THE EFFECTS OF A COMBINED DIETARY AND EXERCISE INTERVENTION VERSUS DIETARY INTERVENTION ALONE IN CHRONICALLY OVERWEIGHT AND OBESE DOGS ENROLLED IN A WEIGHT LOSS PROGRAM

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Faculty of Veterinary Medicine

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ABSTRACT

Obesity is the most common nutritional disorder encountered in small animal medicine, affecting 25-40% of pet dogs and cats. Obesity has been linked to the development of a number of chronic health conditions in both humans and companion animals, potentially compromising the quality of life of affected individuals. Although previous studies in people strongly support obesity as a risk factor for all-cause mortality, it is only recently that a similar relationship has been found between poor physical fitness and mortality. Prospective studies have demonstrated the health benefits of improving physical fitness in both obese and non-obese people. The potential health benefits of routine exercise in companion animals, and its role in the treatment of canine obesity, have not yet been objectively evaluated.

This study evaluated the effects of a combined exercise and diet intervention versus a diet intervention alone in 16 dogs enrolled in a 4-month weight loss program. The subjects were overweight or obese adults of medium to large breed. The dietary intervention consisted of a 30% restriction of the animals' previous caloric intake. The dogs in the combined dietary and exercise intervention group underwent the same dietary restriction and were walked for 45 minutes, three times a week. The subjects lost a mean of 9.3% of their initial body weight. No significant differences ($p>0.05$) between the treatment groups were found with regard to changes in body weight, body condition score, waist circumference, systolic blood pressure, and insulin, triglyceride, and cholesterol concentrations. Although this study did not find a benefit to exercise as an adjunct to dietary restriction in a weight loss program, further studies are required to determine whether a higher intensity exercise program may be beneficial.

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GENERAL INTRODUCTION

Obesity can be defined as an excess of body fat that is sufficient to impair health or body function (1). Obesity is the most common nutritional disorder encountered in small animal medicine, affecting 25%-40% of pet dogs and cats (2-4). Obesity may contribute to the development of chronic conditions such as diabetes mellitus, osteoarthritis, heat and exercise intolerance, respiratory disorders, and certain cancers and may increase the risk of mortality in these patients (4-8). Currently, treatment for canine and feline obesity centers on dietary modifications with a lesser emphasis placed on increased physical activity (9-11).

Recent advances in human medicine have demonstrated an important relationship between physical fitness and mortality, independent of body weight (12-13). These studies showed a negative association between physical fitness and mortality from "obesity-related" diseases, even in overweight and obese people. In addition, studies evaluating weight loss protocols have shown that combining dietary and exercise interventions may be more beneficial to improving the risk profile of obese patients than participating in either intervention alone (14-15). These recent findings and others have caused a shift in treatment recommendations for obesity towards a combination of physical activity and dietary modification, rather than simple weight loss through caloric restriction (16).

Physical fitness is a facet of canine health that requires further study. Few quantitative measures of physical fitness have been established in dogs, making it difficult for the practicing veterinarian to judge fitness in pets. It has been suggested that the sedentary lifestyle of North American pet owners is paralleled in their canine

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counterparts. This decrease in exercise coupled with overfeeding of highly palatable diets is thought to be contributing to the increased prevalence of obesity in pet dogs (11). What is not known, however, is whether improving physical fitness in these animals through increased physical activity would have the same beneficial health effects that have been demonstrated in humans.

The goal of this study was to determine the usefulness of increased physical activity as an adjunct to weight loss achieved through decreased caloric intake in overweight and obese dogs. Based on human data, decreasing obesity through dietary intervention without increasing physical fitness may not be as beneficial to improving overall health as was previously thought. If the same holds true for canine patients, the underlying risks associated with obesity may not be attenuated simply through dietary modifications. This study will provide veterinarians with a better understanding of fatness and fitness in canine health, improved regimens for the treatment of obesity, and result in better methods for prevention of obesity-related diseases.

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1. LITERATURE REVIEW.

1.1. OBESITY

1.1.1. Physiology of Weight Control

Body weight is regulated through a complex system of hormonal, mechanical, and neural signals that are still not fully understood. As both food intake and energy output affect body weight, regulation of feeding and energy efficiency is paramount for the control of body weight. Normally, pathways that send the brain information about the amount of body adiposity allow changes in feeding behavior and energy expenditure to occur, ensuring body weight homeostasis (17).

The lipostatic model of body weight regulation presumes a set point of body adiposity, determined by a combination of genetic and environmental factors. Perturbations of body adiposity are addressed through adaptive responses in energy intake and expenditure to restore adiposity to its predetermined range (18). For this system of body weight regulation to be functional, afferent adiposity signals need to be present in order to communicate the level of body adiposity to the brain. Two hormones, insulin and leptin, have been studied as candidate adiposity signals in human and rodent models (17).

The pancreatic hormone, insulin, was the first hormonal signal to be implicated in the central control of body weight. Although insulin's peripheral effects favor fat deposition, its central effects appear to have an opposing action (19). Obesity reduces peripheral tissue sensitivity to insulin by stimulating compensatory insulin secretion and resulting in increased serum and brain insulin concentrations. Thus, increases in body fat result in increased insulin delivery to the brain (20). Insulin receptors present within

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areas of the brain are important for body weight control, and central administration of insulin has been shown to reduce food intake and increase energy expenditure, thus promoting a decrease in body fat (19, 21). Insulin deficiency results in an increase in appetite but not peripheral obesity, due to the importance of insulin for fat deposition.

The discovery of leptin in 1994 was an important step in further understanding the mechanisms of long-term body weight control. The gene encoding leptin is expressed primarily in white adipocytes (22). Leptin is released by the adipose tissue into the peripheral circulation in proportion to body-fat content (23). Changes in body adiposity are paralleled by changes in circulating leptin levels, resulting in increased levels of leptin also crossing the blood-brain barrier. Within the brain, leptin interacts with its receptor, causing a reduction in appetite and increased thermogenesis, which work to decrease body fat (22). The absence of a functional leptin system has been associated with morbid obesity in both humans and rats possessing mutations in the genes encoding leptin or the leptin receptor (24,25).

Insulin and leptin directly stimulate catabolic neuropeptides and suppress anabolic neuropeptides within the hypothalamus. The primary hypothalamic targets of insulin and leptin are the catabolic proopiomelanocortin/cocaine-and-amphetamine-regulated transcript (POMC/CART) neurons and the anabolic neuropeptide-Y/Agouti-related protein (NPY/AgRP) neurons within the arcuate nucleus (17,18, 26). Neuronal activation by leptin or insulin causes cleavage of POMC, resulting in formation of melanocortins, including alpha-melanocyte-stimulating hormone (α-MSH). Melanocortin receptors are present in areas of the brain that regulate food intake and autonomic activity; their activation results in a decrease in food intake and increase in energy expenditure (17,18).

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Mice lacking certain melanocortin receptors are hyperphagic and grossly obese, further supporting the catabolic role of melanocortins (27). Catabolic CART neurons are co-localized with POMC and are also stimulated by leptin and insulin (18).

Stimulation of anabolic NPY/AgRP neurons occurs in response to negative energy balance, in the absence of leptin and insulin. Central administration of neuropeptide Y increases food intake and decreases energy expenditure in rodents. NPY release also affects hormone regulation, producing hyperinsulinemia and an increase in glucocorticoid production. The resulting hormonal changes promote lipid accumulation in adipocytes and reduce thermogenesis (18). However, mice lacking NPY do not exhibit hypophagia or thinness indicating that other appetite-stimulating systems in the hypothalamus also exist (28). NPY may play a more important role in severe starvation where leptin and insulin concentrations are markedly decreased (18). Agouti-related protein exerts its effects by competitively antagonizing melanocortin signaling, thus enabling NPY/AgRP neurons to both stimulate anabolic pathways and suppress catabolic pathways, to promote weight gain (17).

The second-order neuron model hypothesizes that the central effects of leptin and insulin are mediated through connections between the neurons of the arcuate nucleus (first-order neurons) and neurons in other areas of the brain (second-order neurons). NPY/AgRP and POMC neurons connect with neurons in the lateral hypothalamic area, known as the hunger center, that express anabolic neuropeptides such as melanin-concentrating hormone (MCH) and orexins A and B (17,18, 26). As well as stimulating appetite, MCH is thought to decrease energy expenditure by suppressing the thyroid axis (29). Overexpression of MCH mRNA has been documented in obese leptin-deficient

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mice, and MCH-knockout mice are anorexic and thin, confirming the role of this peptide in body weight control (29,30). The importance of orexins A and B as appetite stimulants has recently been debated. Although central administration of orexins in rodents results in hyperphagia, orexin-knockout mice are not emaciated despite a mild decrease in appetite, and food deprivation in dogs does not increase orexin levels in cerebrospinal fluid (31). Expression of the orexin gene in the hypothalamus does decrease, however, when appetite is inhibited by leptin administration (32).

Neuropeptide Y/Agouti-related protein and POMC neurons communicate with brainstem areas involved in food-intake control, notably the nucleus of the solitary tract. This nucleus has been suggested to be the primary target of food-stimulated satiety signals that contribute to the termination of meals, including mechanical stretch, cholecystokinin, glucagon, glucagon-like peptide-1, and bombesin-related peptides (33). Leptin and insulin may affect the size or frequency of individual meals by modulating hypothalamic sensitivity to these satiety signals (18). Recently, leptin has been shown to potentiate the effect of cholecystokinin on the activation of the nucleus of the solitary tract, thus promoting the sensation of satiety (34).

Finally, projection of the NPY/AgRP and POMC neurons to the hypothalamic paraventricular nucleus (PVN) has been documented. The PVN appears to modulate the sensation of hunger and has been identified as a center of satiety. In contrast to the anabolic lateral hypothalamic region, PVN output is predominantly catabolic and is mediated through the synthesis of thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and oxytocin. These neuropeptides have been demonstrated to reduce food intake and body weight when administered centrally (17,18).

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Leptin's peripheral actions may be as important as its central effects in increasing energy expenditure. Leptin increases norepinephrine turnover in thermogenic tissues, particularly brown adipose tissue, resulting in the activation of uncoupling proteins that augment thermogenesis (35). Leptin may also favor the internal consumption of fatty acids as thermogenic fuels within adipose cells (36). These actions result in a net increase in energy expenditure in mice (37). In humans, however, leptin has not been observed to affect energy expenditure, which may indicate an important interspecies difference in energy regulation (26).

The newly discovered hormone ghrelin, first described in 1999, has been implicated in both the short-term and long-term control of body weight and appetite. Ghrelin is released from endocrine cells of the gastrointestinal tract in humans, rodents, and dogs (38). Contrary to the effects of insulin and leptin, ghrelin has been shown to activate NPY/AgRP neurons in the arcuate nucleus, thus resulting in appetite stimulation (39). Peripheral administration of ghrelin to rodents has been shown to greatly increase food intake (40). In humans, circulating ghrelin concentrations sharply increase before, and fall after, eating a meal, suggesting a role for ghrelin in the initiation of meal intake (41).

The majority of research concerning body weight control has been done using murine and human models, with considerably less focus on companion animals. Canine and feline leptin have been isolated (42,43), and canine leptin DNA has been cloned in order to facilitate further research (44). In both cats and dogs, a linear association has been demonstrated between levels of body adiposity and plasma leptin levels, suggesting a role for leptin as an afferent adiposity signal in these species (45,46). Administration of

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recombinant human leptin in dogs has resulted in decreased body weight, body fat, and food intake, similar to the responses seen in rodents and humans (47). Few studies exist describing the contributions of neuropeptide Y, ghrelin, or melanocortins to body weight regulation in companion animals.

1.1.2. Obesity in Humans

1.1.2.1. Introduction

Obesity is a pathologic condition resulting from an accumulation of excess body fat (1). Obesity has emerged as one of the dominant public health issues of the past century. With over 60% of adults in the U.S. considered overweight and with worldwide rates of obesity also on the rise, the World Health Organization has declared obesity to be a global epidemic (18). Given the range of health problems associated with obesity and the economic impact of this disease, considerable funds have been invested into researching the causes, consequences, and treatment of human obesity.

1.1.2.2. Etiology

Obesity occurs when a positive energy balance occurs due to increased caloric intake or decreased energy expenditure. The excess energy is stored as triglycerides in adipose tissue, over time resulting in adipocyte hypertrophy and obesity. Underlying causes of obesity include genetic abnormalities affecting the pathways regulating body weight, and the presence of environmental factors promoting increased food consumption or decreased physical activity (48). The incidence of obesity in humans has increased dramatically over the past decades (49). Given the unlikelihood of major shifts in

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genotype occurring within that period of time, changes in our environment may be the major contributors to obesity in genetically susceptible individuals (50).

1.1.2.2.1. Genetics

The contribution of genetics to the etiology of obesity has been studied in depth. Monozygotic twins have a much greater concordance in body mass index, an indirect measure of body fat, than do dizygotic twins, despite shared environments (51). Similarly, the body mass index of adopted children is linearly related to that of their biological parents and unrelated to that of their adoptive parents, despite an environment shared by their adoptive, but not biological, parents (52). From these and similar data, it has been concluded that an important heritability component to obesity exists (51).

Monogenic obesity disorders are rare in humans, with even the most common form accounting for only 4% of markedly obese people (53). Mutations in six human genes have been identified as causes of morbid obesity independent of environmental factors or modifier genes. These mutations occur in the genes encoding for the leptin-melanocortin signaling pathway and include the genes for leptin, the leptin receptor, POMC, and the major melanocortin receptor (18). The loss of this pathway results in hyperphagia, a marked decrease in catabolism, and loss of suppression of the obesity–promoting NPY signaling pathway.

Polygenic disorders are more common and appear to increase susceptibility to obesity only under predisposing environmental conditions. Exposure to high caloric intake or reduced energy expenditure will result in a greater increase in body weight in genetically susceptible individuals over that of the normal population (51). Fifty-eight putative susceptibility genes for human polygenic obesity have been identified and 59

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chromosomal regions have been described as likely to encode for obesity-susceptibility genes (18). Numerous polygenic inheritable syndromes that include the obesity phenotype have been described in humans, including Prader-Willi, Bardet-Biedl, and Lawrence-Moon syndromes (51, 54).

Although absolute leptin deficiency in humans is rare with only two of several thousand families with inherited obesity disorders affected by a mutation in the leptin gene (25), relative leptin resistance appears to be common in obese individuals. Plasma leptin levels are increased in the majority of obese humans and correlate positively with the degree of obesity (55). Leptin crosses the blood-brain barrier through a saturable transport mechanism that may be overwhelmed in situations of high circulating leptin concentrations. Leptin resistance may therefore be due to a decrease in transport of leptin from the blood to its effector sites within the hypothalamus (56). A defective intracellular signalling pathway in obese individuals is another hypothesized mechanism of leptin resistance (48). Regardless of the cause, the presence of leptin resistance explains the relative ineffectiveness of leptin therapy to induce weight loss in obese humans that do not have a primary leptin deficiency (48).

