76	9.15	15.33	11	13.2	8.2
Mid point Blood Glucose mmol/L	11.6	7.3	13.7	7.05	12	7.4
Fasting Blood Glucose mmol/L	7.3	5.9	10.1	11.7	16.4	2.6
Serum Fructosamine umol/L	386	417	453	422	417	420
Glycosylated haemoglobin %	4.3		4.9	7		5.4
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	116.5	110.2	176.3	106.4	172.7	100.9

Dog 6 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	1.53	1.57	1.5	1.5	1.62	1.71
Postprandial Blood Glucose mmol/L	20.8	19.4	16.1	15.1	22.2	20.2
Mean Blood Glucose mmol/L	11.8	12.49	13.89	11.81	23.45	20.4
Mid point Blood Glucose mmol/L	11.25	9.1	12.85	11.7	28.3	14.8
Fasting Blood Glucose mmol/L	13.8	15.6	15.3	14.8	25.9	18.8
Serum Fructosamine umol/L	550	435	477	454	502	461
Glycosylated haemoglobin %	8.5		7	8		6
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	134.8	145.1	166.1	138.3	281.9	209.6

Dog 7 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.56	0.48	0.48	0.48	0.48	0.5
Postprandial Blood Glucose mmol/L	15.1	21.2	18.2	17.6	17.3	4.4
Mean Blood Glucose mmol/L	14.8	9.75	15.98	12.71	12.27	7.4
Mid point Blood Glucose mmol/L	13.6	7.2	14	9	9.5	6.2
Fasting Blood Glucose mmol/L	13.4	7.3	17.9	16.8	15.1	13
Serum Fructosamine umol/L	526	466	426	449	440	330
Glycosylated haemoglobin %	4.7		5.2	5.6		5.7
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	170.8	112.2	187.7	143.6	139.4	87.2

Dog 8 Glycemic Parameters

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.55	0.52	0.52	0.52	0.52	0.52
Postprandial Blood Glucose mmol/L	15	21.5	12.8	11	10.4	9.8
Mean Blood Glucose mmol/L	8.9	11.68	11.16	11.55	11.65	9.4
Mid point Blood Glucose mmol/L	6.2	12.5	8.2	11.6	13.8	6.7
Fasting Blood Glucose mmol/L	10.8	10.9	14.2	14.3	14	12.9
Serum Fructosamine umol/L	389	420	547	412	476	476
Glycosylated haemoglobin %	4.3		5.1	5.3		5.7
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	95.8	135.4	131.6	136.5	138.8	109.9

Systemic Arterial Blood Pressure

Dog 1

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	100.4	116.6	96.4	112.25	90.4	103.6
Diastolic Arterial Blood Pressure mm Hg	88.6	87.8	76	89.8	69.6	84
Systolic Arterial Blood Pressure mm Hg	113.8	147.2	133.4	131.8	124.2	133

Dog 2

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	105.3	92	96	79.8	93.3	108.8
Diastolic Arterial Blood Pressure mm Hg	86.6	81	72.8	55	74.5	83.6
Systolic Arterial Blood Pressure mm Hg	113.3	105.8	136.4	112.2	128.6	141

Dog 3

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	122.2	139.8	140	106.3	140.37	92.8
Diastolic Arterial Blood Pressure mm Hg	108.4	119.14	121.28	78.8	115.89	65
Systolic Arterial Blood Pressure mm Hg	140.8	163.4	160.57	127.6	137.86	148.4

Dog 4

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	114.2	105.8	83	99	116.2	105
Diastolic Arterial Blood Pressure mm Hg	74.6	82	68.3	71.8	96	78
Systolic Arterial Blood Pressure mm Hg	144.8	135.6	110	136.6	129	141.16

Dog 5

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	111	91.25	95.5	108	94	103.4
Diastolic Arterial Blood Pressure mm Hg	74.5	78.75	95	76.75	62	82.2
Systolic Arterial Blood Pressure mm Hg	128.2	118.5	103.5	162.5	118.75	128.8

Dog 6

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	98.5	111	125.8	155	135.5	128.14
Diastolic Arterial Blood Pressure mm Hg	76.8	99.16	105.57	109	114.5	109
Systolic Arterial Blood Pressure mm Hg	129.16	121	149	174.14	164.63	182

Dog 7

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	97	101	111.7	110	107	103
Diastolic Arterial Blood Pressure mm Hg	85.75	82.7	88	88	87	82
Systolic Arterial Blood Pressure mm Hg	104.75	126	154.28	148	142	134

Dog 8

	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean Arterial Blood Pressure mmHg	80.6	90.8	144	87.8	85	83
Diastolic Arterial Blood Pressure mm Hg	93.3	76	138	55	74.5	83.6
Systolic Arterial Blood Pressure mm Hg	139.33	110.8	172	111.4	115	119

Appendix C: Summary of Questionnaire Data

Table 1. Summary of the Signalment, Diet and Diabetic History for each of the 8 Dogs enrolled in the study.

Table 2. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 0 of the first arm of the clinical trial.

Table 3. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 28 of the first arm of the clinical trial.

Table 4. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 56 of the first arm of the clinical trial.

Table 5. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 0 of the second Arm of the Experiment.

Table 6. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 28 of the second Arm of the Experiment.

Table 7. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 56 of the second Arm of the Experiment.

Table 8. Results of Hematologic Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment

Table 9. Results of Serum Biochemical Profile Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Table 10. Results of Glycemic Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± SEM of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Table 11. Results of Systemic Blood Pressure Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Table 1. Summary of the Signalment, Diet and Diabetic History for each of the 8 Dogs enrolled in the study.

Dog #	Breed	Age in years	Sex	BW kg	Diet Feed	Duration of time since diagnosed with diabetes	Insulin Type	Insulin Dose	Insulin Dose per kg BW	Time on current insulin dose
1	Poodle X	8.5	MN	16.7	Medical High fiber	6 months	Caninsulin	9 U BID	0.53	5 months
2	Sheltie X	11	FS	31.6	Hill's r/d	12 months	Caninsulin	20 U BID	0.63	14 days
3	Rottweiler	8	FS	45.7	Iams Weight Control	8 months	NPH	27 U BID	0.59	56 days
4	Miniature Schnauzer	7.5	MN	12.5	Hill's w/d	3 months	Lente	10 U BID	0.8	30 days
5	Terrier X	5	MN	12.9	Purina Low Fat	4.5 years	Caninsulin	10.5 U am 9.5 U pm	0.75	14 days
6	Miniature Schnauzer	10	FS	7.8	Medical High fiber	7 months	Caninsulin	12 U BID	1.54	42 days
7	German shepherd X	12-13	FS	21.2	Superstore brand of wet and dry	6 years	NPH	10 U BID	0.47	56 days
8	German shepherd X	12	FS	26.4	Waltham Calorie Reduced wet Iams Weight Control Dry	3 months	NPH	15 U am 14 U pm	0.54	56 days

FS = Female spayed, MN = male neutered, BW = Body weight

Table 2. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 0 of the first arm of the clinical trial.

Dog #	T = 0 Owners assessment of dog's appetite	T = 0 owners assessment of dog's energy and activity level	T = 0 owners assessment of their dog's mental agility	Other Medical problems	Other Medications
1	Excellent	Moderate	Excellent	None Mild diabetic cataracts	None
2	Excellent	Excellent	Good	Overweight Mild diabetic cataracts	None
3	Excellent	Fair	Excellent	Prior history of diabetic ketoacidosis 8 months prior to start of study Arthritis Corneal lipidosis Severe diabetic cataracts – blind	Buffered Aspirin*
4	Excellent	Moderate	Excellent	None Mild diabetic cataracts	Mobicox occasionally*
5	Excellent	Excellent	Good	Mild Diabetic cataracts, Idiopathic anisocoria Urinary tract infection due to diabetes	None
6	Excellent	Moderate	Good	Severe Diabetic Cataracts ultimately leading to bilateral phthisis bulbi and blindness Urinary tract and skin infections due to diabetes in past	Metacam occasionally *
7	Fair	Fair	Good	Epileptic Moderate Diabetic Cataracts Urinary tract and skin infections due to diabetes	Phenobarbital**
8	Excellent	Fair	Excellent	Moderate Diabetic Cataracts Arthritis Urinary tract infection due to diabetes previously	None

*Buffered Aspirin, Mobicox, Metacam are both examples of Non-steroidal anti-inflammatory drugs administered for osteoarthritis to dogs

** Phenobarbital is an anticonvulsant prescribed for seizure disorders in dogs

Table 3. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 28 of the first arm of the clinical trial.