Genetic alterations that cause obesity may not be confined to the pathways associated with body weight control. Genes associated with behavior may also play a role in susceptibility to obesity (54). Certain behavioral traits often associated with obesity, including compulsion, social disaffiliation, and vulnerability to stress have been linked to an alteration in the human serotonin transporter gene (57,58). Altered brain serotonin concentrations may therefore promote behavioral changes that lead to overeating, decreased physical activity, and obesity. Dopamine levels may also play a

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role in the development of obesity. In one study, availability of dopamine D2 receptors was inversely correlated with body-mass index in obese individuals, underlining a potential role for dopamine deficiency in behavior-related obesity (59). Finally, a genotype resulting in increased density of lingual taste receptors may predispose affected individuals to obesity by increasing the palatability of foods and therefore promoting overeating (54). Although none of these genetic abnormalities alone would likely result in obesity, individuals affected by them are more susceptible to weight gain within a favorable environment.

1.1.2.2.2. Environment

The World Health Organization Consultation on Obesity concluded that environmental factors, coupled with behavioral changes, are responsible for the significant rise in obesity over the past twenty years (60). Reliance on automobiles, elevators, escalators, and other labor saving devices, as well as recreational activities that have shifted towards computers, electronic games, and televisions, have led to the development of a highly sedentary population (50). Despite an increase in the number of health clubs, biking trails and gyms, only 22% of adults in the United States engage in physical activity on a regular basis (61). In addition, participation in aerobic activity declines during the passage from adolescence to adulthood, with the greatest deterioration in physical activity occurring between 15 and 18 years of age (62).

Manufacturer emphasis on attractive food packaging and enhanced food flavoring; easy access to restaurants, convenience stores and grocery stores; and increased availability of fast food and energy-dense snacks in schools, shopping centers and other public buildings, encourage caloric over-consumption (50). High-fat foods

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especially may contribute to increased caloric intake, as these foods are typically more calorie-dense (63), and fat has a weak satiating capacity compared to protein and may contribute to overeating (64). Theories on the importance of dietary fat in the development of adiposity have been undermined by the advent of fat-free and reduced-fat products, leading to a decline in fat consumption but a continuing increase in incidence of obesity (65). Consumption of food products that are low in fat but energy-dense still promotes obesity (66).

1.1.2.2.3. Neuroendocrine Factors

Certain neuroendocrine diseases have been implicated in the development of obesity. Hyperadrenocorticism, hypothyroidism, and polycystic ovarian syndrome are some of the hormonal conditions that contribute to increased body fat in humans. These conditions, however, account for only a very small percent of morbidly obese individuals (54).

1.1.2.3. Clinical Assessment of Obesity

Numerous methods for establishing a clinical obesity score have been developed in human medicine to assess and quantify obesity. To be useful, clinical scores need to correlate well with risks of developing obesity-related disorders and they must be practical and easy to calculate in a clinical setting (67).

1.1.2.3.1. Laboratory Measures

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Several technologically advanced methods of determining body composition exist. Although these methods are highly accurate, they are generally used only for research purposes. Hydrostatic weighing, dual-energy x-ray absorptiometry, and bioelectrical impedance analysis are methods of obesity assessment that are used for research (60). In addition, computed tomography and magnetic resonance imagining can be used to quantify and anatomically locate fat deposits in individuals, allowing more accurate assessment of intra-abdominal fat (67). These methods are considered gold standards and are used to assess accuracy of more clinically applicable measures of obesity.

1.1.2.3.2. Body Mass Index

Body mass index (BMI) was first introduced in 1835 and represents a two-dimensional measure that minimizes variability secondary to individual skeletal frame. Body mass index is calculated through the division of weight, in kilograms, by the square of height, in meters. Aside from its ease of calculation, BMI has been shown to correlate highly with most laboratory measures of body fat and is currently the preferred method of expressing body weight (60). Its major limitation is its inability to differentiate between weight due to fat and weight due to muscle, therefore tending to falsely classify very muscular individuals as overweight (60). Grade of obesity is generally defined according to BMI, with BMIs between 25 and 30kg/m^2 being considered overweight (grade I obesity), and individuals with BMIs greater than 30kg/m^2 classified as obese (grade II obesity) (68). The World Health Organization has proposed a sliding scale of BMI scores that allows classification of individuals according to risks of obesity-related morbidities and mortality (69).

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1.1.2.3.3. Waist Circumference

Waist circumference provides an accurate measure of intra-abdominal fat (70). This measurement may have paramount importance in the assessment of obesity-related disorders because visceral obesity has been identified as a more important risk factor than overall obesity (as assessed by BMI) for several co-morbidities (70). Waist measurement is considered simple and reliable, is virtually unaffected by height, and has been recommended by the National Institute of Health as a tool for monitoring and quantifying obesity (71).

1.1.2.3.4. Waist to Hip Ratio

Waist to hip ratio (WHR) assesses visceral adiposity in a manner similar to waist circumference. Several cross-sectional studies have identified WHR as an important prognostic indicator for the development of obesity-related diseases, independent of BMI (70). Waist to hip ratio has been proposed as a more useful measurement of abdominal adiposity than waist circumference because it can account for body frame by comparing waist circumference to hip girth, which should not alter with abdominal adiposity (72). Gluteal adiposity, however, may falsely decrease the WHR, and studies using computed tomography have suggested that waist circumference is a more accurate assessment of intra-abdominal fat content than WHR (73).

1.1.2.4. Health Implications of Obesity

Obesity has long been identified as a major health risk in developed countries. In the US, the direct costs of obesity have been estimated to be 7% of total health care costs

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(74). Multiple studies have affirmed high BMI levels as risk factors for all-cause mortality in men and women (75-77).

1.1.2.4.1. Hypertension

Hypertension is an important consequence of obesity in adults. The prevalence of hypertension in morbidly obese people is greater than 60% (78). Both systolic and diastolic blood pressures increase in a linear manner with increases in body mass index or waist circumference (79). Hypertension is a major contributor to cardiovascular disease in people (80), and can also have adverse effects on kidney function and the central nervous system.

The mechanisms leading to obesity-associated hypertension are still under investigation. Increased sympathetic nervous system (SNS) activity has long been implicated as a hallmark of obesity-associated hypertension (81). An increase in SNS activity results in an increased total peripheral resistance and increased cardiac output, leading to hypertension. Exactly how obesity leads to increased SNS output is not fully understood, but increased circulating concentrations of insulin and leptin have both been considered potential activators of the SNS (81).

Insulin in particular may be related to hypertension, as the estimated prevalence of insulin resistance among hypertensives is 25-47% (82). Although a direct cause-and-effect relationship has not been determined, hypertensive patients have been shown to have higher fasting and postprandial insulin levels than normotensive individuals, independent of body fat distribution (83). In addition to the increased SNS activity associated with hyperinsulinemia, insulin promotes thermogenesis in states of over-nutrition, a process that secondarily increases metabolism, heart rate, and blood pressure

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(84). Hyperinsulinemia and visceral obesity can also cause impaired production of nitric oxide, an important vasodilator, thereby leading to enhanced vasoconstriction and increased peripheral resistance (85). Insulin upregulates angiotensin II receptors, resulting in increased activity of the renin-angiotensin-aldosterone system (RAAS) (86). The RAAS is an important contributor to hypertension in obesity, as will be discussed later.

Renal mechanisms of obesity-associated hypertension have been investigated. Common renal histopathologic findings in animal models of obesity-induced hypertension include endothelial cell proliferation, increased deposition of hyaluronate in the inner medulla, and glomerular basement membrane thickening (87). Normally, an increase in arterial blood pressure increases sodium excretion, a phenomenon known as pressure natriuresis. In animal models of obesity-associated hypertension, however, renal sodium excretion is normal despite increased arterial pressure (88). It may be that the obesity-associated changes in renal structure lead to an increase in intrarenal pressure, resulting in a shift of the pressure-natriuresis curve towards higher blood pressure levels. This shift would ultimately lead to sodium retention, increased intravascular volume, and increased blood pressure (89).

The RAAS is thought to play a major role in obesity-associated hypertension (90). Enhanced activity of the RAAS has been documented in obese hypertensive individuals, with a positive correlation shown between plasma renin, angiotensin, and angiotensin-converting enzyme (ACE) activity, and body mass index (91). Activation of the RAAS in obese individuals has been postulated to be secondary to increased intrarenal pressure from perirenal fat deposition, although increased circulating levels of leptin and tumor

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necrosis factor-alpha may also play a role (92). Increased angiotensin II concentrations lead to hypertension through enhanced SNS activity, stimulation of aldosterone-mediated sodium and water retention, and direct systemic vasoconstriction, thereby increasing peripheral vascular resistance (92).

Although the systemic RAAS plays an important role in blood pressure regulation, a local RAAS within adipose tissue has also recently been documented and may be involved in the pathogenesis of obesity-associated hypertension (91). It has been shown that the expression of genes encoding renin, ACE, and the angiotensin 2 (AT2) receptor in subcutaneous abdominal adipocytes is increased in obese, hypertensive women (93). In addition, a positive correlation has been found between human obesity and the expression of angiotensinogen in subcutaneous and visceral adipose tissue (94,95). In animal models, angiotensin II produced locally in adipose tissue has been shown to enter the systemic circulation thus enabling the hormone to also have systemic effects on blood pressure control (96).

1.1.2.4.2. Insulin Resistance and Diabetes Mellitus

There is a well-accepted association between insulin resistance and obesity in both human and animal models of obesity (97). Insulin resistance in obese people can be associated with a cluster of metabolic abnormalities, including hypertension, dyslipidemia, and microalbuminuria, a grouping that is defined by the World Health Organization as the metabolic syndrome (98). In the US, approximately 25% of people above the age of 55 years have the metabolic syndrome (99). Although insulin resistance is presumed to influence the development of these other abnormalities in obese people, a cause-and-effect relationship has yet to be conclusively demonstrated (100).

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The development of insulin resistance has been shown to be a function of abdominal or visceral obesity rather than peripheral obesity (101). Omental fat is thought to influence insulin sensitivity in several ways. Omental fat is more resistant to insulin's effects than are other fat beds, thereby allowing for greater release of non-esterified fatty acids (NEFAs) into the circulation because of decreased insulin-mediated suppression of lipolysis (102). This is augmented by increased sensitivity of visceral fat to the lipolytic effects of catecholamines and glucocorticoids (103). The anatomic location of excessive omental fat contributes to increased delivery of the NEFAs to the liver via the portal vein (103). Free fatty acids increase hepatic glucogenesis, leading to increased hepatic glucose release and contributing to hepatic insulin-resistance (104). In addition, NEFAs are thought to impair first-pass metabolism of insulin by the liver, thus increasing plasma insulin concentrations (105). Non-esterified fatty acids inhibit glucose oxidation in muscle, resulting in down-regulation of muscle utilization of glucose and promotion of fat oxidation as an alternative energy source. The decreased uptake of glucose by the muscle contributes to hyperglycemia and impaired glucose tolerance (106). Obesity also directly affects insulin sensitivity by down-regulating insulin receptors and impairing post-receptor signaling (106). Although compensation for the insulin resistance initially occurs through increased pancreatic production of insulin, eventually beta-cell exhaustion occurs and hyperglycemia prevails (101).

Insulin resistance and hyperinsulinemia can lead to overt type 2 diabetes mellitus in people. A prospective study of 5042 middle-aged men found that fasting hyperinsulinemia was strongly and significantly associated with the risk of developing type 2 diabetes during a 3-year follow-up (107). Body weight is also significantly

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associated with the risk of development of type 2 diabetes, with some investigators attributing up to 65% of the risk for type 2 diabetes to obesity (108). In recent years, the incidence of diabetes has increased dramatically, paralleling an equally marked rise in the incidence of obesity (109). After adjustment for age, BMI was the dominant predictor of the risk of diabetes in one large study of women (110). Central obesity again appears to be a greater risk factor than overall obesity, with a significant association found between waist to hip ratio or waist circumference and increased risk for diabetes (111,112).

More recent data support the presence of increased circulating inflammatory mediators as a risk factor for the development of type 2 diabetes (113). Adipose tissue has been shown to secrete a variety of inflammatory cytokines, including tumor-necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (103). These cytokines are important mediators of the acute inflammatory response and promote the synthesis of acute phase proteins such as C-reactive protein (CRP) by the liver (105). Circulating levels of CRP are strongly associated with BMI and waist circumference in individuals both with and without type 2 diabetes (114). In addition, one large prospective study demonstrated a significant association between elevated baseline levels of TNF-α, IL-6, and CRP, and risk of developing type 2 diabetes (113). The authors of this study suggested that increased circulating levels of TNF-α could lead to insulin resistance through the stimulation of insulin counter-regulatory hormones or cytokines, increased NEFA oxidation, direct inhibitory effects on glucose transporter proteins, or inhibition of pancreatic release of insulin. These findings suggest that obesity-induced systemic inflammation may be involved in the pathogenesis of type 2 diabetes (113).

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Type 2 diabetes is associated with considerable morbidity and mortality from nephropathy, neuropathy, retinopathy, and cardiovascular disease, and is considered the most expensive public health consequence of obesity (115).

1.1.2.4.3. Dyslipidemias

Obesity has been associated with an abnormal blood lipid profile that includes hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL), increased small and dense low density lipoprotein cholesterol (LDL) particles, increased apolipoprotein B particles, and increased very-low density lipoprotein (VLDL) (116). Several elements in this lipid profile, including hypertriglyceridemia, decreased HDL-cholesterol, and increased LDL and apolipoprotein B have been shown to increase the risk of cardiovascular disease (110). Body mass index has been significantly related to elevations in total serum triglycerides (TG) and cholesterol (117). In addition, HDL concentrations are lower in obese individuals (116,117). Due to the role of HDL in the transportation of cholesterol from the tissues to the liver for elimination, HDL is protective against the development of cardiovascular disease. Although consistent changes in LDL concentrations have not been observed in obese individuals, obesity has been associated with an increase in the number of small, dense LDL-cholesterol particles and associated apolipoprotein B particles (108, 120). Abdominal obesity appears to be particularly associated with changes in lipid profiles, with a significant correlation detected between waist-to-hip ratio and TG and HDL levels (121,123). This association may be more important in women; both abdominal and general obesity appear to equally predispose to the development of dyslipidemias in men (116).

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Several mechanisms have been proposed by which abdominal obesity may cause abnormal lipid profiles. As previously discussed, abdominal obesity is associated with increased serum insulin levels. Insulin resistance in liver, muscle, and adipose tissue causes impaired muscle glucose uptake and decreased suppression of NEFA release from adipose tissue (116). The anatomic location of abdominal fat leads to the delivery of increased amounts of NEFAs and glucose to the liver, promoting hepatic VLDL production (124,125). Insulin resistance also results in a decrease in lipoprotein lipase activity, thereby decreasing normal lipoprotein metabolism and decreasing clearance of VLDL (126,127). The increase in VLDL concentrations causes a parallel increase in small, dense LDL molecules, as their formation is largely dependent on the metabolism of VLDL particles (116). The mechanisms resulting in decreased HDL concentrations in obese individuals are not completely understood, but may involve increased hepatic clearance of HDL due to the presence of smaller HDL particles or changes in insulin-mediated stimulation of hepatic HDL production (116).