Dog #	Study Drug	T = Day 28 Owners assessment of dog's appetite relative to T= Day 0	T = Day 28 owners assessment of dog's energy and activity level relative to T = Day 0	T = Day 28 owners assessment of their dog's mental agility relative to T= Day 0	T= Day 28 owners assessment of their dog's urination and drinking relative to T= Day 0	Comments
1	Placebo	No change from T= Day 0	More active No change from T= Day 0	No change from T = Day 0	Maybe slightly increased	
2	Ginseng	Appetite is good; not as ravenous as when on once daily insulin but no change from day 0	More playful than when on once daily insulin but no change from day 0	No change from Day 0	Big improvement from when on once daily insulin but no change from day 0	
3	Placebo	Normal	Increased but owner home more in the last few weeks	No change	Possibly drinking more	Glucose curve shows only moderate control:
4	Placebo	No change	May be more active but spring weather has allowed him to get more exercise	No change	Possibly drinking more	Glucose curve showed decreased glycemic control but owners do not feel that signs of uncontrolled diabetes have returned
5	Placebo	No change	More active since T0	No change	No change	Glucose curve shows decreased control relative to T0
6	Ginseng	No change	3 - Maybe more active but weather also improved	No change	possibly drinking more	
7	Ginseng	Normal	Improved activity level since T=0	No change	May not be drinking as much	
8	Ginseng	Good but not ravenous now	Improved activity level - 3- owner says dog is playful again	No change	No change	Diarrhea - worms seen by owner – dewormed with Strongid

Table 4. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 56 of the first arm of the clinical trial.

Dog #	Study Drug	T = Day 56 Owners assessment of dog's appetite relative to T= Day 0	T = Day 56 owners assessment of dog's energy and activity level relative to T = Day 0	T = Day 56 owners assessment of their dog's mental agility relative to T= Day 0	T= Day 56 owners assessment of their dog's urination and drinking relative to T= Day 0	Comments
1	Placebo	No change	No change	No change	No change	0 capsules remaining; lost 1.1 kg since last visit and slight hypoglycemia at nadir on Day 56
2	Ginseng	No change	No change	No change	May have increased a little from 4 weeks ago	Excellent compliance 0 pill left over
3	Placebo	No change	No change	No change	No change	Glucose curve showed significantly improved control relative to T0 and T28 day
4	Placebo	No change	Definitely more active than at day 0	No change	Decreased from T= 28 days	Glucose curve shows better control relative to 4 weeks ago; 3 capsules remaining;
5	Placebo	No change	Normal	No change	No change from T=28 days	Improved control indicated by glucose curve relative to T=28 days
6	Ginseng	Maybe increased From day 0	Activity level may be increased relative to day 0 Score 3.5	No change	Increased since T= 0	Glucose curve on day 56 not as good as on day 28
7	Ginseng	No change	No change	No change	No change	Glucose curve shows worse control than on T=28 days: 0 capsules remaining
8	Ginseng	No change	Decreased from T=0 score 3	No change	No change	Appetite unpredictable; good compliance 4 pills remaining, RX: ocufen for scleral injection secondary to corneal lipidosis and uveitis secondary to cataracts

Table 5. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 0 of the second Arm of the Experiment.

Dog #	Study Drug	T = Day 0 Owners assessment of dog's appetite relative to T= Day 0 of 1st arm of the experiment	T = Day 0 owners assessment of dog's energy and activity level relative to T = Day 0 of 1st arm of the experiment	T = Day 0 owners assessment of their dog's mental agility relative to T= Day 0 of the 1st arm of the experiment	T= Day 0 owners assessment of their dog's urination and drinking relative to T= Day 0 of the 1st arm of the experiment	Comments
1	Ginseng	No change	No change	No change		Curve shows good control
2	Placebo	No change	Increased	No change	No change	
3	Ginseng	No change	Decreased due to vestibular disease	No change	No change	During washout period dog developed a head tilt: presumptive diagnosis was idiopathic vestibular disease: Best glucose curve since dx with diabetes.
4	Ginseng	No change	Increased	No change	No change	Curve shows good control
5	Ginseng	No change	No change	No change	No change	Glucose curve shows excellent control
6	Placebo	Increased	No change	No change	Increased	Superficial pyoderma dx put on cephalexin for 2 weeks
7	Placebo	Decreased in last 3 days otherwise normal	No change	No change	No change	2 days prior to returning to WCVM diagnosed with an anal gland abscess - tx with cephalexin by RDVM: glucose curve looked good
8	Placebo	Decreased	No change	No change	No change	

Table 6. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 28 of the second Arm of the Experiment.

Dog #	Study Drug	T = Day 28 Owners assessment of dog's appetite relative to T= Day 0 1st arm of the experiment	T = Day 28 owners assessment of dog's energy and activity level relative to T = Day 0 1st arm of the experiment	T = Day 28 owners assessment of their dog's mental agility relative to T= Day 0 1st arm of the experiment	T= Day 28 owners assessment of their dog's urination and drinking relative to T= Day 0 1st arm of the experiment	Comments
1	Ginseng	No change	No change	No change	No change	Gained back the 1 kg he lost previously; Glucose curve shows excellent control
2	Placebo	No change	No change	No change	No change	
3	Ginseng	No change	Less active due to head tilt	No change	No change	Head tilt is better : glucose curve continues to show excellent control and owners very pleased with how she is doing
4	Ginseng	No change	Increased	No change	No change	Glucose curve shows good control
5	Ginseng	No change	No change	No change	No change	Glucose curve shows excellent control
6	Placebo	Increased	Decreased	No change	Increased	UTI - E.coli heavy RX Amoxicillin for 2 weeks; glucose curve looks worse than at anytime - increased insulin dose by one unit to 13 SC BID; one day of inappetence during last 4 weeks; tx UTI and one week later follow up curve was improved.
7	Placebo	No change	No change	No change	No change	Anal gland area mostly healed up: Glucose curve looks good
8	Placebo	No change	Increased	No change	No change	good month acupuncture is helping

Table 7. Summary of the Owners Assessment of their Dog's Appetite, Energy / Activity level, Mental Agility and Concurrent Medical Problems for the 8 dogs with Type I Diabetes Mellitus on the day 56 of the second Arm of the Experiment.

Dog #	Study Drug	T = Day 28 Owners assessment of dog's appetite relative to T= Day 0 of 1st arm of the experiment	T = Day 28 owners assessment of dog's energy and activity level relative to T = Day 0 of 1st arm of the experiment	T = Day 28 owners assessment of their dog's mental agility relative to T= Day 0 of the 1st arm of the experiment	T= Day 28 owners assessment of their dog's urination and drinking relative to T= Day 0 of the 1st arm of the experiment	Comments
1	Ginseng	No change	No change	No change	No change	1 pill remaining
2	Placebo	No change	No change	No change	No change	0 pills remaining
3	Ginseng	No change	No change	No change	No change	Glucose curve continues to show excellent control - much better in the second arm of the study but restricted exercise and diet may have played a role. Excellent compliance 1 pill left over
4	Ginseng	No change	Increased	No change	No change	Hypoglycemic in the morning : 8 pills remaining of drug A: trace ketonuria likely a lab error as control is excellent
5	Ginseng	No change	No change	No change	No change	Glucose curve showed decreased control
6	Placebo	No change	No change	No change	No change	0 pills remaining
7	Placebo	No change	No change	No change	No change	1 pill remaining
8	Placebo	No change	No change	No change	No change	Good month – 0 pills remaining

Table 8. Results of Hematologic Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment.