1.1.2.4.4. Cardiovascular Disease

Abdominal obesity, as assessed by waist circumference, is highly associated with an increased risk of cardiovascular disease (128). As previously discussed, abdominal obesity is associated with hypertension, increased serum cholesterol and TG, decreased HDL, hyperinsulinemia, and microalbuminuria, collectively known as the metabolic syndrome. The presence of the metabolic syndrome is associated with a 3.4-fold increase in the risk of death from coronary heart disease or cardiovascular disease (129). Insulin resistance may play a particular role in this association, as individuals with type 2 diabetes mellitus are significantly more likely to suffer a cardiovascular event, compared

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with euglycemic individuals (130). In addition, hyperinsulinemia has been shown to predict arterial stiffness, carotid artery wall thickening, hypertension, and vasospastic angina, all contributors to cardiovascular morbidity and mortality (131).

Obesity can result in morphologic changes to the heart. Total blood volume is increased in proportion to body weight in obese individuals, leading to an increase in left ventricular preload. The increase in preload results in an increase in stroke volume and cardiac output. Eccentric hypertrophy of the left ventricular occurs as a result of the increased diastolic filling of the left ventricle and increased stroke volume. Concentric or eccentric hypertrophy can occur if hypertension is present and causing increased systemic resistance. These morphologic changes may compensate for the increased intravascular volume to a certain point; the degree or duration of volume overload, however, may lead to systolic dysfunction as a result of chamber dilatation, and diastolic dysfunction as a result of left ventricular hypertrophy. These changes may progress to clinical congestive heart failure (132).

The risk of coronary heart disease is significantly and proportionately associated with increases in BMI (133). Coronary heart disease results from the presence of atherosclerotic plaques within the coronary vessels. Atherosclerotic plaque formation is a complex process depending on several factors, including an atherogenic lipid profile, vascular endothelium dysfunction and recruitment of inflammatory cells (134). Insulin resistance or the metabolic syndrome can be associated with impaired endothelial function, leading to vasoconstriction and a pro-coagulant state (135). Inflammatory mediators synthesized by adipose tissue may up-regulate production of endothelial adhesion molecules, contributing to vascular endothelium dysfunction (113). The

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dyslipidemic profile, consisting of increased VLDL, decreased HDL, and increased small, dense LDL particles contributes to the formation of atherosclerotic plaques. Individuals with atherosclerotic plaques are more likely to have smaller LDL-cholesterol particles than are individuals without evidence of atherosclerosis (136). The smaller LDL particles are better able to travel through endothelial fenestrations into the subendothelial space, where transformation into the atherosclerotic plaque occurs (137). Protection from the risk of coronary heart disease, which is normally provided by HDL, is decreased or lost in obese individuals because of the decrease in HDL concentrations (116).

Alterations in normal hemostasis, resulting in a prothrombotic state, are thought to be important risk factors for the development of cardiovascular disease. A decrease in fibrinolytic activity has been documented in patients with visceral obesity and hyperinsulinemia, and has been implicated as a risk factor for cardiovascular disease (92). The decrease in fibrinolysis occurs as a result of an increased concentration of plasminogen activator inhibitor-1 (PAI-1), an important inhibitor of clot dissolution (131,138). Insulin resistance due to abdominal obesity may also promote a hypercoagulable state through acquired deficiencies in antithrombotic molecules such as factor C, factor S, and antithrombin III, as well as increased expression of prothrombotic molecules such as tissue factor and fibrinogen (139). An increase in fibrinogen levels has been documented as an independent risk factor for cardiovascular disease (140). The increase in small LDL particles may also potentiate the prothrombotic state. LDL receptors are present in platelets, and their activation can result in increased platelet

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aggregation and increased binding to endothelium, thus contributing to thrombus formation (134).

1.1.2.4.5. Sleep Apnea

Obstructive sleep apnea is a breathing disorder particularly prevalent amongst middle-aged, obese men (141). One study documented a four-fold increase in risk of sleep-disordered breathing in overweight individuals (141). This association between body adiposity and sleep apnea appears logical because an increased amount of fat in the thorax and abdomen leads to a reduction in lung volume and a decrease in lung compliance, especially when the individual is recumbent (132). Sleep apnea consists of a vicious cycle of weight gain, hypoventilation and breath cessation during sleep, disturbed sleep patterns, daytime drowsiness, and further weight gain, and is associated with significant morbidity and mortality (142). Sleep apnea may be independently associated with insulin resistance, even in non-obese subjects (143), and appears to be more prevalent in those individuals with abdominal obesity rather than peripheral obesity (144).

1.1.2.4.6. Musculoskeletal Disorders

Obesity is considered one of the most important preventable risk factors for knee and hip osteoarthritis in people (145). The relationship between body weight and osteoarthritis can be explained by increased joint pressure in the knees and hips of obese individuals (115). However, a metabolic component may also be involved because obesity appears to be related to osteoarthritis in the hands, a non weight-bearing location (145).

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1.1.2.4.7. Cancer

An increased risk of several cancers is thought to be associated with increased body weight, including cancer of the endometrium, prostate, breast, gallbladder, and colon. One panel of experts estimated that 30-40% of all cancers are attributable to inappropriate diet, lack of physical activity and increased body weight (146). In general, the relationship between obesity and cancer may be a result of the altered metabolic milieu. In particular, growth of tumors may be favored by increased availability of glucose, an important fuel for neoplastic cells, due to decreased tissue utilization of glucose in the insulin-resistant state (115). Detection of cancer may also be impeded by the presence of excess adipose tissue, particularly mammographic detection of breast cancer (147). In addition, obese women have been found to be less likely to participate in cervical and breast cancer screening programs than normal-weight women (148).

Obesity has been associated with a two-fold increase in the risk of developing breast cancer in post-menopausal women (149). Conversion of adrenal androgens to estrone has been demonstrated in female adipose tissue, resulting in higher circulating levels of estrogen in obese women (150). Increased levels of estrogen may play a role in the etiology of breast, endometrial and prostate cancer (151). In addition, insulin resistance may contribute to the development of breast cancer because insulin normally down-regulates sex hormone binding globulin, and insulin resistance results in increased levels of bioavailable estrogen and testosterone (152).

Colonic cancer also occurs more frequently in obese men. Although the relationship between colonic cancer and body weight is not fully understood, decreased physical activity, resulting in a slower gastrointestinal transit time, may be involved

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(115). A decreased transit time would result in greater exposure of gut toxins to the colonic mucosa. High-fat diets have also been implicated (67).

1.1.2.4.8. Gallbladder Disease

It has been reported that 28-45% of morbidly obese individuals are affected by gallbladder disease (153). In addition, obese individuals are 3 to 4 times more likely to develop gallstones than are normal-weight individuals (154). It has been hypothesized that obese individuals have impaired gallbladder contraction, resulting in poor emptying of the gallbladder and biliary stasis (155). Gallstones are composed primarily of cholesterol and may occur more frequently in obese individuals because of increased synthesis and subsequent biliary excretion of cholesterol (156). Gallbladder disease, which occurs more frequently in obese women, may also predispose to gallbladder cancer (157).

1.1.3. Obesity in Companion Animals

1.1.3.1. Introduction

Obesity is the most common nutritional disorder in companion animals (4,11,158). The prevalence of obesity in dogs and cats in the United States and the United Kingdom has been found to be between 25% and 40% (2-4). While the health implications of obesity are not as well documented in companion animals as in people, obesity has been implicated in the development of many chronic diseases and may contribute to a shortened life span (6,10,11). Both cats and, in particular, dogs, have been used as models for research focused on human obesity prevention and treatment, thus

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indirectly increasing our knowledge of obesity in veterinary patients. A focus in veterinary medicine on preventative medicine and pet health has made the issue of canine and feline obesity one of great interest and economic impact.

1.1.3.2. Etiology and Risk Factors

At the most simplistic level, the development of obesity in companion animals can be attributed to increased caloric consumption or decreased energy expenditure resulting from either decreased physical activity or decreased metabolic rate. These factors can be influenced by genetic, environmental, and hormonal factors. The combination of sedentary lifestyle and increased access to highly palatable foods is likely responsible for the increased incidence of obesity in both humans and their pets (11).

Obesity as a result of increased caloric intake in domesticated dogs has been attributed, in part, to the evolutionary eating patterns of this species. The "feast or famine" eating pattern of wild canines, characterized by the availability of large and randomly spaced meals as a result of pack hunting, may be retained to some degree in domestic dogs despite the daily availability of food (9).

The occurrence of obesity in dogs and cats may be linked to the behavioral habits of their human companions. Several studies have surveyed owners of obese dogs in order to establish risk factors for obesity. Dogs in a single-pet household, fed once a day, fed snacks, and exercised infrequently were more likely to be overweight in one study (159). A survey of households with obese dogs found that obese dogs were more likely to sleep in their owner's bed and be present during their owner's meals than normal weight dogs. In addition, owners of obese dogs spent more time watching their dogs eat than did owners of normal weight dogs (160). These findings may indicate a relationship

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of exaggerated mutual dependency between owners and their obese dogs, which may result in overindulgence and overfeeding of the pet. Not surprisingly, the number of meals and snacks were greater in obese dogs than in normal dogs in this study (160).

Other risk factors for obesity in dogs and cats include neutering, gender, breed, and increased age (2). Reasons for increased risk of obesity in neutered pets include decreased metabolic rate, decreased physical activity, and increased food consumption following neutering (4,161). Labrador retrievers, cairn terriers, dachshunds, Shetland sheepdogs, and beagles have been determined as breeds at increased risk for the development of obesity, whereas German shepherds, racing greyhounds, and Doberman pinschers appear to be at decreased risk (2). Some studies have documented an increased risk of obesity in female dogs, whereas others have not found gender to influence occurrence of obesity (2,160).

Risk factors for obesity in cats have also been studied. In one survey, overweight cats were more likely to be of mixed-breed, neutered, male, and predominantly confined inside a house (162). Others have suggested that cats confined to apartments may be more likely to gain weight due to decreased opportunity for exercise and increased food consumption from boredom (163). The prevalence of obesity appears to be highest in middle-aged cats, potentially due to a decrease in metabolic rate with aging (162,163).

Genetic causes of obesity have not been studied in depth in companion animals. Genetics are thought to account for a portion of the variability in body mass in humans, and the same could be presumed true for dogs and cats. The increased incidence of obesity in certain dog breeds argues in favor of a genetic contribution to canine obesity (2). Hormonal causes of obesity are uncommon in both humans and companion animals.

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The most common endocrinopathies contributing to weight gain in dogs are hypothyroidism and hyperadrenocorticism, and neither disorder causes overt obesity on its own. The prevalence of these diseases in the general population is also low, with hypothyroidism occurring in only 0.2% of dogs (164).

1.1.3.3. Clinical Assessment of Obesity

Due to immense variation in breed size and build in veterinary patients, body weight alone is a poor assessor of obesity. Many of the earlier surveys of obesity in companion animals used observation rather than any defined criteria to assess obesity (2). In more recent years, various methods, both clinically applicable and research-oriented, have been developed for assessing body condition and composition in companion animals. Many of these methods have been borrowed from human medicine and adapted for the particular body conformation of cats and dogs.

1.1.3.3.1. Laboratory Methods

Various highly accurate methods have been used to assess body fat composition in a research setting. Dual energy x-ray absorptiometry produces precise measurements of bone and soft tissue body components, allowing for appraisal of fat and lean mass (165). Total body water content by deuterium oxide dilution has also been used to assess body composition in dogs, as total body water content provides an indirect measure of lean body mass (166). Magnetic resonance imagining, computed tomography and ultrasonography are other imagining techniques that are useful in a research setting for quantification and qualification of obesity in dogs and cats (167,168).

1.1.3.3.2. Body Condition Score

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Body condition scoring (BCS) is currently the most clinically applicable and frequently used method of estimating obesity in dogs and cats. Scoring systems have been developed and validated for both dogs and cats, and provide a semi-quantitative assessment of body composition. Owners can use predefined charts to objectively assess changes in their pet's body condition (167). Body condition scoring uses palpation of fat over ribs and lumbar vertebrae and visual assessment of the shape of abdomen and waist to assign scores. Although both five and nine point systems exist, the nine-point system may provide a more repeatable, reproducible, and discriminating result. Good correlation between the nine-point BCS system and percent body fat estimated by dual-energy x-ray absorptiometry has been established for both the feline and canine scoring systems (169,170). Guidelines for assessing obesity have been suggested using the nine-point system, with overweight animals having a BCS of 6 or 7 and obese patients scoring 8 or 9 (10). Others have used the five-point scoring system to define obesity, with obese patients scoring 4 of 5 and grossly obese patients scoring 5 of 5 (2).

1.1.3.3.3. Feline Body Mass Index

Although body mass index (BMI) is the most used method of assessing body composition in people, the wide variability of build among breeds makes this method less reliable in dogs. However, a BMI system has been described for use in cats. This system uses the circumference of the ribcage at the 9^{th} rib (in cm) and the distance between the patella and the calcaneal tuber of the left posterior limb (in cm) in order to calculate an estimate of percentage body fat content. A cat with a body fat content of over 30% can be considered overweight. This technique has yet to be fully validated (171).

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1.1.3.4. Health Implications of Obesity

Although much of the data concerning the health impacts of obesity comes from experimental studies where obesity has been artificially induced, consequences of natural-occurring obesity have also been evaluated in cats and dogs. In both cats and dogs, chronic obesity and/or overfeeding has been associated with a shorter life span (8,172). Little information is available, however, as to what degree of overweight or obesity is associated with negative health consequences.

1.1.3.4.1. Hypertension

Increased systolic, diastolic, and mean arterial blood pressures have been repeatedly documented in laboratory dogs made obese through feeding of high-fat diets (173-175). In contrast, few studies have evaluated arterial blood pressure in spontaneously obese dogs and cats. One epidemiological study of blood pressure in dogs documented increased blood pressure associated with increased body condition score. This finding was only statistically significant, however, when healthy and diseased dogs were grouped together, and therefore could be attributed to the presence of diseases that influence both blood pressure and body weight, such as hyperadrenocorticism (176). The most common causes of systemic hypertension in dogs and cats include chronic renal failure, hyperthyroidism, diabetes mellitus, and hyperadrenocorticism, although obesity is sometimes cited as a secondary cause of hypertension in dogs (177). It is still unknown if obesity plays a major role in inducing clinically significant hypertension in chronically obese animals.

1.1.3.4.2. Insulin Resistance and Diabetes Mellitus

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Multiple studies have documented increased fasting insulin concentrations, decreased glucose tolerance, and/or insulin resistance in laboratory dogs made obese through feeding of high-fat diets (178-180). These findings, although suggestive of a link between obesity and insulin resistance, do not necessarily reflect an increased risk of developing diabetes in spontaneously obese dogs. Feeding high-fat diets to dogs has been shown to induce insulin resistance even in the absence of increased body adiposity, presumably due to increased lipid oxidation leading to the inhibition of insulin-stimulated cellular glucose uptake (181). In diabetic dogs, obesity is the most important factor accounting for variations in insulin response, regardless of the type of diabetes (182). Therefore, although obesity does appear to have a profound impact on insulin secretion and sensitivity in diabetic and non-diabetic dogs, it is unknown whether the presence of obesity increases the risk of developing diabetes mellitus in this species (183).