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Red blood cells (RBC) X 10^{12}/L	6.74 ± 0.89	6.79 ± 0.99	6.78 ± 0.89	7.01 ± 0.63	6.77 ± 0.75	6.58 ± 0.86
Hematocrit (HCT) L/L	0.45 ± 0.05	0.46 ± 0.06	0.46 ± 0.05	0.47 ± 0.03	0.45 ± 0.05	0.44 ± 0.05
Hemoglobin (HGB) g/L	155.63 ± 12.33	155.75 ± 18.22	156.38 ± 17.94	162 ± 13.7	156.13 ± 13.78	153.25 ± 15.6
White Blood Cells (WBC) X 10^9/L	9.99 ± 2.69	10.5 ± 3.59	10.06 ± 2.63	8.59 ± 1.96	9.43 ± 2.53	9.44 ± 2.78
Segmented Neutrophils X 10^9/L	7.94 ± 2.45	8.26 ± 2.89	7.77 ± 2.41	6.13 ± 1.79	7.14 ± 2.49	7.01 ± 2.61
Monocytes X 10^9/L	0.62 ± 0.35	0.61 ± 0.46	0.73 ± 0.35	0.49 ± 0.22	0.46 ± 0.22	0.57 ± 0.43
Lymphocytes X 10^9/L	1.27 ± 0.87	1.39 ± 1.16	1.21 ± 0.77	1.54 ± 0.66	1.49 ± 0.69	1.52 ± 0.84
Eosinophils X 10^9/L	0.15 ± 0.28	0.16 ± 0.14	0.29 ± 0.25	0.41 ± 0.19	0.35 ± 0.3	0.32 ± 0.14
Band Neutrophils X 10^9/L	0.01 ± 0.02	0.05 ± 0.01	0.02 ± 0.06	0 ± 0	0.03 ± 0.05	0 ± 0
Platelets X 10^9/L	423.5 ± 21.14	390 ± 21.14	358.13 ± 21.14	422.13 ± 21.14	389 ± 21.14	382.88 ± 21.14

Table 9. Results of Serum Biochemical Profile Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Sodium mmol/L	147.3 ± 2.3	149.13 ± 3.76	149.5 ± 4.66	146.13 ± 4.09	143.63 ±4.96	147.25 ± 2.76
Potassium mmol/L	4.8 ± 0.22	4.84 ± 0.32	4.74 ± 0.46	4.57 ± 0.22	5 ± 0.65	4.66 ± 0.46
Chloride mmol/L	100 ± 27.8	111.63 ± 4.69	110.75 ± 4.71	110.13 ± 3.8	105.25 ± 3.85	110 ± 3.78
Calcium mmol/L	2.76 ± 0.17	2.77 ± 0.13	2.75 ± 0.1	2.74 ± 0.15	2.76 ± 0.11	2.8 ± 0.13
Phosphorus mmol/L	1.48 ± 0.21	1.67 ± 0.18	1.5 ± 0.2	1.32 ± 0.19	1.44 ± 0.29	1.47 ± 0.24
Urea mmol/L	4.79 ± 1.54	4.74 ± 1.94	4.81 ± 0.95	4.69 ± 1.68	5.13 ± 1.45	4.93 ± 1.43
Creatinine umol/L	51.13 ± 13.72	41.25 ± 18.33	45.63 ± 17.96	47.75 ± 22.56	43.75 ± 17.93	47 ± 21.78
Lipase U/L	346.5 ± 146.2	352 ± 178.56	346.88 ± 172.49	380.13 ± 201.43	335.75 ± 141.94	368 ± 183.36
Amylase U/L	521.38 ± 183.53	469.13 ± 134.38	477.75 ± 105.85	520.63 ± 171.93	472.38 ± 167.73	482 ± 166.17
ALT U/L	108.25 ± 87.09	104 ± 58.95	99.63 ± 55.6	89.25 ± 45.75	88.38 ± 43.86	78.5 ± 36.05
Alk Phos U/L	606.13 ± 532.9	658 ± 610.44	590.875 ± 462.26	620.38 ± 538.57	615 ± 530.53	482 ± 516.25
AST U/L	41.88 ± 25.2	38.13 ± 19.9	38.5 ± 16.9	33.88 ± 11.03	32.88 ± 9.12	37.5 ± 14.96
GGT U/L	7.13 ± 5.33	10.38 ± 7.05	7.76 ± 7.74	8.63 ± 9.84	9.13 ± 9.13	5.38 ± 3.11
SDH U/L	13.25 ± 9.93	19.5 ± 12.04	16.25 ± 9.38	10.88 ± 7.38	14.88 ± 7.97	16.63 ± 17.18
Cholesterol mmol/L	11.01 ± 4.15	10.68 ± 3.96	9.6 ± 4.18	11.1 ± 4.5	11.82 ± 4.46	10.26 ± 3.38
Glucose mmol/L	13.53 ± 5.39	12.31 ± 4.54	12.96 ± 6.32	10.6 ± 3.13	21.53 ± 6.7	12.84 ± 6.95
Total Bilirubin umol/L	1.13 ± 0.99	1.13 ± 1.36	1.13 ± 1.25	0.88 ± 0.83	0.75 ± 0.87	0.75 ± 0.71
Creatine Kinase U/L	173.75 ± 112.17	156.5 ± 54.51	217.63 ± 108.58	147.25 ± 70.11	180.63 ± 103.73	325.63 ± 404.26
Total protein g/L	66.63 ± 2.14	66.5 ± 2.78	67.13 ± 3.53	66.63 ± 4.1	66.5 ± 5.1	65.25 ± 4.37
Albumin g/L	31.25 ± 2.05	31.5 ± 2.2	31.4 ± 3.02	31.25 ± 1.64	30.63 ± 1.92	31 ± 1.77
Globulin g/L	35.34 ± 3.38	35 ± 2.13	35.75 ± 2.91	35.5 ± 4.04	35.88 ± 4.55	43.25 ± 4.06
Albumin/globulin ratio	0.9 ± 0.31	0.9 ± 0.09	0.88 ± 0.13	0.89 ± 0.12	0.86 ± 0.12	0.92 ± 0.13

Table 10. Results of Glycemic Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± SEM of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Insulin/kg BW U/kg	0.75 ± 0.12	0.74 ± 0.13	0.74 ± 0.12	0.73 ± 0.12	0.74 ± 0.13	0.77 ± 0.14
Postprandial Blood Glucose mmol/L	14.96 ± 1.28	17.14 ± 1.58	15.69 ± 1.08	16.03 ± 1.23	18.9 ± 1.46	13.51 ± 1.71
Mean Blood Glucose mmol/L	10.57 ± 0.81	9.47 ± 0.74	11.24 ± 1.22	12.04 ± 0.84	15.69 ± 1.38	10.66 ± 1.60
Mid point Blood Glucose mmol/L	9.24 ± 1.13	7.79 ± 0.86	9.31 ± 1.28	9.59 ± 0.73	15.08 ± 2.19	8.7 ± 1.31
Fasting Blood Glucose mmol/L	11.86 ± 1.28	10.25 ± 1.67	11.25 ± 1.98	13.21 ± 1.49	18.02 ± 1.41	12.54 ± 2.04
Serum Fructosamine umol/L	471.63 ± 26.24	469.38 ± 23.63	488.88 ± 15.32	450.13 ± 34.12	511.34 ± 33.18	473 ± 31.13
Glycosylated haemoglobin %	6.2 ± 0.57		5.83 ± 0.29	7.04 ± 0.46		6.27 ± 0.32
Area under 12 hr Glucose Curve (AUC 12 hr) mmol/L/12 hrs	121.5 ± 10.54	113.18 ± 8.40	133.74 ±14.03	149.28 ± 10.19	189.04 ± 17.10	134.91 ± 15.06

Table 11. Results of Systemic Blood Pressure Parameters in 8 dogs with spontaneous diabetes mellitus administered Ginseng versus Placebo. Data represents the mean ± standard deviation of results obtained on days 0, 28, and 56 for each treatment for all 8 dogs.