In contrast, obesity has convincingly been shown to be a risk factor for developing diabetes mellitus in cats. In one study, obese cats were 3.9 times more likely to develop diabetes (6). The type of diabetes (type 1 or type 2) was not indicated in this study, but previous studies suggest that obese cats are more at risk for type 2 diabetes (184,185). Experimentally, non-diabetic obese cats also show glucose intolerance and abnormal insulin sensitivity and secretion when challenged with a glucose load (183,186,187). The cause of the altered insulin secretion in obese cats is not fully understood. Deterioration of beta cell function secondary to increased circulating fatty acids and triglycerides, beta-cell exhaustion from sustained hyperinsulinemia, and increased pancreatic amyloid deposition from beta-cell hyperstimulation have been hypothesized as potential causes (183).

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1.1.3.4.3. Dyslipidemias

Lipid profiles are altered in obese dogs and cats. Obese cats have been shown to have increased VLDL concentrations, similar to obese humans. Obese cats also have increased HDL-concentrations, as opposed to the decreased concentrations seen in obese humans (188). As previously mentioned, high serum HDL concentrations have a protective role in the development of atherosclerosis and cardiovascular disease (189). The maintenance of high HDL concentrations in obese cats may explain the very low incidence of atherosclerosis in obese cats, despite hypertriglyceridemia (188).

In dogs made obese by feeding of a high-fat diet, increases in plasma NEFAs and VLDLs have been documented, as well as decreases in plasma HDL concentrations (190). These lipoprotein abnormalities are identical to those observed in obese humans. Atherosclerosis is rare in dogs compared to humans, and obesity has not been identified as a risk factor in dogs. However, two conditions associated with hypercholesterolemia in dogs, namely diabetes mellitus and hypothyroidism, have been shown to be risk factors for the development of atherosclerotic lesions (191).

1.1.3.4.4. Cancer

Adolescent obesity in dogs has been associated with an increased risk of developing mammary cancer later in life (7). In addition, obese dogs with mammary adenocarcinoma have been found to have a poorer long-term prognosis than do lean animals with the same cancer (192). An increased risk of transitional cell carcinoma development has been associated with exposure to pesticides. This risk is accentuated by

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obesity, presumably through storage of lipophilic carcinogens within excess adipose tissue (193).

1.1.3.4.5. Osteoarthritis

It has been well documented that restriction of food consumption in growing dogs at risk for hip dysplasia is associated with a reduction in the severity of clinical or radiographic signs of hip osteoarthritis (5,194). One study evaluating the risk of orthopedic injuries in American cocker spaniels found that increased body weight was a predisposing factor for humeral condylar fractures, but not for cranial cruciate rupture (CCR) or intervertebral disk disease (IVDD) (195). In contrast, other authors have suggested an association between increased body weight and CCR and IVDD (196-198). Life span in both food-restricted and more freely fed dogs has been evaluated, and a shorter life span was found in the freely fed dogs. The shorter life span in this group was associated with an earlier onset of chronic diseases, with osteoarthritis being diagnosed the most commonly (8). In cats, obesity was associated with a 4.9 fold increase in the likelihood of presentation to the veterinarian because of lameness (6).

1.1.3.4.6. Other

Obesity may exacerbate clinical signs due to chronic respiratory conditions such as tracheal collapse and chronic bronchitis by limiting lung and thoracic cavity expansion during inspiration (199). This alteration in normal respiratory physiology may also contribute to the decreased tolerance to exercise and heat that has been noted in obese dogs (4). Obesity has been associated with compromised immune function in dogs, potentially rendering them more susceptible to viral and bacterial infections (200,201).

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One study documented an increased incidence of circulatory disorders in grossly obese dogs (2); this association has otherwise been poorly described. It has been suggested that obese animals are poorer surgical candidates due to an increased occurrence of intraoperative and postoperative complications (158). Finally, obesity has been identified as a risk factor for the development of acute fatal pancreatitis in dogs (202).

In cats, obesity is associated with an increased risk of developing hepatic lipidosis and of dying during middle age (172). Obese cats have also been found to be 2.3 times as likely to develop non-allergic skin conditions as their lean counterparts (6). This may be secondary to a decreased ability to self-groom in overweight cats. Obesity has also been implicated as a risk factor for the development of feline lower urinary tract disease (203).

1.2. Physical Fitness

1.2.1. Introduction

Physical fitness is defined as a set of traits that relate to the ability to perform physical activity (204). Physical activity is generally neglected in the American population, with only about 15% of American adults regularly engaging in the amount of exercise associated with disease prevention (205). It has been further estimated that approximately a third of individuals over the age of 18 years get no leisure-time physical activity, likely due to the popularity of television and computers as leisure-time activities (205). The US Surgeon General's report of physical activity and health recommends that adults perform 30 minutes or more of moderate-intensity physical activity on most days of the week (61). In one survey, only 17% of adults trying to lose weight were following

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the recommended guidelines for increasing physical activity in addition to lowering energy intake (206).

1.2.2. Assessment of Physical Fitness and Physical Activity Levels

Physical fitness can be roughly estimated through subjective and objective quantification of physical activity, or can be directly assessed through evaluation of cardiovascular and respiratory parameters of the individual (207). Subjectively, survey and interview techniques for self-reporting of physical activity level have been evaluated. These techniques have inherent limitations such as recall errors, deliberate misrepresentations, misapprehensions, and other biases. The correlation between these subjective measures and more objective quantifications of physical activity varies widely (208). These subjective measures are used primarily for epidemiologic studies involving physical activity and fitness.

Objectively, physical activity can be assessed through a number of techniques. Doubly-labeled water, containing radioisotopes of hydrogen and oxygen, has been used to estimate carbon dioxide production over a period of several days, and thus quantify total energy expenditure. This method is considered a gold standard in assessing physical activity, but is rarely used due to the cost and low availability of the radioisotopes (208). Whole body calorimetry has been used to validate other methods of activity assessment. This technique assesses energy expenditure by collecting all the expired gases from a subject within a sealed room (209). It has little use for evaluating daily physical activity due to the restriction of the individual to a room. Less reliable but more practical techniques include heart rate monitoring and motion detectors. The use of heart rate monitoring for assessment of physical activity relies on the linear relationship between

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heart rate and oxygen consumption. This relationship can be affected by many different variables, however, including psychological and environmental stress, caffeine, and fitness level. The robustness of the relationship is also less at lower heart rates (207). Pedometers can be used to estimate the number of steps taken over a period of time. They are inexpensive and moderately reliable, but cannot assess the intensity or pattern of the activities performed (210). Accelerometers are devices that measure accelerations produced by body movement. They are also fairly reliable for assessing physical activity, but have a limited capability to assess certain types of motion (207).

Aerobic cardiorespiratory fitness can be measured more precisely by assessing cardiovascular and respiratory responses to exertion. Three forms of physical fitness tests exist: maximal effort tests, which are considered the best measure of physical fitness; submaximal effort tests, in which maximal effort is extrapolated from the submaximal data; and field-based tests that predict fitness from a field-based performance (211). One of the most widely accepted measures of aerobic fitness is maximal oxygen consumption (VO_2max), which represents the maximum rate at which aerobic metabolism can supply energy (212). This parameter is measured through the use of indirect calorimetry during maximal effort tests. Treadmills or cycle ergometry are typically employed, with the individual experiencing increased workload intensities until volitional fatigue occurs (211). Submaximal exercise tests predict VO_2max based on the heart rate response to the work, with termination of the test occurring at a predetermined heart rate (213). These tests have the advantage of avoiding maximal efforts in patients with diseases or disabilities that preclude severe exertion (214). Submaximal testing can also be used to determine aerobic capacity, another popular index of aerobic fitness. This

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parameter identifies the maximal steady-state exercise speed or workload that can be sustained for extended periods of time (215). Lactate levels are useful for determining the aerobic capacity because lactate is produced during anaerobic conditions when the aerobic threshold has been surpassed. Generally the lactic or anaerobic threshold occurs between 50-70% of the VO_2 max (216). Field tests are used to predict VO_2 max from distances and time to completion of walking and running tests (211).

In comparison to the human literature, there are few studies of methods to assess physical fitness in companion animals. A submaximal exercise testing protocol has been described for evaluation of exercise capacity in dogs with heart failure (217). Submaximal exercise testing has been used to identify the anaerobic threshold in exercise-trained Siberian huskies (218). Submaximal exercise tests have also been described in studies evaluating the effects of training and diet on glycogen storage and lipid metabolites in sled dogs (219-220). A substantial limitation to fitness testing in companion animals may be the difficulty in training some animals to use the treadmill (217). To circumvent this problem, a more easily implemented six-minute walk test, not requiring the use of a treadmill, has been described for dogs. The walk test was designed to assess the cardiovascular reserve and exercise tolerance of veterinary patients with congestive heart failure, and similar tests are widely used for the same purpose in humans (221). To date, none of these fitness tests are used routinely in a clinical setting to assess physical fitness in companion animals.

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1.2.3. Metabolic Effects of Physical Activity

Although physical activity was traditionally considered by much of the general public to be useful only as an aid to weight loss, physical activity has now been shown to have many beneficial effects on metabolism and obesity-related disorders.

Regular exercise can result in a change in body composition, leading to an increase in skeletal muscle mass and a decrease in fat mass, including visceral fat deposits (222). This shift in body composition helps improve insulin sensitivity because skeletal muscle is the major site for glucose disposal (222) and visceral fat has been shown to be a major contributor to insulin resistance (70). In addition, a shift in the type of muscle fibers also tends to occur with regular exercise and may influence insulin sensitivity. Aerobic exercise increases type I muscle fibers which are more insulin-sensitive than are type II fibers. Type II fibers are more predominant in sedentery individuals and may contribute to insulin resistance (139).

Regular exercise also has a profound effect on the metabolic capacity of skeletal muscle, notably increasing the muscle's capacity for glucose uptake and disposal. This is accomplished through increased recruitment of the glucose transporter protein (GLUT 4), a glucose-uptake mechanism that is thought to be insulin-independent, to the skeletal muscle membrane (223). Even in insulin-resistant individuals, muscle glucose uptake may be increased following exercise (223). This improved glucose disposal is short-lived following exercise, lasting only up to 48 hours, but its effects may be increased over time. One study documented a 22% increase in insulin-stimulated glucose disposal after one exercise session, an increase that climbed to 42% after 6 weeks of exercise training (224).

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Regular exercise increases the storage capacity of energy substrates of muscle, such as glycogen and triacylglycerols, and increases the muscle's capacity for oxidative metabolism. Both carbohydrates and lipids are important fuels for the muscle during aerobic exercise, whereas carbohydrates are utilized more by the muscle during high-impact or resistance exercise (225). In addition, fat oxidation is increased following aerobic exercise, an effect that has been shown to last up to one day (225,226). These findings suggest that aerobic exercise may decrease fat mass more than does resistance exercise (225).

Physical activity is the component of daily energy expenditure (EE) that is the most variable and the most likely to be influenced by lifestyle modifications (227). Energy expenditure is elevated not only during the bout of exercise, but also for a certain time period following exercise (225). With aerobic exercise, the degree and duration of this post-exercise effect is dependent on the intensity and duration of the exercise itself, and significant effects may be seen only with high-intensity exercise (228). The major determinant of EE is resting metabolic rate (RMR), which accounts for 60-75% of EE. As the quantity of fat-free mass in an individual is a major determinant of RMR, exercise can also increase RMR via an increase in fat-free mass (225). This effect may be particularly important in instances of weight-loss programs using severe calorie restriction because depression of RMR has been documented during these conditions (229).

Exercise-trained dogs have been used to study various parameters associated with physical activity. Racing dogs, including Alaskan sled dogs and greyhounds, have been used as models to assess cardiovascular adaptations to endurance training (230,231).

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Exercise-associated metabolic changes such as serum hyponatremia (232,233), microalbuminuria (232), decreased serum thyroid hormone concentrations (235), and increased markers of oxidative stress (236) have been studied in endurance-trained dogs.

1.2.4. Health Risks of Poor Physical Fitness

Globally, a low level of aerobic fitness is an independent risk factor for all-cause mortality (237). One epidemiologic study showed that unfit men were found to have a higher all-cause mortality rate than fit men in the same BMI group (12). Erikssen et al. showed that the magnitude and direction of changes in physical fitness were strong predictors of all-cause mortality in men (13). Individuals with a low level of physical activity had a greater body weight and body fat content than their more active counterparts, thus predisposing the former to obesity-related disorders (238). Poor physical fitness in young men has been associated with an increased risk of developing hypertension (239). Physically inactive people appear to be at increased risk for insulin resistance and type 2 diabetes mellitus (239,240). Individuals with one or more chronic conditions, including diabetes, cardiovascular disease, and hypertension, have been shown to have lower levels of physical fitness than their healthier counterparts, independent of BMI (241). The US Surgeon General's Report on Physical Activity and Health suggests that decreased physical fitness is causally related to these conditions (61). Taken as a whole, these data support poor physical fitness as a major health risk in people.

Similar assessment of the risks of poor physical fitness in companion animals has not been performed.

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1.3. Benefits of Weight Loss and Lifestyle Interventions

1.3.1. Weight Loss

1.3.1.1. Humans

The risks of being overweight and obese have been well-documented. Improvement in many obesity co-morbidities has been observed with intentional weight loss. One meta-analysis assessing the effects of weight loss through dietary restriction in obese diabetic subjects demonstrated significant decreases in fasting plasma glucose, serum cholesterol and triglycerides concentrations, and systolic blood pressure (242). Improvements in all cardiovascular disease risk factors, with the exception of cholesterol, have been documented in obese men and women who lost weight through gastric surgery (243). Other studies have individually documented the benefits of weight loss for lowering blood pressure in obese hypertensive individuals (244,245), and improving lipid profiles in obese individuals with dyslipidemias (246).

Despite these documented short-term physiologic improvements, the long-term impact of weight loss and its influence on mortality remains controversial. Several studies have shown conflicting results as to the impact of weight loss on mortality, with many documenting increased mortality rates associated with weight loss (247-249). This may be due to a lack of differentiation between intentional and unintentional weight loss in these studies. Two studies that attempted to differentiate intentional and unintentional weight loss documented 20-30% decreases in mortality rates in individuals with intentional weight loss compared to those whose weight remained stable (250,251). A

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markedly increased mortality rate was seen in individuals whose weight loss was unintentional. Due to the high mortality rates in the individuals with unintentional weight loss, the overall mortality rate associated with weight loss was increased (251). Unintentional weight loss is thought to be a marker of poor health because it may be associated with older age, harmful health behaviors, and chronic diseases such as cancer and congestive heart failure. The inclusion of individuals who have unintentionally lost weight, therefore, may mask the benefits of intentional weight loss in observational studies. Other studies, however, have made the differentiation between intentional and unintentional weight loss, and have found no effect of intentional weight loss on mortality rates (252-254). Pre-existing illness in some of these individuals, however, may be confounding the association between intentional weight loss and health outcomes by contributing to the observed weight loss (255).

Benefits from weight loss are not confined to individuals losing a large percentage of their body weight. A 10-kg loss from an initial body weight of 100kg has been shown to have a beneficial impact on blood pressure, lipid profiles, and glycemic control (256,257). A loss of 5 to 10% of the patient's initial body weight has been suggested as a reasonable therapeutic target for a weight loss program (257).