Variable	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
Mean arterial blood pressure mmHg	103.65 ± 12.68	106.03 ± 16.69	111.55 ± 22.71	107.27 ± 22.41	107.72 ± 21.12	103.44 ± 12.93
Diastolic blood pressure mmHg	86.07 ± 11.4	88.32 ± 14.32	95.62 ± 24.68	80.49 ± 15.72	86.44 ± 20.63	82.22 ± 12.56
Systolic blood pressure mmHg	126.77 ± 14.75	128.54 ± 19.31	139.89 ± 23.97	138.03 ± 22.45	137 ± 21.59	140.92 ± 18.83

Glucose Curves for All 8 Dogs for Days 0, 28 and 56 for Placebo and Ginseng Treatments

Dog 1: Placebo first, ginseng second; Lente Insulin

Time (hrs)	Day Placebo	Day 28 Placebo	Day 56 Placebo		Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng
1	7	15.7	7.3		15.1	12	14.6
2	8.7	20	9.6		9.2	4.5	14.9
3	10.1	11.9	6.6		6.9	5.9	11.4
4	8.8	8.7	5.9		6.6	5.6	8.7
5	7.2	7.3	5.1		7.2	5.8	7
6	8.1	8.2	4		8	6.2	5.2
7	10	8.4	3.3		10.4	6.4	6.3
8	15.2	8.9	4		12.1	6.5	5
9	18.6	11.1	6.6		16.3	8.4	5.5
10	26.3	14.9	11.4		17	14.5	4.8
11	18.7	14.9	18.5		19.1	18	4.4
12	11.2	21.2	17.7		18.9	19.7	4.5
13	9.9	19.3	17.7		19.3	19.6	4.9

*Units for all glucose concentrations are mmol/L

Dog 2: Ginseng first, placebo second; Lente Insulin

Time (hrs)	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng		Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
1	17.4	18.9	15.4		12.8	7	10.9
2	16	17.4	14.8		12.5	7.1	9.5
3	13.5	17.2	13.5		12.3	5.3	8.3
4	13.5	19.6	12.6		9.5	5.6	9.9
5	14.7	18.3	13.1		8.3	6.1	6.4
6	15.7	16.7	13.4		7.9	6.2	6.6
7	16	16.3	12.3		6	6.4	5.6
8	15.2	14.5	13.3		5.3	5.6	5.6
9	15	17.4	12.5		6.3	7.9	8.3
10	16.4	16.5	13.7		7.5	10.9	13.7
11	17.7	18.8	15.4		12.2	19	16.6
12	18.8	18.8	16.6		14.6	18.1	16.7
13	19.5	19	17.8		11.8	17.6	13.7

*Units for all glucose concentrations are mmol/L

Dog 3: Placebo first, ginseng second; NPH Insulin

Time (hrs)	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo		Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng
1	13.5	12.7	10.1		9	14.8	13
2	7.6	6.9	4.8		6.3	14.7	8.7
3	5.6	4.6	4.4		6.1	13.3	8.2
4	4.2	4.3	4.4		7.9	14.2	7.4
5	4.9	4.7	5.6		6.2	13.1	7.2
6	4.1	4.3	6.7		9	14.4	7.5
7	4.2	4.9	5.8		10.4	17.9	9.6
8	6.2	4.9	6		15	17.9	11.4
9	7.4	5.2	8.1		16	20.7	14.9
10	9.4	5.5	8.1		12.7	20.5	14.8
11	9.1	5.3	8.5		15	21.5	14.8
12	12.7	5.8	8.3		18	19.7	13.2
13		2.9	12.1		17.8	20.3	13.3

*Units for all glucose concentrations are mmol/L

Dog 4: Placebo first, ginseng second; Lente Insulin

Time (hrs)	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo		Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng
1	6.2	23.7	14.6		10.2	8.6	3.1
2	13.9	18.7	11.2		8.5	9.8	4.1
3	10.2	14.23	7.8		9.3	10.1	5.3
4	9.9	16.1	7.2		9	11.4	7.5
5	7.3	13.8	7.2		10	10.1	7.5
6	7.5	14	7.7		11.6	9.2	7.9
7	7.3	16	7.5		11.2	9.2	7.7
8	5.8	17.5	6.2		11.6	12	8.6
9	4.3	16.6	4.8		12.2	10.4	8.5
10	4.7	17.3	3.4		8.7	8.9	9.2
11	5.9	17.9	4.2		9.3	6.8	11.7
12	6.3	17.6	5.4		9.4	6.4	12.4
13	8.9	19.6	7		10.1	4.9	17.7

*Units for all glucose concentrations are mmol/L

Dog 5: Placebo first, ginseng second: Lente Insulin

Time (hrs)	Day 0 Placebo	Day 28 Placebo	Day 56 Placebo		Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng
1	11.7	16.4	2.6		11.7	5.9	10.1
2	12.5	17.2	5		13	5.7	16.6
3	9.9	17.6	5.7		11.6	5	17
4	4.5	14.1	6		6.9	4.3	16.1
5	7.7	12.3	5.8		6.6	5.5	13.1
6	7.5	11.1	6.8		7.6	6.1	13.5
7	6.6	12.9	8		11.6	7.3	13.7
8	8.4	.	10.5		10.2	9.8	13.4
9	8.4	14.8	11.6		11.2	13	6.6
10	9.3	15.1	10.4		8.9	13.5	18
11	9.2	16.6	13.1		7.3	16.4	15.8
12	9.2	14.6	11.7		11.2	14.8	19.3
13	14.6	9	9.9		9.1	11.7	16.2

*Units for all glucose concentrations are mmol/L

Dog 6: Ginseng first; placebo second: Lente Insulin

Time (hrs)	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng		Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
1	20.8	15.2	15.3		15.1	22.2	20.2
2	15.6	11	12.1		13.1	20	.
3	10.1	7.8	11.6		12.1	17.2	18
4	10.3	7.8	11.2		13.1	15.6	.
5	10.7	7	11.3		12.5	20.4	16.7
6	10.7	8.4	13.6		12.1	25.2	.
7	11.8	9.8	12.1		11.7	28.3	14.8
8	11.8	12	15		8.5	26.7	.
9	.	15.2	15.1		8.2	27.9	15.8
10	8.1	17.3	15.6		7.8	26.8	.
11	8.8	15.9	17.5		9	24.8	20
12	9.6	15.6	15.3		14.8	25.9	.
13	13.8	19.4	16.1		15.6	23.9	18.8

*Units for all glucose concentrations are mmol/L

Dog 7: Ginseng first, placebo second; NPH insulin

Time (hrs)	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng		Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
1	19.4	21.2	18.2		17.6	17.3	4.4
2	17.7	18.3	.		.	.	.
3	15	13.1	13.9		12.4	15.1	4.5
4	13.3	11.1	.		.	.	.
5	11.8	9.3	13		7.5	9.2	6
6	13.6	7.9	.		.	.	.
7	13.6	7.2	14		9	9.5	6.2
8	14.4	8.2	.		.	.	.
9	14	8.1	17.8		11.4	8.4	7.3
10	14.3	7.1	.		.	.	.
11	12.4	7.3	17.1		14.3	11.3	10.9
12	13.4	7.9	.		.	.	.
13	15.1	.	17.9		16.8	15.1	13

*Units for all glucose concentrations are mmol/L

Dog 8: Ginseng first, placebo second; NPH insulin

Time (hrs)	Day 0 Ginseng	Day 28 Ginseng	Day 56 Ginseng		Day 0 Placebo	Day 28 Placebo	Day 56 Placebo
1	13	21.5	12.8		11	10.4	9.8
2	13.5	11.6	12.1		.	.	.
3	8.5	10	9.1		7	6.4	6.1
4	5.4	9.2	7.7		.	.	.
5	4.8	10.1	6.7		7.6	8.6	4.7
6	4.6	11	6.9		.	.	.
7	6.2	12.5	8.2		11.6	13.8	6.7
8	6.7	12.3	9.4		.	.	.
9	6.6	10.6	12.8		13.6	13.5	12.4
10	6.9	9.7	13.2		.	.	.
11	7.8	10.9	15.8		15.8	14.9	13.7
12	10.8	11.1	16.2		.	.	.
13	15	11.3	14.2		14.3	14	12.9

*Units for all glucose concentrations are mmol/L