1.3.1.2. Companion Animals

There are comparatively fewer studies assessing the benefits of weight loss in companion animals. Cats undergoing weight loss after high-fat diet-induced obesity demonstrated decreases in serum cholesterol, fasting insulin, and basal glucose concentrations (187). A similar study performed in ovariohysterectomized cats that were made obese by feeding an energy-dense diet documented a decrease in cholesterol after

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weight loss but no change in basal glucose or triglyceride concentrations (258). Weight loss induced by a low-fat diet was found to decrease serum cholesterol levels in spontaneously obese dogs (259). Obese dogs with coxofemoral osteoarthritis were found to have a decrease in the degree of hindlimb lameness following diet-induced weight loss (260). Dogs made obese with a high-fat diet then placed on a low-fat diet had significant reductions in total serum cholesterol concentrations and systolic, diastolic and mean arterial blood pressures with weight loss (261). Although these findings support the beneficial effects of weight loss on canine and feline health, the long-term benefits of weight loss and its impact on mortality have not been documented in companion animals. In addition, it is difficult to extrapolate to spontaneously obese dogs and cats, the health benefits seen in animals artificially made obese.

1.3.2. Increased Physical Activity

1.3.2.1. Humans

1.3.2.1.1. Promotion of Weight Loss

Exercise has been shown to play a major role in the successful weight loss program. This is not due to the direct effects of exercise on energy expenditure given that the energy deficit created by exercise alone is small compared to the effects of reduced caloric intake. Exercise alone, in fact, results in a very slow rate of weight loss (225). The combination of exercise and diet restriction has not always been shown to significantly increase weight loss (262-263). However, the addition of exercise to a weight-reducing diet reduces the loss of muscle mass, and increases the loss of fat mass,

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resulting in a more favorable body composition (264-265). In addition, one study demonstrated an improved dietary compliance, and therefore improved weight loss, in individuals participating in an exercise and diet program, as compared to the individuals who were assigned to a diet program (265). The lifestyle changes that are established with regular increased physical activity have been shown to result in more successful long-term maintenance of weight loss (264-266). This is particularly significant in light of the fact that, although most individuals can achieve an initial weight loss, the rate of recidivism in the long-term is very high (267).

1.3.2.1.2. Health Benefits

With poor physical fitness being a powerful predictor of mortality, it is logical to assume that improved physical fitness results in improved health and longevity. This assumption has been supported by the findings of numerous studies. The association between good physical fitness and an improved cardiovascular risk-factor profile has been underlined (268-269). Other studies have shown increased physical activity to have a positive effect on insulin sensitivity (270), glucose tolerance (268), and systolic and diastolic blood pressure (272-273). In a review of published data evaluating colon cancer and physical fitness, a consistent inverse relationship between physical activity level and incidence of colon cancer was observed (274). In addition, increased physical activity is advocated for the treatment of dyslipidemias due to the increase in HDL concentrations that occurs with exercise, an effect not noted with dietary therapy alone (275-277).

The relationship between body weight and physical fitness is often closely linked and it has been questioned to what degree exercise directly impacts health, and whether

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its benefits are strictly related to decreases in body fat. One study, however, has shown a convincing association between health, mortality and physical fitness, unrelated to body weight. This study assessed physical fitness in lean and overweight men and determined that irrespective of body weight, fit men had a lower risk of all-cause mortality and cardiovascular disease mortality than did unfit men. Mildly obese men therefore had a lower risk of mortality than lean men if the obese men were fit and the lean men unfit. This association also held true when body fat mass was assessed rather than body mass index (278).

In addition to the benefits of exercise for the treatment or prevention of obesity-related disorders, exercise has been found to also have important psychologic benefits. In several studies, level of physical activity has been positively correlated with perceived improvement in quality of life and self-esteem, and lower levels of anxiety, depression, and stress (279,280).

1.3.2.2. Companion Animals

Unfortunately, there is little information concerning the effects of regular physical activity on health and weight loss in companion animals. The addition of regular exercise to a pet's routine is presumed to promote maintenance of desirable body weight in a similar fashion to humans (11). It has also been suggested that low-impact physical activity may improve clinical signs of osteoarthritis due to an increase in muscle mass (281).

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1.3.3. Combined Physical Activity and Dietary Interventions

1.3.3.1. Humans

Numerous studies have assessed the benefits of combined physical activity and dietary interventions in obese individuals. The Oslo Diet and Exercise Study assessed improvements in metabolic parameters following physical training and dietary changes, both alone and combined, in sedentary men and women. This study documented benefits of the combined intervention over those of a single intervention to reduce fasting insulin concentrations, reduce insulin response after a glucose load, reduce serum triglyceride concentrations, and increase serum HDL concentrations (14,284). Many studies have since assessed the potential additive effects of exercise and diet, finding positive effects on insulin sensitivity (282), reduction of LDL concentrations (283), and maintenance or increase of HDL concentrations (284,285) in individuals subjected to both dietary modification and exercise. Studies evaluating the effects of combined diet and exercise programs on blood pressure have shown variable results, with some documenting an improvement in blood pressure (15,286) and others demonstrating no additive effect of exercise and diet (287,288). The combination of diet modification and aerobic exercise has been shown to increase sex hormone-binding globulin, an effect that may reduce the risk for breast cancer in postmenopausal women (289). Improved trends in biomechanical data suggest that increasing physical activity as well as losing weight may be beneficial in improving the gait performance of obese patients with knee osteoarthritis (290). Combined exercise and diet modification has also been shown to result in increased fat oxidation, an important factor for improving insulin sensitivity (291). A

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uniform consensus as to the benefits of combination versus a single intervention, however, has not been established. Some studies document limited benefits of combined exercise and diet on improvements in body composition (292,293) and cardiovascular disease risk factors (292).

1.3.3.2. Companion Animals

To the author's knowledge, there are no studies evaluating the benefits of combined diet and exercise in dogs participating in a weight loss program. One study of household cats demonstrated that cats in an enriched environment that promoted increased physical activity had a trend towards greater weight loss when placed on a calorie-restricted diet than did cats receiving the diet alone (294).

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RATIONALE

Given the previously described health benefits of improved physical fitness in obese people, it was hypothesized that these same benefits would be evident in obese dogs participating in a routine exercise regime. The primary objective of this study was to determine whether the addition of an exercise program to a dietary intervention exerted any additional improvements in health parameters over dietary intervention alone in overweight and obese dogs enrolled in a weight loss program. The secondary objective of this study was to determine if a moderate exercise protocol would be well-tolerated by untrained, overweight and obese dogs.

Routine exercise has become an integral part of therapy for obesity in humans. By investigating the possible benefits of exercise in canine obesity, more precise recommendations may be made for the development of canine weight loss protocols, thus improving health and quality of life in pet dogs.

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2. MATERIALS AND METHODS

2.1. Subject Selection

Sixteen overweight or obese dogs, owned by staff and clients of the Atlantic Veterinary College Teaching Hospital, were enrolled in this study. To be eligible for the study, the dogs had to be assessed as having a body condition score, as described and validated by LaFlamme (167), of 6 out of 9 or greater and be free of concurrent illnesses. None of the dogs had abnormal thyroid function at initial evaluation, or physical or historical evidence of adrenal disease. The enrolled dogs were also free of clinical evidence of orthopedic disease that might preclude them from participating in the exercise portion of the study. Owners were informed of the study protocol and signed consent forms were obtained. The study design was approved by the Animal Care Committee of the Atlantic Veterinary College.

2.2. Initial Evaluation

The dogs were initially evaluated through a detailed history (Appendix A), physical examination, body weight, body condition score, waist circumference measurement, serum biochemistry panel (Appendix B), complete blood count (CBC) (Appendix C), urinalysis, insulin and triglyceride concentrations, systolic blood pressure, and serum thyroxine (T4) and thyroid-stimulating hormone (TSH) concentrations, all performed after a 12-hour fast. Body condition was assessed according to the nine-point body condition scoring (BCS) system (Appendix D). The primary investigator performed the body condition scoring throughout the study to maintain consistency; for logistical reasons, this investigator was not blinded as to the treatment groups. For the purpose of discussion, dogs with a BCS for 6-7/9 were considered overweight or mildly obese, those

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with a BCS of 8/9 were considered moderately obese, and dogs with a BCS of 9/9 were classified as severely obese. Waist circumference was measured just caudal to the last rib using a standard tape measure. Indirect blood pressure measurements were performed in a quiet area after the dog was given at least 10 minutes of acclimatization time and prior to other assessments. An automated oscillometric device (Dinamap™ Veterinary Blood Pressure Monitor, Critikon Inc, Tampa, FL, USA) and a distal limb cuff measuring 40% of the limb circumference were used to measure systolic blood pressure. Six consistent measurements were taken, and the average of the readings calculated.

2.3. Treatment Assignment

The first dog enrolled was randomly assigned to the diet only (DO) group. Subsequent dogs were matched according to BCS and placed in opposite groups so as to keep the ratio of mildly to severely obese dogs similar for both the DO and the combined diet and exercise (DE) groups.

2.4. Treatment

All dogs had their caloric intake restricted to 70% of that being fed prior to the study, as determined by a detailed diet history that included type and quantity of the primary diet fed as well as all other sources of food intake (Appendix A). No change in diet was prescribed other than this restriction in quantity. Dogs in the DE group were also walked briskly for 45 minutes, three times a week, by hired veterinary students so that the exercise was not dependent on owner compliance. For ethical reasons, no effort was made to restrict physical activity in the DO groups or to modify physical activity beyond the prescribed walks in the DE group. All owners were advised to maintain their regular routines with regards to walking and playing activities regardless of whether their

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dogs received the additional exercise treatment. Owners were supplied with a diary in which they recorded daily observations concerning appetite and activity level as well as amount of food fed, in an attempt to verify that dietary compliance was being maintained (Appendix E). Owners of dogs in the DE group were advised to report any problems such as lameness, extreme fatigue, or respiratory difficulties that occurred following the assigned exercise. The study was 4 months in duration.

2.5. Evaluations During Treatment

Each dog was evaluated at 2-week intervals during the study. Body weight and waist measurement was recorded at each time period. At the mid-point (2 months) and end (4 months) of the treatment period, body condition score, CBC, serum biochemical panel, serum insulin concentration, serum triglyceride concentration, and systolic blood pressure were assessed after a 12-hour fast.

2.6. Analytical Methods

Complete blood counts, urinalyses, serum biochemistry profiles, serum triglyceride concentrations, and serum T4 and TSH concentrations were performed by the Atlantic Veterinary College Diagnostic Laboratory using established assay methods. Serum insulin concentrations were determined using a commercially available chemiluminescent assay kit (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA), previously validated for canine serum by the Endocrinology Laboratory of Colorado State University (personal communication). All analyses were run immediately after sample collection, with the exception of the insulin assay. For the insulin measurements, the samples were centrifuged and the serum frozen at –20 degrees Celsius until the end of the study.

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2.7. Data Analaysis

A statistical software package was used for the statistical analysis (Minitab 13.32™ for Windows, Minitab Inc, State College, PA). Outcome variables measured repeatedly over time per dog (repeated measurements) were plotted against time and inspected for patterns common to multiple dogs (in or between treatment groups). The development over time of each outcome variable was summarized in the gain (last value minus initial value) computed separately for each dog. The analysis of gains is an example of analysis of a summary statistic for repeated measurements. The gains were compared statistically to zero to detect any overall change over time, as well as compared statistically between the treatment groups. Outcome variables measured only once per dog were compared between the treatment groups only. The Anderson-Darling normality test was used to check for normal distribution. For normally distributed continuous data, comparisons within each treatment group were made using a one-sample Student's t-test, and comparisons between the treatment groups were made using a two-sample Student's t-test. For continuous data that were not normally distributed, the Wilcoxon signed rank test was used for within treatment group analyses, and the Kruskal-Wallis ANOVA was used for comparisons between treatment groups. All normally-distributed results were reported as mean +/- standard deviation, whereas non-normally distributed data were reported as median; range. All statistical tests were carried out using two-tailed alternative hypotheses, and a p-value of less than 0.05 was considered significant.

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3. RESULTS

3.1. Initial Questionnaire Data and Dietary History

All dogs entering the study were fed commercially available maintenance-type dog foods. The brands of dog foods included Science Diet Canine Maintenance®, Eukanuba®, and Purina Dog Chow® in the DE group, and Eukanuba®, Kibbles n' Bits®, Purina Dog Chow®, Pedigree®, and Science Diet Canine Maintenance® in the DO group. Four of the dogs in the DE group and 6 of the dogs in the DO group were fed treats or table scraps in addition to their regular diet. Common table scraps fed in both treatment groups included cheese, bread, apples, and carrots. Commercial treats fed in the DE group include Dentabone® treats and rawhides, whereas Medical® treats and rawhides were fed to the dogs in the DO group. Owners rated their dogs' appetite as fair (n=5), good (n=10), and excellent (n=1). None of the owners reported a change in their dog's appetite within the past 2 months. Six of the dogs in the DE group and 4 of the dogs in the DO group were assessed as spending most of their time outdoors. Most of the dogs were thought by their owners to have a moderate energy level (n=13). One dog each in the DE and DO groups were assessed as having a fair energy level, and one dog in the DO group as having an excellent energy level. The owners of 14 of the dogs assessed their dogs' mental agility as excellent, whereas two assessed it as good. The chronicity of obesity in the enrolled dogs was estimated as ranging from 1 year to lifelong, with three owners uncertain of the period of time that their dog had been overweight. None of the dogs had any previous medical conditions or major operations, and all but one had been vaccinated within the past two years.

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3.2. Baseline Data

Sixteen dogs were enrolled in the study. There were 4 neutered male and 12 spayed females, all of medium to large breed. Represented breeds included Labrador retrievers (n=3), golden retrievers (n=4), rottweilers (n=1), and mixed breeds (n=8). Ages ranged from 1.5 to 9 years, with a median of 4.5 years. Median age was not statistically different between the groups. Fifteen dogs completed the study. One dog was withdrawn from the DO group due to poor dietary compliance; the data from this dog were included until the time the dog became exposed to an additional food source in the household.

Body condition scores initially ranged from 6 to 8 out of 9, with a median of 7. Baseline BCS, waist circumference, systolic blood pressure, serum triglycerides, serum cholesterol, serum insulin, and other biochemical parameters were not significantly different between groups. The mean values for systolic blood pressure (130 +/- 15.4mmHg), serum cholesterol (5.34 +/- 0.81mmol/L), serum insulin (9.93 +/- 6.16 uIU/L), serum triglycerides (0.806 +/- 0.342mmol/L), serum glucose (5.04 +/- 0.49mmol/L) and other biochemical parameters were within normal limits when all dogs were assessed together at baseline. Only two dogs had elevated serum triglyceride concentrations at the beginning of the study; both were in the DO group and one of these dogs remained hypertriglyceridemic throughout the duration of the study.

3.3. Diary Data

The diary supplied to the owners consisted of a list of parameters to be assessed, including amount of food and snacks fed, duration of assigned exercise (if in DE group), and quantification of appetite, activity, alertness, water consumption, urination, and

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defecation. Despite the dietary restriction that all dogs underwent, there were few owners that rated their dog's appetite as increased above normal during the course of the study. Two dogs in the DO group and one in the DE group were rated as having an increased appetite in the first 1-3 weeks of the study. In general, owners of dogs in both treatment groups considered activity, alertness, water consumption, urination and defecation to be normal in their dogs throughout the study. There was no trend for owners of dogs in the DE group to consider their dogs less active secondary to exhaustion from the enforced exercise routine. No adverse effects attributable to the exercise regime, as determined by owner assessment of attitude and well-being were noted among the dogs in the DE group. In addition, the individuals hired to walk the dogs in the DE group did not report any episodes of dyspnea, lameness, or inability to complete the scheduled exercise.

3.4. Combined Diet and Exercise (DE) Group

Dogs within the DE group lost a mean of 9.44 +/- 2.29% of their initial body weight over the 4 month study period (p=0.014) (Fig 1). The decrease in BCS (1 unit; range, 0.5-2 units) from the beginning of the study to 4 months was statistically significant (p=0.014) (Fig 2) as was the decrease in waist measurement (2.38 +/- 1.53 inches; p=0.003) (Fig 3). On the serum biochemistry profiles, significant decreases in serum albumin concentration (1 +/- 1.07g/L; p= 0.033) (Fig 4), globulin concentration (2.38 +/- 2.33g/L; p=0.023) (Fig 5), sodium concentration (3.12 +/- 2.23; p=0.005) (Fig 6), and alkaline phosphatase concentration (4.71 +/- 4.57U/L; p=0.034) (Fig 7), were found at 4 months compared to baseline. None of these parameters was outside of the normal reference range. A significant decrease in serum triglyceride concentration (0.235 +/- 0.273 mmol/L; p=0.045) (Fig 8) was seen at 2 months, but this increased again

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by 4 months to a mean concentration not significantly lower than baseline concentration (p=0.223). The systolic blood pressure was insignificantly increased above baseline at 2 months, but decreased over the second half of the study period to a mean measurement that was significantly lower at 4 months than at 2 months (17 +/- 12 mmHg; p=0.009), but not statistically different from baseline (p=0.127) (Fig 9). Serum calcium increased significantly (0.06 +/- 0.07mmol/L; p=0.043) in the exercised dogs over the course of the study (Fig 10). In addition, serum phosphorus was significantly (p=0.042) increased over baseline at 2 months (0.16; range, -0.3– 0.2), but it declined slightly at 4 months and was not significantly different from baseline at that time (p=0.059) (Fig 11). The serum calcium and serum phosphorus concentrations remained within the reference range at all evaluation times. Hematocrit, serum concentrations of cholesterol, insulin, creatine kinase, and other liver enzymes and electrolytes were not significantly changed (Appendix F). Two dogs within the DE group achieved their ideal body weight by the end of the study.

3.5. Diet Only (DO) Group

Dogs within the DO group lost a mean of 9.10 +/- 3.31 % of their initial body weight over the 4 month period (p<0.001) (Fig 1). A significant decrease in waist circumference (2.5 +/- 1.26 inches; p=0.002) was also seen (Fig 3). The decrease in body condition score in this group, however, did not achieve statistical significance (p=0.059) (Fig 2). Similar to dogs in the DE group, dogs in the DO group had a significant decrease in serum albumin concentration (1.71 +/- 0.76 g/L; p=0.001) at 4 months compared to baseline (Fig 4), although serum globulin did not significantly decrease (p=0.321) in this group (Fig 5). The serum albumin concentration at 4 months

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remained within the normal range. No other variables were significantly changed in the DO group (Appendix F). Three dogs within the DO group achieved their ideal body weight by the end of the study.

3.6. Comparison of DO and DE Groups

There was no significant difference in weight loss ($p=0.826$), decrease in BCS ($p=0.490$), or decrease in waist circumference ($p=0.722$) between treatment groups. There was also no significant difference in the observed changes in systolic blood pressure ($p=0.487$), and serum concentrations of glucose ($p=0.650$), cholesterol ($p=0.145$), triglycerides ($p=0.581$), and insulin ($p=0.908$) between the groups. A trend ($p=0.065$) towards an increase in gamma glutamyl transpeptidase (GGT) observed in the DE group was the only biochemical change that was significantly different from the DO group ($p=0.048$).

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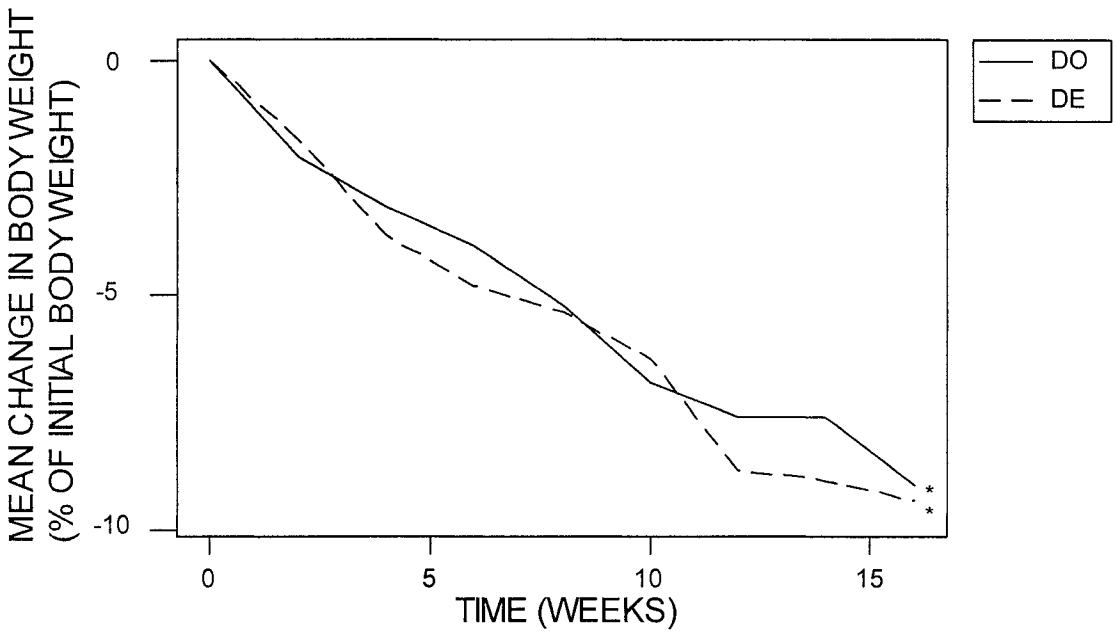

Figure 1: Plot of mean change in body weight over the course of the study period. " * " indicates a significant ($p<0.05$) change at 4 months from baseline.

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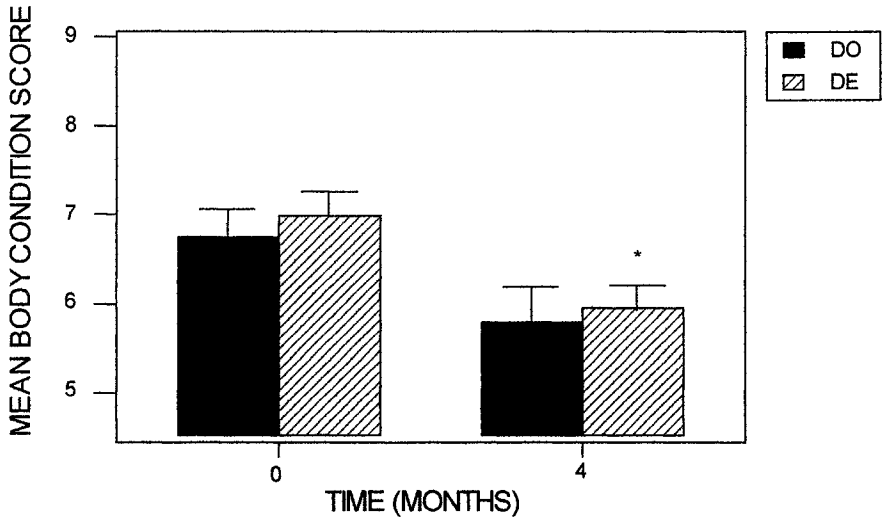

Figure 2: Mean body condition score at the beginning and end of the study period. " * " indicates a significant ($p<0.05$) difference from baseline.

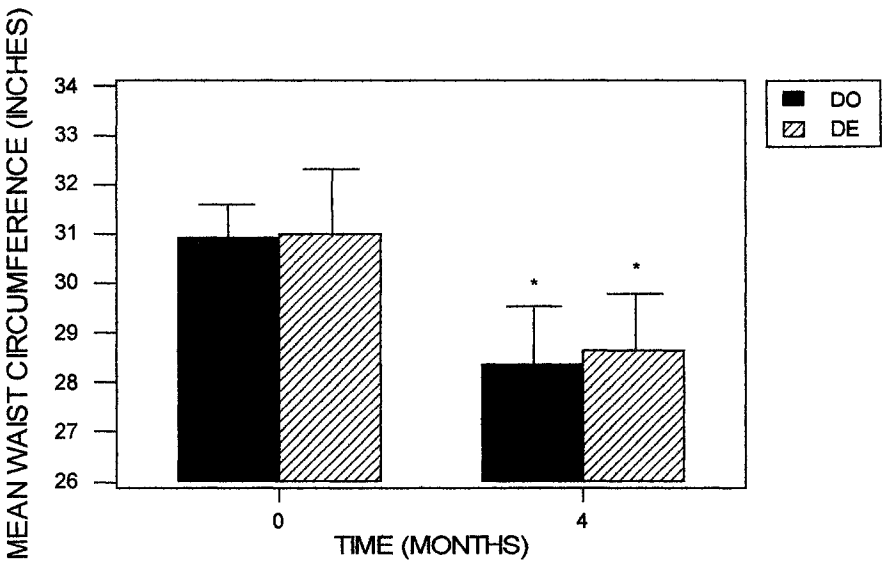

Figure 3: Mean waist circumference at the beginning and end of the study period. " * " indicates a significant ($p<0.05$) difference from baseline.

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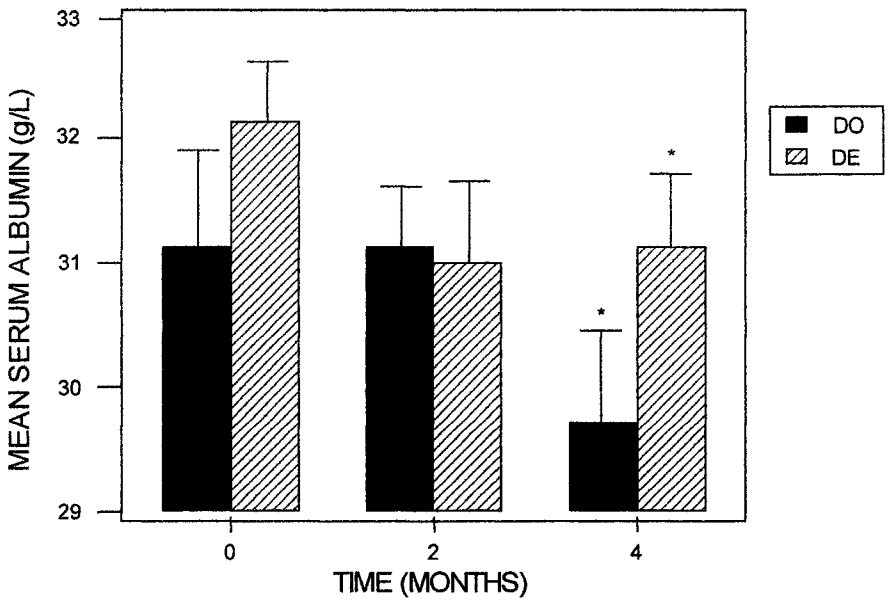

Figure 4: Mean serum albumin concentrations at the beginning, mid-point, and end of the study period. " * " indicates a significant ($p < 0.05$) difference from baseline.

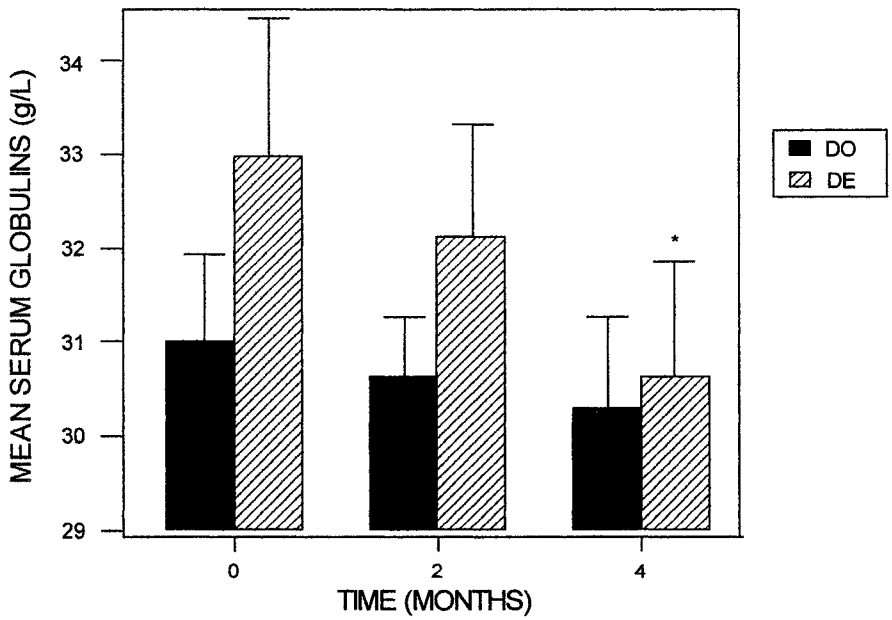

Figure 5: Mean serum globulin concentrations at the beginning, mid-point, and end of the study period. " * " indicates a significant ($p < 0.05$) difference from baseline.

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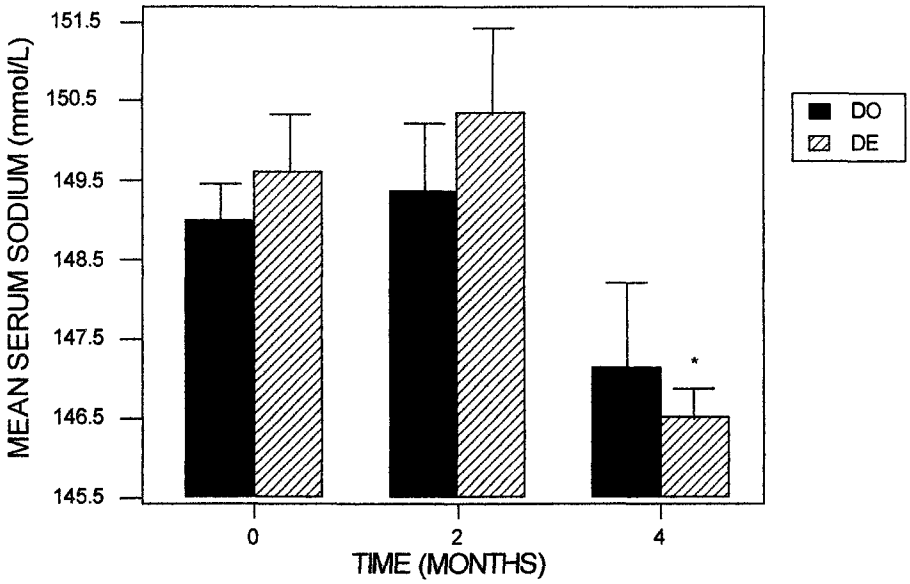

Figure 6: Mean serum sodium concentrations at the beginning, mid-point, and end of the study period. " * " indicates a significant ($p<0.05$) difference from baseline.

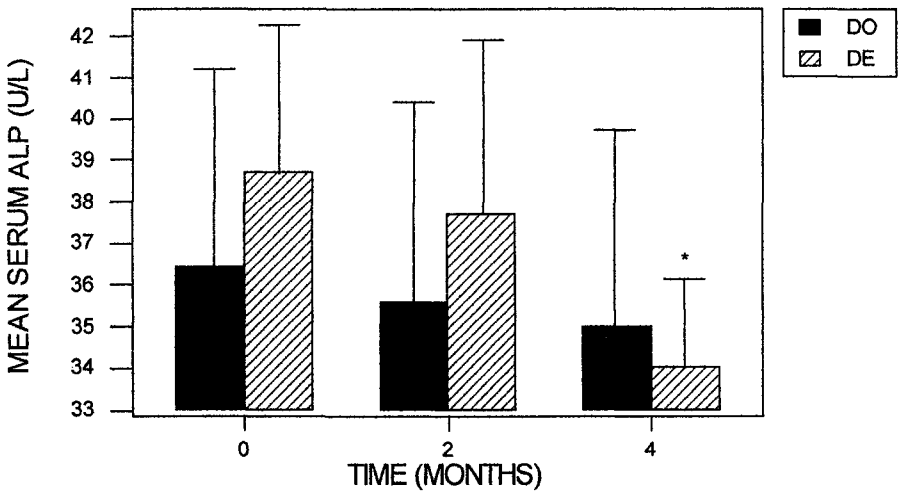

Figure 7: Mean serum ALP concentrations at the beginning, mid-point, and end of the study period. " * " indicates a significant ($p<0.05$) difference from baseline.

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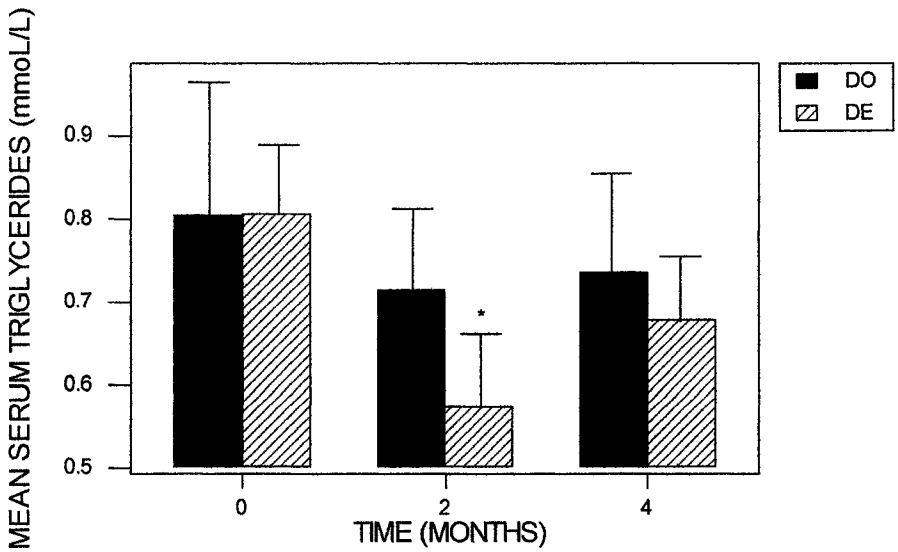

Figure 8: Mean serum triglyceride concentrations at the beginning, mid-point, and end of the study period. " * " indicates a significant ($p<0.05$) difference from baseline.

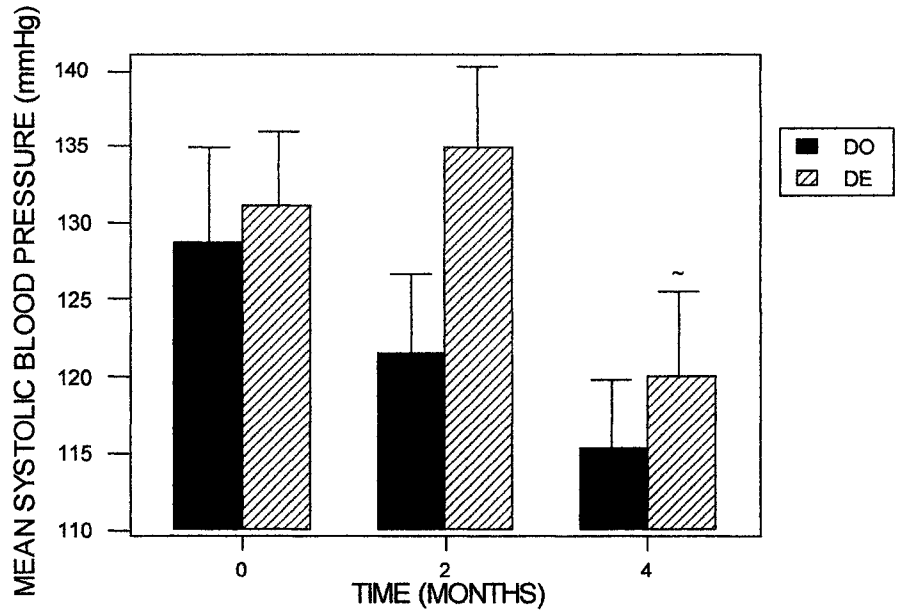

Figure 9: Mean systolic blood pressure at the beginning, mid-point, and end of the study period. " ~ " indicates a significant ($p< 0.05$) difference from mid-point.

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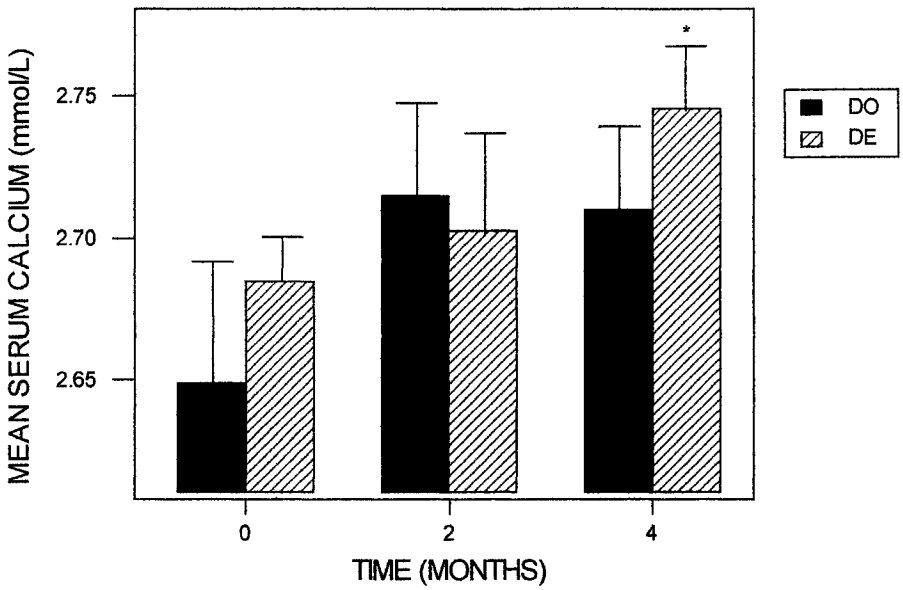

Figure 10: Mean serum calcium concentrations at the beginning, mid-point, and end of the study period. "*" indicates a significant ($p < 0.05$) difference from baseline.

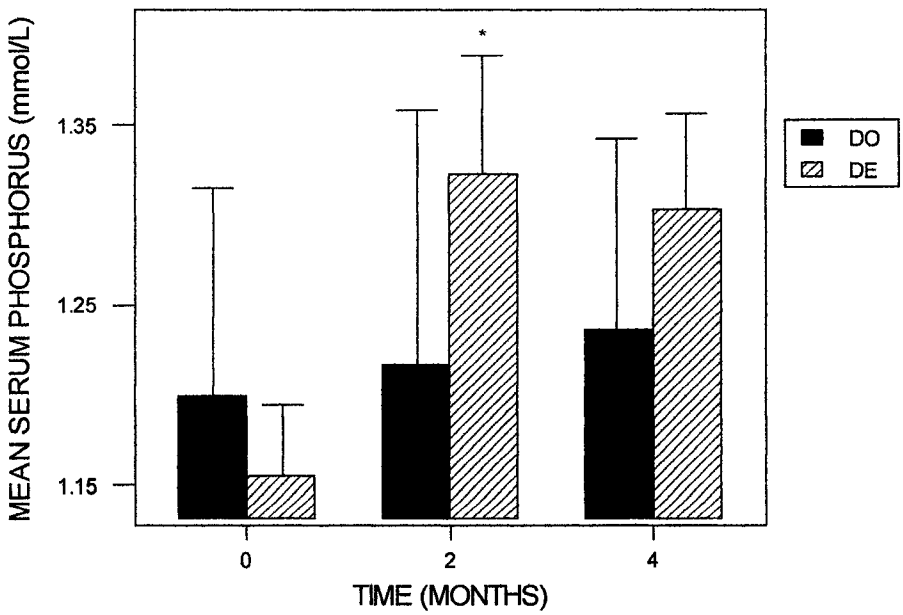

Figure 11: Mean serum phosphorus concentrations at the beginning, mid-point, and end of the study period. "*" indicates a significant ($p < 0.05$) difference from baseline.

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4. DISCUSSION

To the author's knowledge, this is the first study to assess whether the addition of a regular exercise regime to a calorie-restricted diet is of benefit to chronically overweight or obese dogs participating in a weight loss program. This study did not find a benefit of low-impact exercise on the reduction of body weight, waist circumference, or body condition score, in mildly to moderately obese dogs receiving a 30% dietary calorie restriction. These findings are in accordance with the results of several studies involving obese humans, where the addition of exercise to a dietary weight-loss program did not result in a quicker or more significant weight loss (260-261). The primary investigator who was performing the BCS was not blinded as to the treatment groups, as the same investigator performed the random assignment of dogs to treatment groups and arranged walking schedules for the DE dogs. This lack of blinding could have introduced a bias; however, the lack of statistical difference seen between groups with regard to BCS does not support this.

In this study, no difference between treatment groups was seen in regards to changes in systolic blood pressure, and serum concentrations of cholesterol, triglycerides, and insulin, parameters that have been identified as having potentially harmful health implications in both humans and dogs (4, 130). Fasting serum insulin concentrations in this study were quite variable, and no meaningful pattern was observed in either treatment group over the course of the study. Glucose tolerance testing may have identified more subtle changes in glucose metabolism, but such multiple-sample tests were not included because this study utilized only client-owned dogs.

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Previous studies have documented decreases in blood pressure, serum insulin concentrations, and serum triglyceride concentrations in obese dogs that lost weight through dietary interventions. Most of these studies, however, were performed on dogs made obese relatively acutely through the feeding of a high-fat diet (172-173, 178, 188). The dogs in this study were chronically obese, were not consuming diets formulated for weight gain, and did not have baseline elevations in mean systolic blood pressure or serum insulin, triglyceride, or cholesterol concentrations. The lack of significant reductions in these parameters may therefore be attributable to metabolic differences in chronically obese dogs compared to the high-fat diet model of obesity.

Several statistically significant but clinically insignificant biochemical changes were identified within the treatment groups. Potentially the most interesting were the significant reductions in serum albumin and globulin concentrations seen in the DE group. The decreases in these substances were not severe enough to fall outside of normal reference ranges. Decreases in blood proteins have been documented in Alaskan sled dogs and humans following endurance training (230-231,295). It has been shown that endurance training results in an increase in plasma volume, leading to relative decreases in serum proteins secondary to hemodilution (296). Exercise-induced hypervolemia has been documented in people both in the immediate period following strenuous exercise, and chronically in exercise-trained individuals (297). The decrease in blood proteins observed in the DE dogs is unlikely to be wholly attributable to plasma volume expansion for several reasons. First, the exercise regime utilized in this study was not nearly as strenuous as the training described to induce the plasma volume changes in sled dogs, although the relative degree of exertion experienced by the untrained study dogs versus

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the trained sled dogs is unknown. In addition, exercise-induced hypervolemia typically also results in a decrease in hematocrit due to hemodilution (230-231). The dogs in the DE group did not have a significant decrease in hematocrit, red blood cell counts, or hemoglobin. Finally, the dogs in the DO group also had a significant drop in serum albumin levels, suggesting the shared dietary intervention may have been responsible for the decrease in blood proteins in both groups. The 30% calorie restriction used in this study has been previously recommended for weight loss (156), and is well above the 50% restriction of maintenance energy requirement (based on target body weight) that has been found to be safe for weight loss in dogs (298). It has been suggested that feeding the dog's regular diet in reduced quantities is not ideal for weight reduction because nutritional deficiencies may occur with strict restrictions, and weight loss may not be achieved due to increased efficiency of fat and carbohydrate extraction (11, 299). These claims are poorly substantiated, however, and all dogs in this study achieved significant weight loss with this protocol. Restriction of the regular diet was chosen over the use of diets specifically formulated for weight loss in order to avoid potential gastrointestinal and dermatological complications, as well as palatability issues, that can be associated with a diet change.

The reduction in serum sodium concentrations observed in the DE dogs over the course of the study is difficult to explain. Clinical hyponatremia is well documented in humans following strenuous exercise and is attributable to a combination of hemodilution from increased water intake and massive sodium losses from sweating (300-301). Non-clinically significant decreases in serum sodium levels have also been documented in Alaskan sled dogs following races. In sled dogs, the decrease in serum sodium is

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suggested to be secondary to selective expansion of the extracellular space during a race and/or urinary sodium loss due to the large urine volume induced by the high-protein diets these dogs consume (231). Decreases in sodium concentrations in these dogs were documented in the period immediately following strenuous exercise. The same mechanisms are not likely responsible for the decrease in serum sodium concentrations that occurred in the DE dogs. Dogs in this study had blood samples collected in the morning prior to any scheduled exercise interventions. The exercise regime in this study was not strenuous and, unlike the sled dogs, the DE dogs were not receiving diets formulated to provide higher protein levels that would result in increased urinary solute excretion. In addition, no previous studies have shown a chronic downward trend in resting serum sodium levels with increasing levels of physical fitness. As previously mentioned, exercise-induced plasma volume expansion has been documented in humans and animals and may result in decreases in serum sodium concentrations, but an expected parallel decrease in hematocrit was not seen in the dogs in our study. Decreased sodium intake is also unlikely to be the cause of the decrease in serum sodium concentration because most commercial dog foods have more than adequate sodium concentrations to maintain normal intake, even at a 30% calorie restriction. Weight loss itself has been associated with increased natriuresis in previously obese rats, an effect that may be mediated in part by alterations in circulating atrial natriuretic peptide; this may have implications for the treatment of obesity-induced hypertension (302-303). Although the dogs in the DE group did have a trend towards a decrease in systolic blood pressure over the course of the study, this same trend was seen in the DO group and was not associated with a decrease in serum sodium concentrations in that group. As urinary sodium

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concentrations were not assessed in this study, the degree of natriuresis and its potential contribution to the observed decrease in serum sodium concentrations in the DE dogs is unknown.

Increases in serum calcium and phosphorus concentrations were observed in the dogs in the DE group, although neither of these parameters increased outside of the normal reference ranges. One potential explanation for these changes lies in the influence of exercise on bone turnover. Studies evaluating the impact of regular exercise on bone metabolism in humans have yielded conflicting results, with some studies demonstrating an increase in bone turnover and decrease in bone mineral density associated with endurance exercise, and others documenting an opposite and protective effect (304-305). Total serum calcium levels were increased in some groups of endurance-trained athletes (306-307), and exercise-induced rises in intestinal calcium absorption have been documented (308). Increased bone turnover could also explain a rise in serum phosphorus. Bone turnover associated with exercise has not been evaluated in companion animals. Bone alkaline phosphatase (B-ALP) has been used as a marker of bone turnover in people, with B-ALP increasing with endurance training in some people (309). The dogs in the DE group had a significant decline in total serum ALP, but ALP isoenzymes were not individually assessed. This decrease in total ALP may not necessarily argue against an increase in bone turnover in these dogs because the liver specific fraction of total ALP may have declined with weight loss. An increase in total ALP due to lipid accumulation within hepatocytes has been documented in severely obese humans; this pathology has been shown to improve with weight loss (310). It is unknown whether the exercise regime in this study was sufficient enough to induce an

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increase in bone turnover, or whether the documented increases in serum calcium and phosphorus in the DE dogs were of another origin.

Despite the lack of differences between the two treatment groups with regards to weight loss, body conformation, and major biochemical parameters, the addition of regular exercise to a weight loss protocol may still have beneficial effects in dogs. In people, the rate of recidivism after weight loss is very high when dietary therapy alone is used. In contrast, people who incorporated regular exercise into their routine were more likely to maintain their weight loss in the future (265). The dogs in this study were not followed long-term to determine the rate of recidivism, and it is unknown if the owners of the dogs within the DE group maintained the exercise regime after the conclusion of the study. Aerobic exercise has beneficial effects on maintaining a favorable body composition and preventing loss of muscle during weight loss (263). Body composition was not quantitatively assessed in the dogs participating in this study. Waist circumference was measured in an attempt to assess changes in abdominal adiposity between the two treatment groups. No significant difference in waist circumference was observed between the groups; however, this technique has not been validated in companion animals as an assessor of abdominal fat deposition.

There were a number of limitations inherent to this study. Many studies assessing the health implications of obesity, exercise, and weight loss in humans and dogs involve severely obese individuals. The dogs in this study ranged from mildly to moderately obese. No severely obese dogs (BCS 9/9) were included within the study due to their paucity within the population of dogs that frequent the Atlantic Veterinary College and due to concerns regarding their ability to tolerate the exercise regime employed in this

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study. Serum hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and hypertension may be more prevalent in grossly obese dogs; more subtle effects of the treatment protocols on these parameters may therefore have been missed. This study was also limited by the fact that the quantity and intensity of exercise necessary to result in improved physical fitness has not been determined in companion animals. It is unknown if the physical fitness level of the dogs in the DE group improved over the course of the study, or if the dogs were physically unfit at the start of the study. In humans, physical fitness can be quantified through measures of maximal oxygen consumption and aerobic capacity using exercise tests (211-214). These methods have not been well validated in companion animals. The exercise regime in this study, involving three 45-minute brisk walks per week, was chosen for two reasons. First, it was presumed to be low-impact exercise that would be tolerated even by moderately obese, and presumably unfit, dogs. Indeed, none of the dogs in the DE group had difficulties completing the exercise, nor did they suffer any adverse effects from the walks. Second, this protocol was thought to be clinically applicable and practical for most owners to maintain after the study's conclusion, due to the relatively minimal time and human fitness demands. Tailoring of the exercise protocol to minimize impact on dog and owner, however, may have reduced its efficacy. Finally, for ethical reasons, no attempt was made to curtail physical activities of the dogs in the DO group, or to curtail non-prescribed physical activities in the DE group. Some owners of dogs within the DO group reported that their dogs' willingness to participate in play activities increased as the dogs lost weight. In addition, although owners of dogs in the DE group were instructed to maintain their regular routines with regards to playing and walking, dogs in this group may have been less

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inclined to participate in these activities due to increased tiredness after the scheduled walks. The potential increase in daily exercise in the DO dogs and decrease in non-study-associated exercise in the DE dogs may have additionally masked any differences between the treatment groups.

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5. CONCLUSIONS

The addition of exercise to a dietary intervention did not result in reductions of body weight, waist circumference, or body condition score in overweight and obese dogs that were greater than the effects of the dietary intervention alone. No significant reductions in systolic blood pressure, or serum concentrations of glucose, triglycerides, insulin, and cholesterol were observed in either treatment group at the end of the study as compared to baseline values. None of these parameters were outside of the normal range at the beginning of the study. The dietary intervention, consisting of a 30% reduction in the regular quantity of food fed, was successful in inducing significant weight loss over a 4-month period, with or without the addition of an exercise routine. The exercise regime used in this study was well tolerated by mildly to moderately obese dogs of medium to large breed and could be safely recommended as an adjunct to a weight loss protocol in otherwise healthy dogs of similar stature and degree of obesity. Further studies involving a larger sample size are needed to investigate the more subtle benefits of exercise in regards to metabolism and body composition, and long-term studies are needed to assess the benefits of exercise in the maintenance of weight loss in dogs. Further investigation of metabolic abnormalities and fitness levels in chronically obese dogs would also be useful in helping to establish the general state of health of spontaneously obese dogs.

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APPENDIX A - Questionnaire and Dietary History

Owner's name:_____ Date:_____
Dog's name:_____ Age of dog:_____
Sex of dog: Male Female
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 and how often do you feed your dog?_____
Does your dog get any treats or table scraps? Yes No
If yes, what and how often?_____
Rate your dog's appetite (circle one): Poor Fair Good Excellent
Poor – very selective and/or rarely eats all food provided
Fair – somewhat selective but usually eats all food provided
Good – readily eats all food provided but does not have an insatiable appetite
Excellent – eats all food provided, is constantly hungry, will eat anything edible
How much water does your dog drink on a daily basis (estimate)?_____
Has there been any change in your dog's appetite in the last 2 months? Yes No

General Health

Do you have any other pets in your household? Yes No
If yes, how many and what type?_____
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 – likes to sleep most of the day
2- fair – exercises minimally but enjoys slow walks
3- moderate – runs and plays when interacted with
4- excellent – very energetic, hard to keep quiet
Any additional comments?_____
Rate your dog's mental agility (circle one): Poor Good Excellent
Poor – slow to learn commands, disobedient
Good – shows ability to learn but is only moderately obedient
Excellent – readily learns new commands and is very obedient
Any additional comments?_____
How long has your dog been overweight?_____
Are you aware of any change in your dog or your household that coincided with the weight gain? Yes No
If yes, what was it?_____
Please check below if your dog (elaborate if possible):

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Has ever had a major operation (other than spay or neuter procedure):_____

_____

Has ever had a major medical problem requiring hospitalization or extended outpatient care_____

Suffers from chronic (recurring) eye, ear or skin infections_____

Has received antibiotics for any reason in the last 3 months?_____

If so, for what reason?_____

Has ever had an adverse drug reaction_____

Has vomited more than once in the last month_____

Has had an episode of diarrhea lasting more than 24 hours in the last month___

_____

Regularly coughs or sneezes_____

Has a history of seizures_____

Has experienced any weight gain or weight loss in the last 3 months_____

_____

Has any unusual behavioral habits?_____

Is there anything else regarding your dog hat you think is important for us to know?___

_____

_____

_____

_____

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APPENDIX B

COMPONENTS OF THE SERUM BIOCHEMICAL PROFILE	
BIOCHEMICAL TEST	**NORMAL RANGE**
Sodium concentration (Na)	144-162 mmol/L
Potassium concentration (K)	3.6-6.0 mmol/L
Chloride concentration (Cl)	106-126 mmol/L
Calcium concentration (Ca)	2.24-3.04 mmol/L
Phosphorus concentration (P)	0.82-1.87 mmol/L
Urea concentration	3.0-10.5 mmol/L
Creatinine concentration	33-113 umol/L
Glucose concentration	3.3-5.6 mmol/L
Cholesterol concentration	2.5-7.0 mmol/L
Total Bilirubin concentration	0-17 umol/L
Alkaline phosphatase activity (ALP)	23-87 IU/L
Creatine kinase activity (CK)	< 300 IU/L
Aspartate aminotransferase activity (AST)	20-50 IU/L
Alanine aminotransferase activity (ALT)	5-69 IU/L
Gamma glutamyl transpeptidase (GGT)	< 8 IU/L
Total protein concentration (TP)	51-72 g/L
Albumin concentration	22-38 g/L
Globulin concentration	29-34 g/L
Amylase concentration	300-1400 U/L
Lipase concentration	30-560 U/L

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APPENDIX C

COMPONENTS OF THE COMPLETE BLOOD COUNT	
HEMATOLOGICAL TEST	**NORMAL RANGE**
Hemoglobin	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)	60-77 fL
Mean corpuscular hemoglobin (MCH)	19.5-24.5 pg
Mean corpuscular hemoglobin concentration (MCHC)	320-360 g/L
Reticulocytes	1-1.5%
White blood cell count (WBC)	6.0-17.1 x 10^{9}/L
Segmented neutrophils	3.6-11.5 x 10^{9}/L
Band neutrophils	0.0-0.3 x 10^{9}/L
Eosinophils	0.01-1.25 x 10^{9}/L
Basophils	Rare
Lymphocytes	1.0-4.8 x 10^{9}/L
Monocytes	0.15-1.35 x 10^{9}/L
Platelets	200-900 x 10^{9}/L
Total protein	51-72 g/L

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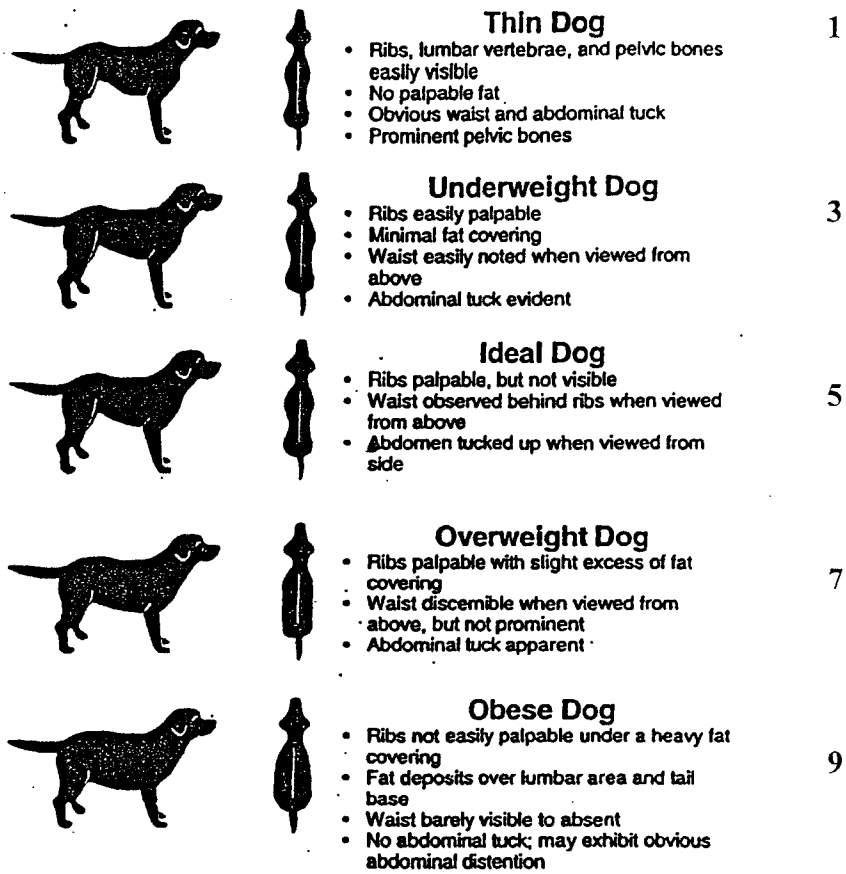
APPENDIX D

9-Point Body Condition Scoring System

Body Condition Score



From: Sunvold GD, Bouchard GF. Recent Advances in Canine and Feline Nutrition, Vol II: 1998. Iams Nutrition Symposium Proceedings.

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APPENDIX E – Daily Diary

Owner's name:_____ Date:_____
Dog's name:_____

Day	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Date	__/__/__ D M Y	__/__/__ D M Y	__/__/__ D M Y	__/__/__ D M Y	__/__/__ D M Y	__/__/__ D M Y	__/__/__ D M Y
Time of day fed and amount fed							
Snacks fed – time and amount							
Appetite I-increased N-normal D-decreased							
Assigned exercise – time and duration							
Activity I-increased N-normal D-decreased							
Alertness I-increased N-normal D-decreased							
Water consumption I-increased N-normal D-decreased							
Urination I-increased N-normal D-decreased							
Defecation I-increased N-normal D-decreased							
Additional comments							

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APPENDIX F – Additional Biochemical and Hematological Data

Biochemical or Hematological Parameter	Mean At Baseline (All Dogs)	Mean At 2 months (All Dogs)	Mean At 4 months (All Dogs)
Insulin (uIU/L)	9.93	9.85	9.49
Cholesterol (mmol/L)	5.34	5.21	5.28
Glucose (mmol/L)	5.01	4.97	5.23
Creatinine (umol/L)	93.8	89.5	95.6
Blood Urea Nitrogen (mmol/L)	5.18	4.53	4.97
Creatine Kinase (IU/L)	80.3	77.6	84
Aspartate aminotransferase (U/L)	30	31	25.6
Alanine aminotransferse (U/L)	42.69	80.06	38.07
Gamma glutamyl transpeptidase (U/L)	2.81	3.38	3.27
Potassium (mmol/L)	4.44	4.52	4.50
Chloride (mmol/L)	114.63	114.25	115.93
Hematocrit (L/L)	46.75	45.95	45.89
Hemoglobin (g/L)	160.06	159.69	159.53
Red blood cell count ($x10^{12}$/L)	6.83	6.73	6.75
White blood cell count (x 10^9/L)	9.93	8.59	9.19
Segmented neutrophils (x 10^9/L)	7.56	6.73	7.30
Lymphocytes (x 10^9/L)	1.09	1.15	1.05
Monocytes (x 10^9/L)	0.90	0.55	0.59
Eosinophils (x 10^9/L)	0.38	0.16	0.25
Platelets (x 10^9/L)	389	322	341

Note: None of these values were significant changed ($p>0.05$) from baseline to 4 months in either treatment group.

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